Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

# und

# Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

## Vorgang: 2021-B-064 Dupilumab

Stand: Mai 2021

## I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

| **Dupilumab<br>zur Behandlung von Asthma** | |
|---|---|
| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | *siehe Übersicht II:* Zugelassene Arzneimittel im Anwendungsgebiet: |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | Nicht angezeigt |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL):<br>- Mepolizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 21. Juli 2016)<br>- Reslizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 6. Juli 2017)<br>- Benralizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 2. August 2018)<br>*Hinweis:alle drei Beschlüsse nur für Erwachsene*<br><br>- Mepolizumab (Anlage XII- Nutzenbewertung nach §35a SGB V, Beschluss vom 22. März 2019)<br><br>- Dupilumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 20. Februar 2020)<br>*Hinweis: Beschluss für Asthma-Patienten ≥ 12 Jahre)* |

## I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

| **Dupilumab<br>zur Behandlung von Asthma**<br><br>**Kriterien gemäß 5. Kapitel § 6 VerfO** | |
|---|---|
| | Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL) - Anlage IV: Therapiehinweis zu Omalizumab (Beschluss vom 17. Dezember 2015)<br><br>DMP-Richtlinie (DMP-RL): Asthma |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | *siehe Evidenzsynopse* |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff<br>ATC-Code<br>Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Dupilumab<br>*ATC-Code*<br>*Handelsname*® | Geplantes Anwendungsgebiet laut Beratungsanforderung:<br>Dupixent ist angezeigt als Add-On-Erhaltungstherapie bei pädiatrischen Patienten zwischen 6 und 11 Jahren mit schwerem Asthma mit Typ-2-Inflammation, siehe Abschnitt 5.1, gekennzeichnet durch eine erhöhte Anzahl der Eosinophilen im Blut und/oder eine erhöhte exhalierte Stickstoffmonoxid-Fraktion (FeNO), das trotz mittel- bis hochdosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist.<br>*Mögliche alternative Formulierung*: … das trotz hochdosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| | |
|---|---|
| | Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist. |
| **Beta-2-Sympathomimetika (inhalativ; kurzwirkend) (SABA)** | |
| Salbutamol<br>R03AC02<br>generisch | Symptomatische Behandlung von Erkrankungen mit reversibler Atemwegsobstruktion wie z. B. Asthma bronchiale oder chronisch<br>obstruktive bronchiale Erkrankung (COPD) mit reversibler Komponente<br>— Verhütung von durch Anstrengung oder Allergenkontakt verursachten Asthmaanfällen<br>*Salbutamol-ratiopharm® N Dosieraerosol wird angewendet bei Erwachsenen, Jugendlichen und Kindern im Alter von 4 bis 11 Jahren (für die*<br>*Anwendung bei Kleinkindern und Kindern unter 4 Jahren siehe Abschnitte 4.2 und 5.1*).<br>(FI Salbutamol-ratiopharm®, Stand 11/ 2017) |
| Fenoterol<br>R03AC04<br>Berotec N® | - Symptomatische Behandlung von akuten Asthmaanfällen.<br>- Prophylaxe von belastungsinduziertem Asthma bronchiale.<br>- Symptomatische Behandlung von Asthma bronchiale allergischer und nichtallergischer Ursache und/oder anderen Erkrankungen, die mit einer reversiblen Obstruktion der Atemwege einhergehen, z.B. chronisch obstruktive Bronchitis mit und ohne Lungenemphysem.<br>Hinweis:<br>- Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen.<br>Dosierung: *Die Dosierung richtet sich nach Art und Schwere der Erkrankung. Soweit nicht anders verordnet, gelten für Erwachsene und Kinder ab 6 Jahren folgende Empfehlungen:*<br>(FI Berotec, Stand 09/2015) |
| **Beta-2-Sympathomimetika (systemisch; kurzwirkend) (SABA)** | |
| Reproterol<br>R03CC14<br>Bronchospasmin | Zur kurzfristigen Behandlung des schweren bronchospastischen Anfalls und des Status asthmaticus.<br><br>*Dosierung und Art der Anwendung: Kinder (Säuglinge ab 3. Monat, Klein- und Schulkinder) […]*<br><br>(FI Bronchospasmin, Stand 09/2020) |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| **Beta-2-Sympathomimetika (inhalativ; langwirkend) (LABA)** | |
| Salmeterol<br>R03AC12<br>Serevent® | Zur Langzeitbehandlung von Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive<br>Atemwegserkrankungen), wie z. B.Asthma bronchiale (anfallsweise auftretende Atemnot durch Atemwegsverkrampfung, insbesondere nächtliches Asthma), chronische Bronchitis und Blählunge (Lungenemphysem).<br>Gleichzeitig soll beim Asthma bronchiale eine regelmäßige Therapie mit entzündungshemmenden Arzneimitteln (inhalative und/ oder orale Kortikoide) sichergestellt werden, da Serevent kein Ersatz hierfür ist. Diese Behandlung mit Kortikoiden ist regelmäßig weiterzuführen.<br>Warnhinweis:<br>Serevent Dosier-Aerosol und Serevent Diskus sollen nicht für die Akutbehandlung eines Asthmaanfalls eingesetzt werden.<br><br>*Dosierung. Für Erwachsene und Kinder ab 4 Jahren gelten folgende Empfehlungen […]*<br>(FI Serevent ® Dosier-Aerosol, Stand 07/2020) |
| Formoterol<br>R03AC13<br>Formoterol CT® | - Symptomatische Langzeitbehandlung des chronischen mäßigen bis schweren Asthma bronchiale in Kombination mit einer entzündungshemmenden Dauertherapie (z. B. Kortikosteroide).<br>- […]<br>Hinweis:<br>Bisher liegen keine Hinweise darauf vor, dass Formoterol eine Behandlung mit Kortikosteroiden ersetzen kann. Bei Asthma bronchiale muss Formoterol in jedem Fall mit Kortikosteroiden zur Inhalation kombiniert werden.<br>*Dosierung: Kinder ab 6 Jahren, Jugendliche und Erwachsene (auch Ältere) […]*<br>(FI Formoterol-CT, Stand 04/2019) |
| **Beta-2-Sympathomimetika (oral; kurz-, langwirkend)** | |
| Terbutalin<br>R03AC03<br>Aerodur Turbohaler® | Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z. B. Asthma bronchiale, chronische Bronchitis und Blählunge (Lungenemphysem).<br><br>*Dosierung und Art der Anwendung: […] Für Erwachsene und Kinder ab 5 Jahren gelten folgende Empfehlungen […]*<br>(FI Aerodur Turbohaler, Stand 04/2020) |
| Salbutamol | Zur Verhütung und Behandlung von Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| R03CC02<br>Sultanol® | Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z. B. Asthma bronchiale, chronische Bronchitis und Blählunge (Lungenemphysem).<br>*Sultanol Dosier-Aerosol wird angewendet bei Erwachsenen, Jugendlichen und Kindern im Alter von 4 bis 11 Jahren (für die Anwendung bei Kleinkindern und Kindern unter 4 Jahren siehe Abschnitte 4.2 und 5.1).*<br>Hinweis:<br>Eine längerfristige Behandlung soll symptomorientiert und nur in Verbindung mit einer entzündungshemmenden Dauertherapie erfolgen.<br>(FI Sultanol®, Stand: 11/ 2013) |
| Bambuterol<br>R03CC12<br>Bambec® | Verhütung und Behandlung von Atemwegserkrankungen, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur<br>einhergehen (obstruktive Atemwegserkrankungen).<br>Hinweis:<br>Bambec ist nur für Patienten, die nicht symptomorientiert mit inhalativen Beta-2-Sympathomimetika behandelt werden können, geeignet. Bei Patienten mit Asthma bronchiale sollte eine Behandlung mit Bambuterol in Ergänzung zu einer entzündungshemmenden Dauertherapie, z. B. mit Glukokortikoiden zur Inhalation oder Leukotrien- Rezeptor-Antagonisten, erfolgen.<br>*Dosierung und Art der Anwendung: Kinder von 6 – 12 Jahren […]*<br>(FI Bambec®, Stand 05/2016) |
| Clenbuterol/<br>Ambroxol<br>R03CC63<br>Spasmo<br>Mucosolvan Saft® | Akute und chronische Atemwegserkrankungen, die mit spastischen Verengungen, veränderter Sekretbildung und gestörtem Sekrettransport einhergehen, insbesondere spastische Bronchitiden, Emphysembronchitiden und Asthma bronchiale.<br>Hinweis<br>Spasmo-Mucosolvan Saft ist nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Sofern eine Dauerbehandlung eines Asthma bronchiale mit Spasmo-Mucosolvan Saft erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie (z. B. mit Kortikoiden) erfolgen.<br>*Dosierung und Art der Anwendung: Soweit nicht anders verordnet wird, ist bei Kindern bis zu 12 Jahren […]*<br>(FI Spasmo-Mucosolvan® Saft, Stand 03/2020) |
| **Anticholinergika (inhalativ)** | |
| Tiotropiumbromid<br>R03BB04 | […]<br>Spiriva Respimat ist indiziert als zusätzlicher dauerhaft einzusetzender Bronchodilatator *bei Patienten ab 6 Jahren* mit |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| | |
|---|---|
| Spiriva® Respimat® | schwerem<br>Asthma, die im Vorjahr mindestens eine schwere Exazerbation erfahren haben (siehe Abschnitte 4.2 und 5.1). (FI Spiriva® Respimat®, Stand 10/2018) |
| **Inhalative Corticosteroide (ICS)** | |
| Beclometason R03BA01 Beclometason-ratiopharm® | Zur Behandlung von Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z. B. bei<br>– Asthma bronchiale<br>-<br>Hinweis:<br>Beclometason-ratiopharm® Dosieraerosol ist nicht zur Behandlung von plötzlich auftretenden Atemnotanfällen (akuter Asthmaanfall<br>oder Status asthmaticus) geeignet.<br>Beclometason-ratiopharm® Dosieraerosol wird angewendet *bei Erwachsenen, Jugendlichen und Kindern ab 5 Jahren*.<br>(FI Beclometason-ratiopharm®, Stand: 05/2017) |
| Budesonid R03BA02 Budiair ® | Budiair wird angewendet bei *Erwachsenen und Kindern ab 6 Jahren* zur Dauerbehandlung des persistierenden Asthma bronchiale.<br>[…]<br>Hinweis: Budiair ist nicht zur Behandlung des akuten Asthmaanfalls geeignet.<br>(FI Budiair ®, Stand: 10/2020) |
| Fluticason R03BA05 FLUTIDE® | Dauerbehandlung eines persistierenden Asthma bronchiale aller Schweregrade.<br>Hinweis:<br>Fluticason-17-propionat ist nicht für die Akutbehandlung eines Asthmaanfalles geeignet.<br>*Dosierung: Jugendliche sowie Kinder von 4 bis 16 Jahren […]*<br>(FI Flutide®, Stand 07/2017) |
| **Corticosteroide (systemisch, oral)** | |
| Prednisolon, Prednisolon JENAPHARM® | […]<br>Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren.<br><br>*Prednisolon JENAPHARM wird angewendet bei Erwachsenen, Kindern aller Altersgruppen und Jugendlichen.* |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| | (FI Prednisolon JENAPHARM® Stand 05/2020) |
| Prednison,<br>Prednison acis ® | […]<br>Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren.<br><br>*Prednison acis wird angewendet bei Erwachsenen, Kindern aller Altersgruppen und Jugendlichen.*<br>FI Prednison acis ®, Stand 08/2020) |
| **Weitere** | |
| Theophyllin (systemisch)<br>R03DA04<br>z.B. Theophyllin retard-ratiopharm® | Bronchospasmolytikum/Antiasthmatikum<br>Behandlung und Verhütung von Atemnotzuständen aufgrund von Verengung der Atemwege (Bronchokonstriktion) bei Patienten mit persistierendem Asthma bronchiale oder mittel- bis schwergradiger obstruktiver Atemwegserkrankung (z. B. chronische Bronchitis und Lungenemphysem).<br>Hinweis:<br>Es wird empfohlen die Dauertherapie dieser Erkrankungen mit Theophyllin in Kombination mit anderen die Bronchien erweiternden und entzündungshemmenden Arzneimitteln, wie z. B. lang wirksamen β-Sympathomimetika und Glukocortikoiden durchzuführen. Arzneimittel mit verzögerter Theophyllin- Freisetzung, wie Theophyllin retardratiopharm®, sind nicht zur Akutbehandlung des Status asthmaticus oder der akuten Bronchospastik bestimmt. Theophyllin sollte nicht als Mittel der ersten Wahl zur Behandlung von Asthma bei Kindern angewendet werden.<br>*Kinder und Jugendliche: Theophyllin darf bei Kindern unter 6 Monaten nicht angewendet werden.*<br>(FI Theophyllin retard-ratiopharm®, Stand 04/2014) |
| Omalizumab<br>R03DX05<br>Xolair® | Xolair wird angewendet bei Erwachsenen, Jugendlichen und Kindern (6 bis < 12 Jahre). Die Behandlung mit Xolair sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE-(Immunglobulin E-) vermittelten Asthma ausgegangen werden kann (siehe Abschnitt 4.2).<br>Erwachsene und Jugendliche (ab 12 Jahren)<br>Xolair wird als Zusatztherapie zur verbesserten Asthmakontrolle bei Patienten mit schwerem persistierendem allergischem Asthma angewendet, die einen positiven Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und sowohl eine reduzierte Lungenfunktion (FEV1 < 80 %) haben als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und trotz täglicher Therapie mit hoch dosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta2-Agonisten mehrfach dokumentierte, schwere Asthma-Exazerbationen hatten.<br>*Kinder (6 bis < 12 Jahre)* |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| | Xolair wird als Zusatztherapie zur verbesserten Asthmakontrolle bei Patienten mit schwerem persistierendem allergischem Asthma angewendet, die einen positiven Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und trotz täglicher Therapie mit hoch dosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta2-Agonisten mehrfach dokumentierte, schwere Asthma-Exazerbationen hatten.<br>(FI Xolair®, Stand 07/2020) |
| Mepolizumab<br>R03DX09<br>Nucala® | Nucala ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei Erwachsenen, Jugendlichen und Kindern ab 6 Jahren (siehe Abschnitt 5.1).<br>(FI Nucala; Stand 08/2020) |
| **Kombinationspräparate (ICS/LABA)** | |
| Beclometason/<br>Formoterol<br>R03AK08<br>Foster® | Foster ist angezeigt für die regelmäßige Behandlung von Asthma, bei der die Anwendung eines Kombinationsprodukts (von inhalativem Kortikosteroid und langwirksamem Beta-2-Agonisten) angezeigt ist:<br>• Patienten, die mit inhalativen Kortikosteroiden und inhalativen schnellwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation<br>nicht ausreichend eingestellt sind oder<br>• Patienten, die mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination bereits ausreichend eingestellt sind.<br>*Kinder und Jugendliche; Die Sicherheit und Wirksamkeit der Anwendung von Foster bei Kindern und Jugendlichen unter 18 Jahren ist bisher nicht erwiesen. Vorliegende Daten zu Kindern im Alter von 5 bis 11 Jahren und Jugendlichen im Alter von 12 bis 17 Jahren werden in den*<br>*Abschnitten 4.8, 5.1 und 5.2 beschrieben; eine Dosierungsempfehlung kann jedoch nicht gegeben werden.*<br>(FI Foster, Stand 12/2016) |
| Salmeterol/<br>Fluticason<br>R03AK06<br>Viani® | Viani Diskus ist indiziert für die regelmäßige Behandlung von Asthma bronchiale, bei der die Anwendung von langwirksamem Beta2- Agonisten und inhalativem Kortikoid in Kombination angezeigt ist:<br>– bei Patienten, die mit inhalativen Kortikoiden und kurzwirksamen Beta2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind oder<br>– bei Patienten, die mit inhalativen Kortikoiden und langwirksamen Beta2-Agonisten ausreichend eingestellt sind.<br>Hinweis: Die Stärke Viani 50 µg/100 µg ist nicht angezeigt bei Erwachsenen und Kindern mit schwerem Asthma bronchiale.<br>*Dosierempfehlungen: Kinder ab 4 Jahren […]* |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| | (FI Viani®, Stand 08/2020) |
| Formoterol/ Fluticason R03AK11 FLUTIFORM® | Die Fixkombination aus Fluticason-17-propionat und Formoterolfumarat-Dihydrat (flutiform) wird angewendet zur regelmäßigen Behandlung von Asthma bronchiale in Fällen, in denen ein Kombinationspräparat (ein inhalatives Kortikosteroid und ein langwirksamer Beta-2-Agonist) angezeigt ist:<br>• bei Patienten, die mit inhalativen Kortikosteroiden und bedarfsweise angewendeten, kurzwirksamen inhalativen Beta-2-Agonisten nicht ausreichend eingestellt sind. oder<br>• bei Patienten, die bereits mit einem inhalativen Kortikosteroid und einem langwirksamen Beta-2-Agonisten adäquat eingestellt sind.<br>*flutiform 50 Mikrogramm/5 Mikrogramm pro Sprühstoß wird angewendet bei Erwachsenen, Jugendlichen und Kindern ab 5 Jahren.*<br>(FI flutiform®, Stand 10/2018) |
| **Kombinationspräparate: Anticholininergika/ Beta-2-Sympathomimetikum** | |
| Ipratropiumbromid/ Fenoterol R03AL01 Berodual N® | Zur Verhütung und Behandlung von Atemnot bei chronisch obstruktiven Atemwegserkrankungen: Asthma bronchiale allergischer und nichtallergischer (endogener) Ursache, Anstrengungsasthma und chronisch obstruktive Bronchitis mit und ohne Emphysem.<br><br>Hinweis: Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen.<br>*Die Dosierung richtet sich nach Art und Schwere der Erkrankung. Für Erwachsene und Kinder ab 6 Jahren gelten folgende Empfehlungen[…]*<br><br>(FI Berodual®, Stand 10/2014) |

Quellen: AMIce, Fachinformationen

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

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## Abkürzungsverzeichnis

ACQ Asthma Control Questionnaire
AE adverse events
anti-IL-5 anti-interleukin-5
AQLQ Asthma Quality of Life Questionnaire
AWMF Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BUD budesonide
CI confidence interval
F formoterol
FEV1 forciertes exspiratorisches Volumen (engl. Forced Expiratory Volume in 1 second)
FP fluticasone
FVC Forced vital capacity
GIN Guidelines International Network
GINA Global Initiative for Asthma
GoR Grade of Recommendations
HR Hazard Ratio
ICS Inhaled Corticosteroid
IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV intravenous
KI Konfidenzintervall
LABA long-acting beta2-agonists
LAMA long-acting muscarinic antagonist
LoE Level of Evidence
NICE National Institute for Health and Care Excellence
NMA Netzwerkmetaanalyse
OCS orales Glucocorticosteroid
OR Odds Ratio
PEF Peak expiratory flow
RCTs randomized controlled trials
RR Relatives Risiko
SABA short-acting beta-agonist
SAE Serious adverse events
SAL salmeterol
SC subcutaneous
SIGN Scottish Intercollegiate Guidelines Network
SiT single inhaler therapy
TRIP Turn Research into Practice Database
WHO World Health Organization

# 1 Indikation

Behandlung von (schwerem) Asthma, das trotz mittel- bis hochdosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist.

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Asthma* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 24.03.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1484 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 38 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

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# 3 Ergebnisse

## 3.1 G-BA-Beschlüsse/IQWiG-Berichte

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**G-BA, 2018 [18].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Juli 2016 / 06. Dezember 2018 – Mepolizumab.

**Anwendungsgebiet**

„Nucala® ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei erwachsenen Patienten."

**Vergleichstherapie**

eine patientenindividuelle Therapieeskalation der mittel- bis hochdosierten inhalativen Corticosteroide und der langwirksamen Bronchodilatatoren (LABA) ggf. mit oralen Corticosteroiden (kurzzeitig) in der niedrigst-wirksamen Dosis oder mit Tiotropium oder ggf. bei IgE-vermittelter Pathogenese des Asthmas Omalizumab zusätzlich zu hochdosierten inhalativen Corticosteroiden und langwirksamen Bronchodilatatoren (LABA) und ggf. der oralen Corticosteroidtherapie.

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

a) Patienten mit schwerem refraktärem eosinophilem Asthma, die nicht oder nur im Rahmen von akuten Exazerbationen mit oralen Corticosteroiden behandelt werden: Ein Zusatznutzen ist nicht belegt.

b) Patienten mit schwerem refraktärem eosinophilem Asthma, die auch über die Behandlung akuter Exazerbationen hinaus regelmäßig mit oralen Corticosteroiden behandelt werden: Anhaltspunkt für einen geringen Zusatznutzen.

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**G-BA, 2017 [16].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Juli 2017 / 6. Dezember 2018 – Reslizumab

**Anwendungsgebiet**

CINQAERO wird angewendet als Zusatztherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus einem anderen Arzneimittel zur Erhaltungstherapie nur unzureichend zu kontrollieren ist.

**Zweckmäßige Vergleichstherapie**

Die zweckmäßige Vergleichstherapie für die Behandlung (Add-on-Therapie) des schweren eosinophilen Asthmas bei erwachsenen Patienten, welche trotz hoher Dosen an inhalativen Corticosteroiden und einem weiteren Controller unkontrolliert sind, ist:

eine patientenindividuelle Therapieeskalation:

- der hochdosierten inhalativen Corticosteroide und der langwirksamen Bronchodilatatoren (LABA) mit Tiotropium und ggf. orale Corticosteroide* oder

- bei IgE-vermittelter Pathogenese des Asthmas ggf. Omalizumab zusätzlich zu hochdosierten inhalativen Corticosteroiden und langwirksamen Bronchodilatatoren (LABA) und ggf. orale Corticosteroide* oder
- ggf. der hochdosierten inhalativen Corticosteroide und der Bronchodilatatoren (LABA) mit oralen Corticosteroiden*

*Orale Corticosteroide sollten nur kurzzeitig und in der niedrigst-wirksamen Dosis eingesetzt werden.

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

a) Patienten mit schwerem eosinophilem Asthma, die nicht oder nur im Rahmen von akuten Exazerbationen mit oralen Corticosteroiden behandelt werden: Ein Zusatznutzen ist nicht belegt.

b) Patienten mit schwerem eosinophilem Asthma, die auch über die Behandlung akuter Exazerbationen hinaus regelmäßig mit oralen Corticosteroiden behandelt werden: Anhaltspunkt für einen geringen Zusatznutzen.

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**G-BA, 2018 [15].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02.August 2018 - Benralizumab

**Anwendungsgebiet**

Fasenra ist angezeigt als Add-on-Erhaltungstherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist.

**Vergleichstherapie**

eine patientenindividuelle Therapieeskalation:

- der hochdosierten inhalativen Corticosteroide (ICS) und der langwirksamen Beta-Agonisten (LABA) mit Tiotropium und ggf. orale Corticosteroide (OCS)[a] oder
- bei IgE-vermittelter Pathogenese des Asthmas ggf. Omalizumab zusätzlich zu hochdosierten ICS und LABA und ggf. OCSa oder
- ggf. der hochdosierten ICS und LABA mit OCS[a,b] oder
- ggf. der hochdosierten ICS und LABA mit Mepolizumab bei Patienten, die nicht anderweitig eskaliert werden können

[a] Orale Corticosteroide sollten nur kurzzeitig und in der niedrigst-wirksamen Dosis eingesetzt werden. Bei der Behandlung des Asthmas mit OCS ist darauf zu achten, dass die Dosierung von OCS die Cushing-Schwelle möglichst nicht dauerhaft überschreitet. Eine Behandlung von Exazerbationen ist davon abzugrenzen.

[b] Eine Therapie mit OCS ist im Vergleich zu den anderen genannten Wirkstoffen - sofern diese geeignet sind - nicht als zu präferierende Therapieoption anzusehen.

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

a) Erwachsene Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist und für die die weiteren Möglichkeiten der Therapieeskalation noch nicht ausgeschöpft sind: Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist und für die die weiteren Möglichkeiten der Therapieeskalation bereits ausgeschöpft sind: Anhaltspunkt für einen geringen Zusatznutzen.

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**G-BA, 2021 [13].**

Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL), zuletzt geändert am 17. Dezember 2020, in Kraft getreten am 01. Januar 2021

**Fazit**

1.5.8.1 Dauertherapie bei Erwachsenen

Vorrangig sollen zur Dauertherapie die folgenden Wirkstoffgruppen verwendet werden:

1. Basistherapie

- inhalative Glukokortikosteroide,

2. als Erweiterung dieser Basistherapie kommen zusätzlich zur Gabe von inhalativen Glukokortikosteroiden in Betracht:

- inhalative lang wirksame Beta-2-Sympathomimetika
- Wenn trotz dieser erweiterten Basistherapie ein unkontrolliertes Asthma bronchiale besteht, stehen zur Modifikation bzw. Eskalation zur Verfügung:
  - langwirksame Anticholinergika
  - systemische Glukokortikosteroide
  - Leukotrien-Rezeptor-Antagonisten
  - Theophyllin (Darreichungsform mit verzögerter Wirkstofffreisetzung)
  - Antikörper

  Bei Patientinnen und Patienten mit trotz Ausschöpfung einer erweiterten Basistherapie nicht ausreichend kontrollierbarem schwerem persistierendem Asthma bronchiale kann eine Behandlung mit Antikörpern (z. B. Anti-IgE-Antikörper oder Anti-IL-5-Antikörper) erwogen werden. Hierfür soll eine Überweisung zum qualifizierten Facharzt oder zur qualifizierten Fachärztin oder zur qualifizierten Einrichtung erfolgen.

Bei Undurchführbarkeit einer Therapie mit inhalativen Glukokortikosteroiden (z. B. Ablehnung oder Unverträglichkeit) als Basismedikation ist vor Verordnung einer unterlegenen alternativen antientzündlichen Therapie ein Aufklärungsgespräch über Risiken dieser Therapieoptionen zu führen.

1.5.8.2 Dauertherapie bis zum vollendeten 18. Lebensjahr

Vorrangig sollen zur Dauertherapie die folgenden Wirkstoffgruppen verwendet werden:

1. Basistherapie

- niedrig dosierte inhalative Glukokortikosteroide
- in begründeten Fällen alternativ Leukotrien-Rezeptor-Antagonisten

2. als Erweiterung dieser Basistherapie kommen in Betracht:

- Steigerung der Dosis des inhalativen Glukokortikosteroids
- Kombination von inhalativen Glukokortikosteroiden und Leukotrien-Rezeptor-Antagonisten
- bei Kindern ab vier Jahren inhalative lang wirksame Beta-2-Sympathomimetika (nur in Kombination mit inhalativen Glukokortikosteroiden)

Im Ausnahmefall, bei einem trotz der erweiterten Basistherapie nicht ausreichend kontrolliertem Asthma bronchiale, können zusätzlich erwogen werden:

- systemische Glukokortikosteroide
- Theophyllin (Darreichungsform mit verzögerter Wirkstofffreisetzung)
- eine Behandlung mit Antikörpern (z. B. Anti-IgE-Antikörper) bei schwerem persistierendem Asthma bronchiale

Die Verordnung von Medikamenten nach 3. sollte durch die jeweils qualifizierte Fachärztin oder den jeweils qualifizierten Facharzt oder durch die qualifizierte Einrichtung erfolgen.

Bei der Verordnung sind die altersabhängigen Zulassungseinschränkungen zu berücksichtigen.

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**G-BA, 2020 [14] ivm. G-BA, 2015 [12].**

Anlage IV zum Abschnitt H der Arzneimittel-Richtlinie Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung Therapiehinweise gemäß § 92 Abs. 2 Satz 7 SGB V i. V. m. § 17 AM-RL zur wirtschaftlichen Verordnungsweise von Arzneimitteln.

**Zugelassene Anwendungsgebiete**

Omalizumab ist zugelassen als Zusatztherapie zur verbesserten Asthmakontrolle bei:

Erwachsenen und Jugendlichen (ab 12 Jahren)

- mit schwerem persistierendem allergischem Asthma,
- die einen positiven Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und
- sowohl eine reduzierte Lungenfunktion (FEV1 < 80%) haben
- als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und
- trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta-2-Agonisten mehrfach dokumentierte, schwere Asthma - exazerbationen hatten.
- Die Behandlung mit Omalizumab sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE-vermittelten Asthma ausgegangen werden kann.

2. Kindern (6 bis < 12 Jahre)

- mit schwerem persistierendem allergischem Asthma,
- die einen positiven Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und
- unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und
- trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta-2-Agonisten mehrfach dokumentierte, schwere Asthma-exazerbationen hatten.
- Die Behandlung mit Omalizumab sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE-vermittelten Asthma ausgegangen werden kann.

Empfehlungen zur wirtschaftlichen Verordnungsweise:

Der Therapiehinweis bezieht sich ausschließlich auf die Indikation Asthma bronchiale.

Die Verordnung von Omalizumab ist als Zusatztherapie bei Jugendlichen ab 12 Jahren und Erwachsenen nur wirtschaftlich, die kumulativ folgende Voraussetzungen erfüllen:

- schweres persistierendes allergisches Asthma,
- reduzierte Lungenfunktion (FEV1 < 80%),
- positiver Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes und vom Patienten nicht vermeidbares Aeroallergen,

- das Asthma ist IgE-vermittelt mit IgE-Werten zwischen ≥ 76 und ≤ 1500 I.E./ml vor Beginn der Behandlung,
- häufige dokumentierte Symptome während des Tages oder nächtliches Erwachen,
- trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden (entsprechend > 1000 µg pro Tag Beclometason oder Äquivalent) und mindestens einem lang wirkenden inhalativen Beta-2-Agonisten als Kontroller traten
  - in den letzten 12 Monaten mindestens zwei unabhängige, dokumentierte schwere Asthmaexazerbationen, die mit systemischen Kortikosteroiden behandelt wurden, oder
  - eine Exazerbation, die systemische Kortikosteroidgabe notwendig machte und zur Krankenhausaufnahme bzw. Notfallbehandlung führte, auf.
- das Körpergewicht liegt innerhalb der Grenzen der Dosierungstabelle also ≥ 20 kg und ≤ 150 kg.
- Nichtraucher

Die Verordnung von Omalizumab ist als Zusatztherapie bei Kindern zwischen 6 und 12 Jahren nur wirtschaftlich, die kumulativ folgende Voraussetzungen erfüllen:

- schweres persistierendes allergisches Asthma,
- positiver Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes und vom Patienten nicht vermeidbares Aeroallergen,
- das Asthma ist IgE-vermittelt mit IgE-Werten zwischen ≥ 200 und ≤ 1300 I.E./ml vor Beginn der Behandlung,
- häufig dokumentierte Symptome während des Tages oder nächtliches Erwachen,
- trotz täglicher Therapie mit hoch dosierten inhalativen Kortikosteroiden (entsprechend > 400 µg pro Tag Beclometason oder Äquivalent) und mindestens einem lang wirken-den inhalativen Beta-2-Agonisten als Kontroller traten
  - in den letzten 12 Monaten mindestens zwei unabhängige, dokumentierte Asthmaexazerbationen oder
  - in den letzten 24 Monaten drei Exazerbationen, davon eine in den letzten 12 Monaten oder
  - eine Exazerbation, die zur Krankenhausaufnahme bzw. Notfallbehandlung in den letzten 12 Monaten führte, auf.
- Das Körpergewicht liegt zwischen 20 kg und 150 kg und innerhalb der Grenzen der Dosierungstabelle also ≥ 20 kg und ≤ 150 kg.

Die Dosierung erfolgt in Abhängigkeit vom Körpergewicht und dem Basis IgE-Spiegel. Die empfohlene Maximaldosis beträgt 600 mg Omalizumab alle zwei Wochen oder 600 mg alle vier Wochen, eine Überschreitung ist unzweckmäßig.

Die weitere Behandlungsnotwendigkeit sollte spätestens 16 Wochen nach Beginn der Therapie mit Omalizumab durch den Arzt überprüft werden.

Sollte eine Dosisreduktion des inhalativen Kortikosteroids auf eine mittlere bis niedrige Dosis möglich sein, ohne dass Exazerbationen auftreten, ist die Therapiestrategie zu überdenken, spätestens jedoch alle 12 Monate.

[…]

Bezüglich der Zweckmäßigkeit ist darüber hinaus zu beachten, dass die doppelblinde randomisierte Zulassungsstudie (Humbert 2005) für Jugendliche und Erwachsene bei Asthma keine statistisch signifikante Überlegenheit für den primären Endpunkt der Asthmaexazerbationsrate ergab. Nicht alle Patienten erhielten einen zusätzlichen Kontroller, wie es nach aktuellen Versorgungsleitlinien gefordert wird. Die Ergebnisse der Studien, die auch Patienten mit mittelschwerem Asthma aufnahmen, sind widersprüchlich in Hinsicht auf die Rate der Asthmaexazerbationen. Bei der Therapieentscheidung ist auch die mangelnde Konsistenz der Ergebnisse zu berücksichtigen (siehe Abschnitt Wirksamkeit, Jugendliche und Erwachsene).

40 % der in die Hauptstudie (Lanier 2009) aufgenommenen Kinder hatten eine der Zulassung entsprechende Indikation für die Therapie mit Omalizumab. Der primäre Endpunkt, Rate der Exazerbationen, wurde erreicht; allerdings findet sich für eine Vielzahl von weiteren vom

primären Endpunkt klinisch differierend definierten sekundären Zielgrößen, die auch als klinisch relevant einzuschätzen sind, keine statistisch signifikante Überlegenheit gegenüber Placebo, so dass die Ergebnisse hinsichtlich der tatsächlichen klinischen Überlegenheit und Relevanz hinterfragt werden können (siehe Abschnitt Wirksamkeit, Kinder im Alter von 6 bis 12 Jahren).

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**G-BA, 2020 [17].**

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Dupilumab (neues Anwendungsgebiet: Asthma bronchiale); Vom 20. Februar 2020

**Neues Anwendungsgebiet (laut Zulassung vom 6. Mai 2019)**

Dupixent ist angezeigt als Add-on-Erhaltungstherapie bei Erwachsenen und Jugendlichen ab 12 Jahren mit schwerem Asthma mit Typ-2-Inflammation, gekennzeichnet durch eine erhöhte Anzahl der Eosinophilen im Blut und/oder erhöhtes FeNO (siehe Abschnitt 5.1), das trotz hoch-dosierter inhalativer Kortikosteroide (ICS) plus einem weiteren Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist.

**Zweckmäßige Vergleichstherapie**

a) Jugendliche von 12 bis 17 Jahren mit schwerem Asthma mit Typ-2-Inflammation, gekennzeichnet durch eine erhöhte Anzahl der Eosinophilen im Blut und/oder erhöhtes FeNO, das trotz hoch-dosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist:

eine patientenindividuelle Therapieeskalation unter Berücksichtigung der Vortherapie unter Auswahl von:

- hochdosiertes ICS und LABA und LAMA oder
- hochdosiertes ICS und LABA und ggf. LAMA und Omalizumab, sofern die für die Anwendung von Omalizumab notwendigen Kriterien erfüllt sind

b) Erwachsene mit schwerem Asthma mit Typ-2-Inflammation, gekennzeichnet durch eine erhöhte Anzahl der Eosinophilen im Blut und/oder erhöhtes FeNO, das trotz hochdosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist:

eine patientenindividuelle Therapieeskalation unter Berücksichtigung der Vortherapie und der Pathogenese des Asthmas unter Auswahl von:

- hochdosiertes ICS und LABA und LAMA oder
- hochdosiertes ICS und LABA und ggf. LAMA und Omalizumab, sofern die für die Anwendung von Omalizumab notwendigen Kriterien erfüllt sind

oder

- hochdosiertes ICS und LABA und ggf. LAMA und Mepolizumab oder Reslizumab oder Benralizumab, sofern die für die Anwendung der jeweiligen Antikörper notwendigen Kriterien erfüllt sind

**Fazit / Ausmaß des Zusatznutzens**

a) Ein Zusatznutzen ist nicht belegt

b) Ein Zusatznutzen ist nicht belegt

## 3.2 Cochrane Reviews

**Farne HA et al., 2017 [10].**

Anti-IL5 therapies for asthma.

**Fragestellung**

We considered in this review whether taking the new drugs mepolizumab, reslizumab or benralizumab in addition to standard treatment (e.g. inhaled steroids and combination inhalers) are better than a placebo for people with asthma.

**Methodik**

Population:

- adults and children with a diagnosis of asthma. We focused on collating data from people who had been reported as having eosinophilic asthma to analyse these individuals as a subgroup

Intervention:

- anti-IL-5 therapy

Komparator:

- Placebo

Endpunkte:

- primary: 'Clinically significant' asthma exacerbation, as defined by treatment with a course (three days or more) of systemic corticosteroids (with or without hospital admission); secondary: 1. Asthma exacerbation requiring hospital admission, 2. HRQoL (as measured by a validated questionnaire e.g. ACQ, AQLQ, SGRQ), 3. Measures of lung function (e.g. FEV1), 4. Serious adverse events, 5. 'Clinically significant' adverse events, as defined by those that prompted discontinuation of the intervention and withdrawal from the study, 6. Eosinophil counts in peripheral blood Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for the review.

Recherche/Suchzeitraum:

- The search was first conducted in 11/2013 and was updated in 11/2014 and 03/2017

Qualitätsbewertung der Studien:

- risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions

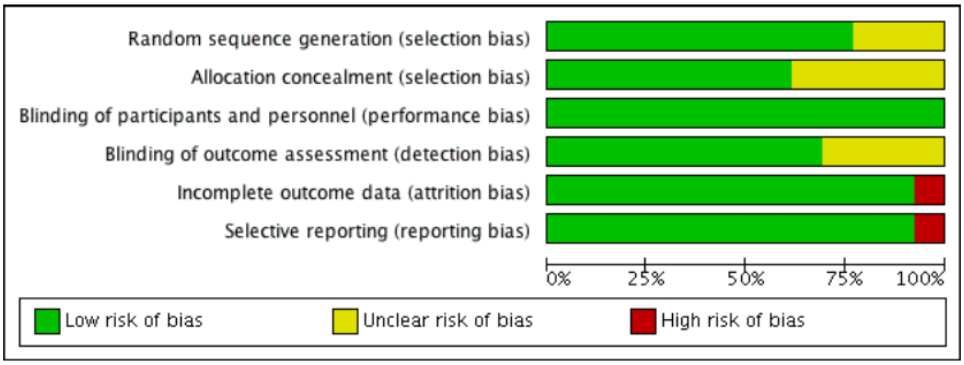
**Ergebnisse**

Anzahl eingeschlossener Studien:

- 13 studies included in the qualitative synthesis; 12 studies included in the quantitative synthesis

Qualität der Studien:

- The evidence included in this review is provided by very well-designed studies. We consider these studies to be at low risk of bias in the following important respects: the procedure that determined who received which treatment, the blinding processes and the clarity of detail concerning participants who did not complete the study. Overall the evidence was high to moderate quality.




Studienergebnisse:

- four included studies comparing mepolizumab versus placebo (N=1809)
- four included studies comparing reslizumab versus placebo (N=1764)
- five studies comparing benralizumab versus placebo (N=3232)

**Mepolizumab (SC) compared to placebo for asthma**

**Patient or population:** people with asthma
**Setting:** community
**Intervention:** mepolizumab (SC)
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with mepolizumab (SC) | | | | |
| Rate of exacerbations requiring systemic corticosteroids<br>Follow-up: range 24 to 32 weeks | The mean rate in the placebo group was 1.48 events per participant per year[a] | The mean rate in the intervention group was 0.81 fewer events per participant per year (95% CI 0.66 fewer to 0.94 fewer) | Rate ratio 0.45 (0.36 to 0.55) | 936 (2 RCTs) | ⊕⊕⊕⊕ High | |
| Rate of exacerbations requiring emergency department treatment or admission<br>Follow-up: range 24 to 32 weeks | The mean rate in the placebo group was 0.15 events per patient per year[b] | The mean rate in the intervention group was 0.10 fewer events per participant per year (95% CI 0.05 fewer to 0.12 fewer) | Rate ratio 0.36 (0.20 to 0.66) | 936 (2 RCTs) | ⊕⊕⊕⊕ High | |
| Health-related quality of life (ACQ)<br>Scale from: 0 to 6 (lower is better)<br>Follow-up: range 24 to 32 weeks | The mean change in the placebo group ranged from −0.4 to −0.5 units | The mean in the intervention group was -0.42 units fewer (-0.56 fewer to -0.28 fewer) | - | 936 (2 RCTs) | ⊕⊕⊕◯ Moderate[c] | A change of ≥ 0.5 is considered the minimum clinically significant difference |

| | | | | | | |
|---|---|---|---|---|---|---|
| Health-related quality of life (SGRQ)<br>Scale from: 0 to 100 (lower is better)<br>Follow-up: range 24 to 32 weeks | The mean change in the placebo group ranged from −7.9 to −9.0 units | The mean change in the intervention group was -7.4 units fewer (-9.5 fewer to -5.29 fewer) | - | 936<br>(2 RCTs) | ⊕⊕⊕⊕<br>High | A change of ≥ 4 is considered the minimum clinically significant difference |
| Pre-bronchodilator $FEV_1$ (L)<br>Follow-up: range 24 to 32 weeks | The mean change in the placebo group ranged from 0.086 L (± 0.031 L) to 0.120 L (0.047 to 0.192 L) | The mean difference from placebo was a further 0.11 L (0.06 L to 0.17 L) | - | 936<br>(2 RCTs) | ⊕⊕⊕⊕<br>High | |
| Adverse events leading to discontinuation<br>Follow-up: range 24 to 32 weeks | 15 per 1000 | 7 per 1000<br>(2 to 27) | Risk ratio 0.45<br>(0.11 to 1.80) | 936<br>(2 RCTs) | ⊕⊕⊕◯<br>Moderate[d] | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**ACQ**: Asthma Control Questionnaire; **CI:** confidence interval; **$FEV_1$** : forced expiratory volume in 1 second; **RR:** risk ratio; **SC**: subcutaneous; **SGRQ**: St. George's Respiratory Questionnaire

**GRADE Working Group grades of evidence**
**High quality:** we are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low quality:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
**Very low quality:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Rounded mean of the rate in the placebo group of the two studies: 1.21 and 1.74.
[b] Rounded mean of the rate in the placebo group of the two studies: 0.10 and 0.20.
[c] The mean difference (-0.42) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).
[d] The 95% CI crosses the line of no effect, thus we downgraded the quality of evidence to moderate because of imprecision.

**Reslizumab (IV) compared to placebo for asthma**

**Patient or population:** people with asthma
**Setting:** community
**Intervention:** reslizumab (IV)
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with reslizumab (IV) | | | | |
| Rate of exacerbations requiring systemic corticosteroids<br>Follow-up: 52 weeks | The mean rate in the placebo group was 1.54 events per participant per year | The mean rate in the intervention groups was 0.93 fewer events per participant per year (1.09 fewer to 0.73 fewer) | Rate ratio 0.43<br>(0.33 to 0.55) | 953<br>(2 RCTs) | ⊕⊕⊕⊕<br>High | |
| Rate of exacerbations requiring emergency department treatment or admission<br>Follow-up: 52 weeks | The mean rate in the placebo group was 0.12 events per participant per year | The mean rate in the intervention groups was 0.04 fewer events per participant per year (0.07 fewer to 0.02 more) | Rate ratio 0.67<br>(0.39 to 1.17) | 953<br>(2 RCTs) | ⊕⊕⊕⊕<br>High | |
| Health-related quality of life (AQLQ)<br>Scale from: 1 to 7 (higher is better)<br>Follow -p: range 16 weeks to 52 weeks | The mean change in the placebo group ranged from 0.779 to 0.89 units | MD 0.28 higher<br>(0.17 higher to 0.39 higher)[a] | - | 1164<br>(3 RCTs) | ⊕⊕⊕⊕<br>High | A change of ≥ 0.5 is considered the minimum clinically significant difference |
| Health-related quality of life (ACQ)<br>Scale from: 0 to 6 (lower is better)<br>Follow-up: range 16 | The mean change in the placebo group ranged from −0.368 to −0.80 units | MD -0.25 lower<br>(-0.33 lower to -0.17 lower)[b] | - | 1652<br>(4 RCTs) | ⊕⊕⊕⊕<br>High | A change of ≥ 0.5 is considered the minimum clinically significant difference |

| | | | | | |
|---|---|---|---|---|---|
| weeks to 52 weeks | | | | | |
| Pre-bronchodilator $FEV_1$ (L) Follow-up: range 16 weeks to 52 weeks | The mean change in the placebo group ranged from 0.002 L (± 0.1216 L) to 0.215 (± 0.0484 L) | MD 0.11 L higher (0.07 L higher to 0.15 L higher) | - | 1652 (4 RCTs) | ⊕⊕⊕⊕ High |
| Serious adverse events Follow-up: range 16 weeks to 52 weeks | 91 per 1000 | 72 per 1000 (51 to 102) | RR 0.79 (0.56 to 1.12) | 1656 (4 RCTs) | ⊕⊕⊕⊕ High |
| Adverse events leading to discontinuation Follow-up: range 16 weeks to 52 weeks | 58 per 1000 | 38 per 1000 (25 to 59) | RR 0.66 (0.43 to 1.02) | 1659 (4 RCTs) | ⊕⊕⊕⊕ High |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**ACQ**: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **$FEV_1$** : forced expiratory volume in 1 second; **MD**: mean difference; **IV**: intravenous; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] The mean difference (0.28) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).
[b] The mean difference (-0.25) is smaller than the minimum clinically significant difference (a reduction of 0.5 points)

**Benralizumab (SC) compared to placebo for asthma**

**Patient or population:** people with asthma
**Setting:** community
**Intervention:** benralizumab (SC)
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with benralizumab (SC) | | | | |
| Rate of exacerbations requiring systemic corticosteroids Follow-up: range 48 weeks to 56 weeks | The mean rate in the placebo group was 0.98 events per participant per year[a] | The mean rate in the intervention groups was 0.37 fewer events per participant per year (0.44 fewer to 0.29 fewer) | Rate ratio 0.62 (0.55 to 0.70) | 2456 (3 RCTs) | ⊕⊕⊕⊕ High | |
| Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 48 weeks to 56 weeks | The mean rate in the placebo group was 0.11 events per participant per year[b] | The mean rate in the intervention groups was 0.04 fewer events per participant per year (0.06 fewer to 0.002 fewer) | Rate ratio 0.68 (0.47 to 0.98) | 1537 (2 RCTs) | ⊕⊕⊕◯ Moderate[c] | There is greater heterogeneity ($I^2$ = 43%) owing to inclusion of less severe participants in FitzGerald 2016 (a larger proportion who had only suffered one exacerbation the previous year, with correspondingly less potential for exacerbation) |
| Health-related quality of life (AQLQ) Scale from: 1 to 7 (higher is better) Follow-up: range 48 weeks to 56 weeks | The mean change in the placebo group ranged from 0.98 to 1.31 units | MD 0.23 higher (0.11 higher to 0.35 higher)[c] | - | 1541 (3 RCTs) | ⊕⊕⊕⊕ High | A change of ≥ 0.5 is considered the minimum clinically significant difference |

| | | | | | | |
|---|---|---|---|---|---|---|
| Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow up: range 48 weeks to 56 weeks | The mean change in the placebo group ranged from −1.19 to −0.76 units | MD -0.20 lower (-0.29 lower to -0.11 lower)[d] | - | 2359 (3 RCTs) | ⊕⊕⊕⊕ High | A change of ≥ 0.5 is considered the minimum clinically significant difference |
| Pre-bronchodilator $FEV_1$ (L) Follow-up: range 48 weeks to 56 weeks | The mean change in the placebo group ranged from -0.01 L to 0.239 L | MD 0.10 L higher (0.05 L higher to 0.14 L higher) | - | 2355 (3 RCTs) | ⊕⊕⊕⊕ High | |
| Serious adverse events Follow-up: range 48 weeks to 56 weeks | 135 per 1000 | 109 per 1000 (89 to 136) | RR 0.81 (0.66 to 1.01) | 2648 (4 RCTs) | ⊕⊕⊕⊕ High | |
| Adverse events leading to discontinuation Follow-up: range 48 weeks to 56 weeks | 9 per 1000 | 19 per 1000 (9 to 41) | RR 2.15 (1.02 to 4.57) | 2597 (3 RCTs) | ⊕⊕⊕⊕ High | |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**ACQ:** Asthma Control Questionnaire; **AQLQ:** Asthma Quality of Life Questionnaire; **CI:** confidence interval; **$FEV_1$** : forced expiratory volume in 1 second; **MD:** mean difference; **IV:** intravenous; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High quality:** we are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low quality:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
**Very low quality:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Rounded mean of the rate in the placebo group of the eosinophilic and non-eosinophilic arms (as applicable) or the three studies: 1.33, 1.21, 0.68, 0.49, 0.93, 1.21.
[b] Rounded mean of the rate in the placebo group of the two studies: 0.18 and 0.04.
[c] The mean difference (0.23) is less than the minimum clinically significant difference (≥ 0.5).

**Anmerkung/Fazit der Autoren**

We found that participants with severe asthma, who had high numbers of a certain type of inflammatory cell (eosinophils) in the blood, benefited from taking mepolizumab, reslizumab or benralizumab through reduced asthma attacks. There were small improvements in quality of life and breathing tests, but these may be too small to be detected by patients. We agree with international guidelines that say that these treatments can be added to standard treatment for people with severe asthma. However, we think that further research is needed to clarify some aspects, such as how to assess treatment response and how long to give treatment for.

## 3.3 Systematische Reviews

**Rogliani P et al., 2021 [29].**

Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies

**Fragestellung**

To compare and rank the efficacy and safety profile of triple ICS/LABA/LAMA combination therapies in patients with uncontrolled asthma with respect to the risk of exacerbation and lung function. We also investigated the impact of triple therapies on asthma control and serious adverse events (SAEs).

**Methodik**

Population:

- symptomatic patients suffering from uncontrolled asthma

Intervention:

- any triple combination therapy in asthma

Komparator:

- ICS/LABA FDCs BDP/FOR, FF/VI, MF/IND, and FP/SAL

Endpunkte:

- moderate to severe asthma exacerbation
- forced expiratory volume in the 1st second (FEV1)
- asthma control questionnaire (ACQ)
- safety

Recherche/Suchzeitraum:

- ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, EU Clinical Trials Register, MEDLINE, Scopus, and Web of Science up to 23 September 2020

Qualitätsbewertung der Studien:

Cochrane Risk of Bias 2 (RoB 2) and Jadad score

quality of evidence was assessed for the primary endpoint via GRADE

A network meta-analysis was performed via full Bayesian random-effect model to compare the impact of the different triple combination therapies and comparators in asthmatic patients. Subset and sensitivity analyses were performed in agreement with average patients' characteristics at baseline. Results are expressed as relative effect (RE) and 95% credible interval (95%CrI) or 95% confidence interval (95%CI). The SUCRA was calculated for both the co-primary and secondary endpoints; the SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst. The statistical significance was assessed for $P<0.05$.

**Ergebnisse**

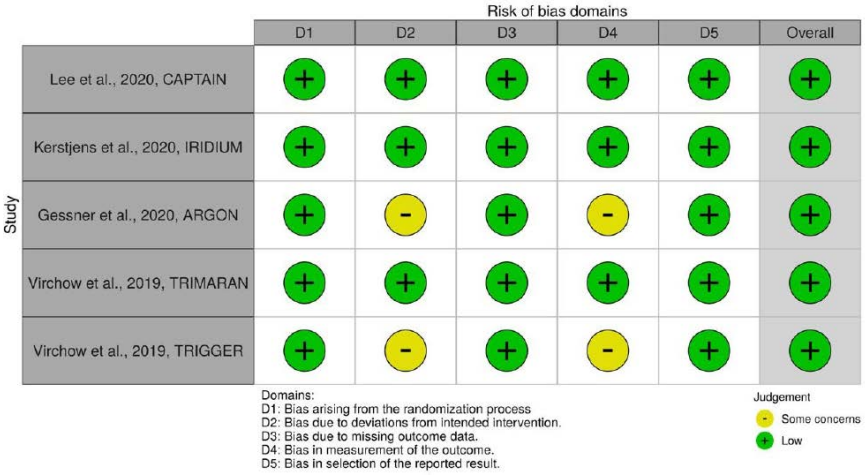
Anzahl eingeschlossener Studien:

- 5 Phase III RCTs with 9535 asthmatic patients
- the investigated ICS/LABA/LAMA FDCs included beclomethasone dipropionate (BDP)/formoterol fumarate (FOR)/glycopyrronium bromide (GLY) in 2 studies, momethasone furoate (MF)/indacaterol (IND)/glycopyrronium bromide (GLY) in 2 studies, and fluticasone furoate (FF)/vilanterol (VI)/umeclidinium (UMEC) in 1 study. The investigated free combination ICS/LABA FDC + TIO included BDP/FOR + TIO in 1 study and FP/SAL + TIO in 1 study.

Charakteristika der Population:

- Symptomatic or uncontrolled asthma

Qualität der Studien:




Studienergebnisse:

- Relative effects with 95%CrI resulting from the overall network meta-analysis. Treatments comparisons have been sorted in agreement with SUCRA§
- Risk of exacerbation: High dose (HD) ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO were equally effective (P>0.05) in preventing the risk of moderate to severe asthma exacerbation. HD ICS/LABA/LAMA FDC significantly (P<0.05) reduced the risk exacerbation compared to medium dose (MD) ICS/LABA/LAMA FDC and MD ICS/LABA FDC, whereas a trend toward significance (P=0.05) was detected vs. HD ICS/LABA FDC. The SUCRA analysis indicated that both HD ICS/LABA FDC + TIO and HD ICS/LABA/LAMA FDC were the most effective treatments in reducing the risk of moderate or severe asthma exacerbation (first quartile), followed by HD ICS/LABA FDC (borderline second/third quartile), MD ICS/LABA/LAMA FDC (third quartile), and MD ICS/LABA FDC (fourth quartile).
- ACQ: Both MD and HD ICS/LABA/LAMA FDCs and HD ICS/LABA FDC + TIO were equally (P>0.05) effective in improving ACQ, although a trend toward significance (P=0.05) was detected for HD ICS/LABA/LAMA vs. MD ICS/LABA/LAMA FDC
- Safety: No significant (P>0.05) difference was detected across the investigated combinations concerning the risk of SAEs, pneumonia, and serious CV AEs

**Anmerkung/Fazit der Autoren**

Concluding, both ICS/LABA/LAMA FDC and free combination of TIO added to ICS/LABA FDC are effective and safe therapeutic strategies in patients suffering from uncontrolled asthma, with the level of the ICS dose representing the discriminating factor to treat patients with a history of moderate or severe exacerbation. Furthermore, here we provide the clinical evidence that triple FDCs by adding either a LAMA or increase ICS dose on a background of ICS/LABA/LAMA FDC may reduce the risk of severe exacerbation and improve lung function, and that adding a LAMA along with escalating ICS provides incremental effects. Indeed, the evidence raised by this quantitative synthesis may help to solve the inconsistencies across the primary publications with respect to the beneficial impact of triple combination therapy against asthma exacerbation. However, there remains the question concerning the correct positioning of triple combination therapy in the GINA stepwise approach for adjusting treatment for individual patient needs. In this respect, MD and HD ICS/LABA/LAMA FDCs should be tested in well-designed Phase III RCTs enrolling separately asthmatic patients at Step 4 and 5 in order to guide clinicians to correctly practice personalized medicine. In any case, the decision of whether or not to first add a LAMA or escalate the dose of ICS, or both, in a poorly controlled patient on MD ICS/LABA FDC remains a clinical matter that may be driven by the overall level of disease control, available biomarkers, or concerns over potential AEs.

**Agache I et al., 2020 [1].**

Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma

Siehe auch [2]; [3]

**Fragestellung**

The current SR is focusing on eosinophilic asthma assessing the current evidence regarding efficacy, safety and economic impact of the biologicals with current regulatory approval for patients with uncontrolled severe asthma (ie benralizumab, dupilumab, omalizumab, mepolizumab and reslizumab, in alphabetical order).

**Methodik**

Population:

- patients with uncontrolled severe asthma

Intervention:

- benralizumab, dupilumab, omalizumab, mepolizumab and reslizumab

Komparator:

- standard of care/placebo

Endpunkte:

- Severe asthma exacerbation rate, asthma control, quality of life, safety, Reduction in oral corticosteroids use, Reduction of rescue medication use, Lung function - FEV1

Recherche/Suchzeitraum:

- MEDLINE (via PubMed, January 2019), Embase (via Ovid, January 2019) and CENTRAL (via The Cochrane Library, January 2019) databases were searched using predefined algorithms for individual studies

Qualitätsbewertung der Studien:

- The risk of bias (ROB) was assessed using the Cochrane risk of bias assessment tool
- The risk of bias and the certainty of the evidence were assessed using GRADE

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Twenty-eight publications from 19 RCTs were evaluated.
- These included three RCTs for benralizumab39-41; three for dupilumab42-44; three for mepolizumab45-47; five for omalizumab48-51; and five for reslizumab.

Charakteristika der Population:

- All studies included subjects aged 12-75 years old, and studies of omalizumab also included children from 6 years old.

Qualität der Studien:

The systematic review included only English language articles; however, the risk of selection bias is probably small because we screened previous systematic reviews and the GDG included several international experts in the field; thus, the possibility of missing results from non-English articles is unlikely. We did not include observational studies that could have been

informative for some of the outcomes with low or very low-quality evidence from RCTs (eg serious AE).

Studienergebnisse (siehe Anhang):

- Severe asthma exacerbation rate
  - The annualized exacerbation rates were reported in three benralizumab trials,39-41 three dupilumab trials,42-44 three mepolizumab trials,45-47 three omalizumab trials48,50,51 and five reslizumab trials.52-55 All biologicals reduced asthma exacerbations rate compared to standard of care with high certainty of evidence: benralizumab IRR 0.53; 95% CI 0.39 to 0.72; dupilumab IRR 0.44; 95% CI 0.32 to 0.59; mepolizumab IRR 0.49 95% CI 0.38 to 0.66; omalizumab IRR 0.56; 95% CI 0.40 to 0.77; and reslizumab IRR 0.46; 95% CI 0.37 to 0.58.
- Asthma control
  - The change in asthma control following biologicals addition was evaluated using Asthma Control Questionnaires (ACQ) scores and the Total Asthma Symptoms Scores (TASS). Dupilumab, omalizumab and mepolizumab probably improve asthma control with moderate certainty of evidence: dupilumab (ACQ-5) MD −0.48; 95% −0.88 to −0.09 42-44; omalizumab (TASS) MD −0.16; 95% −0.51 to 0.19 48-51 and mepolizumab (ACQ-5) MD −0.43; 95% CI −0.56 to −0.31.45-47 Nevertheless, none of the biologicals showed an improvement above the MID threshold of 0.5.
- Quality of life
  - QoL was reported in three benralizumab trials 39-41; two dupilumab trials42,43; three mepolizumab trials45-47; one omalizumab trial 48 and three reslizumab trials.53-55 Changes in QoL were evaluated using the Asthma Quality of Life Questionnaire (AQLQ) for all biologicals, except for mepolizumab that used the St. George's Respiratory Questionnaire (SGRQ) score. All the addition of all biologicals improved QoL with moderate to high certainty, although below the MID: benralizumab MD + 0.23 (95% CI 0.11 to 0.36); dupilumab MD + 0.42 (95% CI + 0.25 to + 0.59); mepolizumab (SGRQ) MD −7.14 (95% CI −9.07 to −5.21); omalizumab MD + 0.13 (95% CI +0.11 to +0.37); and reslizumab MD + 0.17 (95% CI +0.08 to +0.25).
- Safety
  - Drug-related AE were assessed in two trials for benralizumab,40,41 one trial for dupilumab,42 three mepolizumab trials,45-47 one trial for omalizumab 48 and three trials for reslizumab.52,53,55 For mepolizumab, there is an increased likelihood of drug-related AE (RR 1.35; 95% CI 1.01 to 1.80; high certainty of evidence). Benralizumab and reslizumab probably increases drug-related AE (moderate certainty of evidence): benralizumab RR 1.41, 95% CI 0.87 to 2.27; reslizumab RR 1.18, 95% CI 0.89 to 1.56. For dupilumab and omalizumab, the RR is rather small: dupilumab RR of 1.00, 95% CI 0.88 to 1.13; and omalizumab RR 1.01, 95% CI 0.91 to 1.1.
  - There is low to very low certainty of evidence that drug-related serious AE may increase with the use of dupilumab RR 1.46 (95% 0.60 to 3.54) and reslizumab RR 4.71 (95% 0.54 to 41.31). For benralizumab and mepolizumab, results are inconclusive: benralizumab RR 0.56 (95% CI 0.22 to 1.44) and mepolizumab RR 0.98 (95% CI 0.06 to 15.63). Data were not fully reported in all trials; thus, the certainty of evidence was downgraded due to the low number of events.
- Reduction in oral corticosteroids use
  - Benralizumab, dupilumab and mepolizumab showed with high certainty of evidence, a reduction in daily OCS: benralizumab >50% (RR 1.76, 95%CI 1.26 to 2.47); dupilumab 29.4% (95% CI 43.2 lower to 15.57 lower); and mepolizumab >50% (RR 1.61; 95%CI 1.07-2.41).41,44,46 Mepolizumab showed a reduction in OCS to 5mg/day or less (crude RR 1.71; 95%CI 1.11 to 2.55, P = .01) and a reduction of 100% in daily OCS (crude RR 1.91; 95% CI 0.69 to 5.30, P = .2) compared to placebo.
- Reduction of rescue medication use
  - This end point was assessed only for mepolizumab and showed no clinically significant reduction in the daily use of rescue medication after 24 weeks (MD—0.1 puffs/day; CI 95% −0.35 to 0.15).45
- Lung function - $FEV_1$
  - The change from baseline of $FEV_1$ was assessed for benralizumab,39-41 mepolizumab,45-47 omalizumab 48 and reslizumab.52-55 Compared to standard of care, there was an increase in $FEV_1$, but below the MID agreed by the GDG (moderate certainty of evidence): benralizumab MD + 140mL (95% CI +90 to +190); mepolizumab

MD + 110.9 mL (95% CI +58.91 to +162.89), reslizumab MD + 141.82 mL (95% CI +89.23 to +194.41); and omalizumab mean percentage change + 3.7% (95% CI 2.1% to 9.5%). There is low certainty of evidence that for patients with baseline eosinophils ≥300 cells/µL dupilumab may increase FEV1 compared to standard of care [MD + 180 mL (95% CI 110 to 250)].

**Anmerkung/Fazit der Autoren**

Our systematic review of efficacy shows high certainty for reducing the rate of severe asthma exacerbations for all the biologicals evaluated (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) as add-on treatment for patients with severe uncontrolled eosinophilic asthma. The certainty is moderate for improving asthma control, QoL and lung function (FEV1) improvement, not reaching the MID. Only benralizumab, dupilumab and mepolizumab provided data about the use of OCS, showing a reduction in the daily dose of OCS compared to standard of care (high certainty of evidence).

*Kommentare zum Review*

- There are several limitations: The basal exacerbation rate was used to estimate the absolute benefit for each drug/analysis. However, we did not perform a subgroup or sensitivity analysis based on that variable (basal exacerbation rate), as it was not predefined or requested in the protocol or during the systematic review.
- Interressenskonflikte wurden von den Autoren offengelegt. Es bestand zum Teil Funding durch die Industrie.
- Siehe auch Ramonell RP et al., 2020 [27]

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**Fu Z et al., 2020 [11].**

Efficacy and safety of omalizumab in children with moderate-to-severe asthma: a meta-analysis

**Fragestellung**

To assess the efficacy and safety of omalizumab in children with moderate-to severe asthma.

**Methodik**

Population:

- children with moderate-to severe asthma.

Intervention:

- Omalizumab

Komparator:

- Placebo

Endpunkte:

- number of patients with asthma exacerbations, global evaluation of treatment effectiveness (GETE) assessed by physicians, decrease in ICS dose
- drug-related adverse events.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) to January 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 3 RCTs
- Of these four papers, three compared the efficacy and safety of omalizumab versus placebo in patients with moderateto- severe asthma; one was conducted in patients with severe asthma. Treatment duration in two papers was within less than 30 weeks, and two was prolonged for more than 30 weeks.

Charakteristika der Population:

- The age of the children included ranged from 6 to 12 years old in three papers, and one enrolled patients aged 6–20 years old.

Qualität der Studien:

- the selection bias of the sequence generation and allocation concealment was unclear in all studies. Two papers had low risk of performance bias, detection bias, and attrition bias, and two were unclear. All studies were unclear in selective outcome reporting bias.

Studienergebnisse:

- Asthma exacerbations: The data of asthma exacerbations were offered in all studies. Of the 817 patients in the omalizumab group, there were 185 patients with asthma exacerbations (22.6%) and 193 asthma exacerbations occurred in 512 patients in the placebo group (38.2%). Omalizumab therapy decreased asthma exacerbations rate (OR 0.51, 95% CI: 0.44–0.58, p<0.001) compared with placebo with no evidence of heterogeneity (I2=30.8%, p=0.23)
- Global evaluation of treatment effectiveness (GETE) assessed by physicians: Two studies reported GETE which was assessed by physicians. Omalizumab treated patients showed an excellent or good response rate of GETE assessed by physicians than placebo-treated patients (OR 2.75, 95% CI: 2.45–3.09, p<0.001).
- Decrease in inhaled corticosteroid (ICS) dose: Two studies reported mean and SD values of decrease in ICS dose. The results showed people receiving omalizumab had a bigger reduction in the dosage of ICS than placebo group (weighted mean difference, -108 lg/d, 95% CI: -151.19 to -64.81 lg/d, p<0.001; I2=0%, p=1.0) at the end of follow-up.
- Adverse Events: Patients receiving omalizumab had a lower incidence of severe adverse events (OR 0.36, 95% CI: 0.22–0.57). The results of analysis showed that omalizumab therapy had no effects on incidence of any other adverse events

**Anmerkung/Fazit der Autoren**

These findings suggested that omalizumab had beneficial effects on moderate-to-severe asthma in children. Patients may benefit more from long-term use of omalizumab. In addition, omalizumab reduces the rate of serious adverse events requiring hospitalizations. Future research should involve large-scale multicenter RCTs with high quality and long-term followup durations to realize its full potential in children.

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**Ando K et al., 2020 [4].**

Comparative Efficacy and Safety of Dupilumab and Benralizumab in Patients with Inadequately Controlled Asthma: A Systematic Review

**Fragestellung**

We conducted an indirect treatment comparison to estimate differences in the efficacy and safety between dupilumab and benralizumab for inadequately controlled asthma using the Bayesian approach.

**Methodik**

Population:

- Patients with Inadequately Controlled Asthma

Intervention:

- dupilumab and benralizumab

Komparator:

- placebo

Endpunkte:

- primary efficacy endpoint was annual exacerbation rate (AER); the primary safety endpoint was the incidence of any adverse events (AAEs)
- secondary efficacy endpoints was change in forced expiratory volume at 1.0 s (FEV1.0) and asthma quality of life questionnaire (AQLQ score)

Recherche/Suchzeitraum:

- a systematic literature review (PubMed, Embase, CENTRAL and SCOPUS)
- Suchzeitraum: k. A.

Qualitätsbewertung der Studien:

- The risk of bias tool recommended by the Cochrane Collaboration was used to assess the qualities of RCTs included in the present analysis.

**Ergebnisse**

Anzahl eingeschlossener Studien:

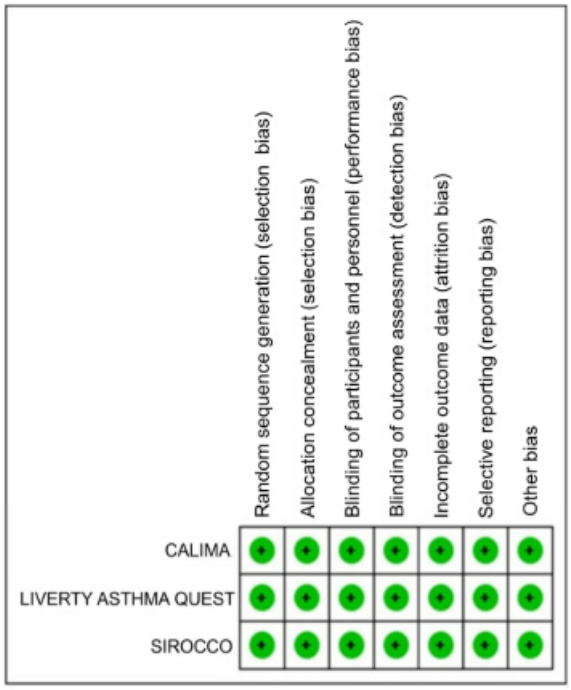
- 3 RCTs

Charakteristika der Population:

- Adolescent or adult patients with asthma who met the GINA guidelines diagnostic criteria of 12 years of age or older [2];
- patients with moderate-to-severe persistent asthma who received 200 µg/day fluticasone or an equivalent or more ICS with at least one clinically significant episode (require administration of systemic steroids or consultation at an emergency outpatient center or admission);
- FEV1.0 before bronchodilator administration of less than 80% (an adolescent with less than 90% was acceptable);
- FEV1.0 reversibility after administration of short-acting beta-2 agonist of ≥12%, or ≥200 mL; and the ACQ score of ≥1.5 before inclusion.

Qualität der Studien:

- Evaluating the risk of bias using the Cochrane risk of bias tool revealed a low risk of bias for all studies included in this analysis.




Studienergebnisse:

- AER
  - Dupilumab and benralizumab reduced the AER compared with that of the placebo with the respective rate ratio (RR) and 95% credible interval (CrI) of 0.54 (0.43–0.67) and 0.65 (0.55–0.77) in the overall population and 0.32 (0.24–0.45) and 0.57 (0.46–0.70) in the subgroup with the blood eosinophil count of ≥300.
  - In the subgroup with blood eosinophil ≥150 and <300, dupilumab reduced AER compared to placebo with RR and 95% CrI of 0.40 (0.26 to 0.61), whereas benralizumab did not show a significant AER difference compared to placebo (RR and 95% CrI of 0.77 (0.52 to 1.15).
  - In the sub-group with a blood eosinophil count of <150, neither dupilumab nor benralizumab showed a significant difference in AER compared to the placebo with RR and 95% CrI of 1.15 (0.75 to 1.72) and 0.73 (0.48 to 1.10), respectively.
  - The comparison between the drugs showed that AER was significantly better in the dupilumab group than the benralizumab group for the subgroup with a blood eosinophil count of ≥300 and a blood eosinophil count of ≥150 but <300 with RR and 95% CrI of 0.58 (0.39 to 0.84) and 0.51 (0.29 to 0.92), respectively (Figure 3B,C). We found no significant difference in the AER between both drugs in the overall population and in the subgroup with the blood eosinophil count of <150 with the RR and 95% CrI of 0.83 (0.62–1.09) and 1.57 (0.73–2.82), respectively.
- Secondary Efficacy Endpoint Changes in FEV1.0 and AQLQ Score from Baseline
  - The changes in FEV1.0 from the baseline for the dupilumab and benralizumab groups were significantly better than those for the placebo with the respective mean difference (MD) and 95% CrI of 0.130 (0.068–0.194) and 0.099 (0.051–0.146) in the overall population, and 0.251 (0.155–0.347) and 0.146 (0.088–0.204) in the subgroup with the blood eosinophil count of ≥300 (Figure 4A,B).
  - The comparison of the two drugs showed no significant difference in the change in FEV1.0 from the baseline in the overall population and the subgroup with the blood eosinophil count of ≥300.
  - The changes in AQLQ score from baseline in the dupilumab group and benralizumab group were significantly better than the placebo with respective MD and 95% CrI of 0.261(0.111 to 0.408) and 0.220 (0.106 to 0.333) in the overall population, and 0.342 (0.120 to 0.565) and 0.300 (0.161 to 0.439) in the subgroup with a blood eosinophil count of ≥300.
  - The comparison between the two drugs showed no significant difference in the AQLQ score from the baseline in the overall population and the subgroup with the blood eosinophil count of ≥300 with the MD and 95% CrI of 0.041 (−0.145 to 0.227) and 0.042 (−0.220 to 0.304), respectively

- Incidence of AAE and SAE
  - o There were no significant differences in the incidence of AAEsbetween dupilumab or benralizumab and placebo, with the odds ratio (OR) and 95% CrI of 0.830 (0.591–1.165) and 0.811 (0.619–1.061), respectively, and between dupilumab and benralizumab with the OR and 95% CrI of 1.023 (0.688–1.526), and there were no significant differences in the incidence of any SAEs between dupilumab or benralizumab and placebo, with OR and 95% CI of 1.039 (0.657 to 1.639) and 0.787 (0.550 to 1.129), respectively, and between dupilumab and benralizumab, with 1.319 (0.768–2.265)

**Anmerkung/Fazit der Autoren**

In this study, we compared the efficacy and safety of dupilumab and benralizumab in patients with inadequately controlled asthma. Dupilumab revealed a better efficacy profile than benralizumab in the group with a high eosinophil count, and it was generally well tolerated. Considering that this analysis is an indirect comparison, a further analysis, such as an RCT by direct comparison, is required to confirm the results reported herein.

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**Henriksen DP et al., 2018 [20]**

Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti-IL-5 treatments of severe asthma - a systematic review and meta-analysis

Siehe auch: Yan K et al., 2019 [37].

**Fragestellung**

Which adult patients with severe eosinophilic asthma should be offered anti-IL-5 therapy?

Is there clinically relevant difference between mepolizumab and reslizumab in the treatment of patients with severe, eosinophilic asthma?

**Methodik**

Population:

- Patients ≥18 years of age with severe, eosinophilic asthma.

Intervention:

- Anti-IL-5 therapy (reslizumab 3 mg/kg intravenous administration every 4 weeks, or mepolizumab fixed dose 100 mg subcutaneous administration every 4 weeks) on top of standard care.

Komparator:

- Placebo on top of standard care.

Endpunkte:

- excacerbation rate (a reduction in annual rate of at least 25%, corresponding to a minimum reduction of 0.5 excerbations per year);
- OCS
  - o average %-reduction in daily dose [maintenance-treatment] (at least 20% and at least 2.5-mg prednisolone- equivalent dose),
  - o percentage of patients who discontinued OCS (a minimum of 5%-points,
  - o percentage of patients who achieve a ≥50% reduction of OCS dose (a minimum of 10%-points).
- Asthma Control, Lung function, QoL, SAEs, Dropout rate

Recherche/Suchzeitraum:

- on 15 June 2017 in MEDLINE and Embase

Qualitätsbewertung der Studien:

- Cochrane risk of bias assessment
- GRADE approach to assess the quality of evidence provided by the metaanalyses

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 4 randomised controlled trials which examined the efficacy of mepolizumab, and 5 trials which examined the efficacy of reslizumab
- one was not included in the meta-analysis because the study design differed significantly from the other studies

Charakteristika der Population:

- all mepolizumab studies included patients with a treatment-intensity equalling severe asthma whereas the majority of all reslizumab studies included patients with a treatment intensity equalling moderate to severe asthma
- The study characteristics varied significantly between the included studies, especially in regard to design, follow-up length (range from 15 to 52 weeks), intensity of the standard of care asthma therapy asthma), eosinophil count at treatment initiation and number of previous exacerbations

Qualität der Studien:

- Siehe GRADE Bewertung der Ergebnisse

Studienergebnisse:

- Exacerbations: In total, five randomised trials reported in four papers comprising a total of 2197 patients were included in the meta-analysis. The rate ratio for the number of annual exacerbations showed a favourable effect in the anti-IL-5 group compared to placebo (rate ratio 0.47 [95% CI 0.41; 0.54), which can be translated into an absolute risk reduction of 53% (95% CI 46; 59)
  - Mepolizumab. Three studies were included comprising 1244 patients. The rate ratio of annual exacerbations was 0.47 [95% CI 0.40; 0.56] in favour of the mepolizumab group compared to placebo. The heterogeneity was low (I2 = 0%).
  - Two RCTs reported in the same paper were included comprising 953 patients. The rate ratio of annual exacerbations was 0.46 [95% CI 0.37; 0.59] in favour of the reslizumab group compared to placebo. The heterogeneity was low (I2 = 0%).
- Number of patients who experience 0 exacerbations annually Combined. In total, four randomised trials reported in three papers comprising a total of 1837 patients were included in the meta-analysis. We found a relative improvement of 1.42 (95% CI 1.3; 1.56) on the percentage of patients experiencing 0 exacerbations in favour of the anti-IL-5 group (Figure 3). The calculated absolute difference was 16.9% (95% CI 12.1; 22.5) compared to placebo, which can be translated to 40 out of 100 who experience 0 exacerbations in the placebo group compared to 57 out of 100 in the anti-IL-5 group. This was larger than the predefined MCID of 10 percentage points. The heterogeneity was low (I2 = 0%, p = 0.48) and quality of evidence was considered moderate.
  - Mepolizumab. Two studies were included comprising 884 patients. The relative improvement was 1.58 (95% CI 1.33; 1.87) on the percentage of patients experiencing 0 exacerbations in favour of the anti-IL-5 group. The heterogeneity was considered low (I2 = 0, p = 0.56).
  - Reslizumab. Two RCTs reported in the same paper were included comprising 953 patients. The relative improvement was 1.36 (95% CI 1.22; 1.52) on the percentage of patients experiencing 0 exacerbations in favour of the anti-IL-5 group. The heterogeneity was considered low (I2 = 0, p = 0.99).
- Oral corticosteroid (OCS) treatment
  - Median reduction and percentage of patients who experienced ≥50% reduction of OCS. A single randomised study (n = 135) of mepolizumab was included for further analysis,

which showed a median reduction of OCS of 50% (95% CI 20; 75) compared to a 0% (95% CI −20; 33.3) reduction in the placebo group. Due to the lack of statistical evaluation of the average reduction in OCS between mepolizumab and placebo, it was not possible to assess the predefined MCID of 20%. Instead, we assessed the percentage of patients, who experienced ≥50% reduction in OCS treatment. The relative difference was 1.61 (95% CI 1.07; 2.41) in favour of mepolizumab (22/66 in the placebo group experienced a ≥50% reduction in OCS compared to 37/69 in the mepolizumab group). We calculated an absolute effect of 20.3%- points (95% CI 2.3; 47.0), which was larger than the defined MCID of 10 percentage points. The quality of evidence was considered low.

- Percentage of patients who were discontinued OCS.
  - In the mepolizumab group, 10 out of 69 patients were discontinued OCS, whereas 5 out of 66 were discontinued OCS in the placebo group, which accounted for a relative difference of 1.91 (95% CI 0.69; 5.30) in favour of the mepolizumab group. This yielded a 6.9% (95% CI −2.3; 32.6%) in favour of mepolizumab. The quality of evidence was considered low.We found no studies on the reduction in OCS when using reslizumab. The quality of evidence was considered low.
- Lung Function: Nine randomised trials of 3160 patients were included in the meta-analysis (four regarding mepolizumab, and five regarding reslizumab [26–29]). No studies presented the number of patients experiencing the MCID of 200 mL in forced expiratory volume (FEV1). We found an absolute difference of FEV1 of 112.93 ml (95% CI 82.44; 143.31) in favour of the anti- IL-5 treatment compared to placebo, which is below the minimal clinically important difference. We found no significant heterogeneity (I2 = 0%, p = 0.44). The quality of evidence was considered moderate.
- Asthma Control: Nine studies of 3165 patients were included; four mepolizumab studies (three using Asthma Control Questionnaire [ACQ]5 , and one ACQ6), and reslizumab studies (all used ACQ7). We pooled the results fromthe different ACQ versions in themeta-analysis and found a change of −0.29 points (95% CI −036; −0.23) in the anti-IL-5 group compared to placebo, which was below the minimal clinically important effect of 0.5 points. No significant heterogeneity was observed (I2 = 6%, p = 0.38). The quality of evidence was considered low.
- Quality of Life: We included four studies using the Asthma Quality of Life Questionnaire (AQLQ): one mepolizumab study and three reslizumab studies. Further three studies were included, which used SGRQ, in which the MCID is 4 points, which gave a total of 2562 included patients. We pooled all the results by recalculating the scores to SMD and found a significant improvement of quality of life among patients in the anti-IL-5 group compared to the placebo group (SMD 0.32 [95% CI 0.22; 0.43). We thereafter backtransformed the SMD to AQLQ points by assuming a SD of 1 (the SD was observed to be 0.88–1.12), which showed an improvement of 0.32 (95% CI 0.22; 0.43) in the anti-IL-5 group compared to placebo that was below the MCID of a 0.5 point improvement. Moderate heterogeneity (I2 = 43%) was observed, but this was not significant (p = 0.12). The quality of evidence was considered low.
- Dropout Rate: We included nine studies of 3201 patients (four regarding mepolizumab , and five regarding reslizumab), and found a larger dropout rate in the placebo group compared to the anti-IL-5 group (relative risk reduction of 0.85 [95% CI 0.69; 1.05]). Recalculated to absolute values, we found −2.3%-point (95% CI −4.7;-0.7) difference in dropout in the anti-IL-5 group compared to the placebo group, which was below the MCID of 10%. We found no significant heterogeneity (I2 = 0%, p = 0.28). The quality of evidence was considered moderate.
- SAE: We included nine studies of 3193 patients (four regarding mepolizumab, and five regarding reslizumab), and found an increased risk of SAE in the placebo group compared to the anti-IL-5 group with a relative risk reduction of 0.73 [95% CI 0.57; 0.92] in favour of the anti-IL-5 group. This was recalculated to an absolute value of −2.4%-points (95% CI −0.7; −3.8). The effect estimate was not greater than that MCID of ±5% points. The effect was positive for anti-IL-5 treatment and therefore it did not imply a negative impact on the assessment of the medicines. We found no significant heterogeneity (I2 = 0%, p = 0.67). The quality of evidence was considered moderate.

Comparison of the effect of mepolizumab and reslizumab

Using Bucher's method of indirect comparison between two effects, we found no significant difference between mepolizumab and reslizumab in any of the predefined clinical outcomes

**Anmerkung/Fazit der Autoren**

Mepolizumab and reslizumab provide significant and clinically relevant improvement in exacerbation rate and OCS reduction, whereas improvement in FEV1, asthma control, and asthma-related quality of life is below MCIDs. Indirect inter-study comparisons revealed no differences between the anti-IL-5 drugs in efficacy or safety measures, whilst differences in OCS reduction could not be investigated due to the lack of reslizumab studies with this outcome. Neither of the available studies incorporated novel standards of systematic assessment of difficult-to-treat asthma prior to onset of treatment. To optimise use of healthcare resources, an increasing focus on systematic assessment to differentiate difficult-to-treat asthma from severe asthma before commencing

biological agents is developing.

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**Busse W et al., 2019 [8].**

Anti–IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison.

**Fragestellung**

to compare the efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with SEA, according to baseline blood eosinophil counts.

**Methodik**

Population:

- patients with SEA aged 12 years or greater

Intervention:

- mepolizumab, reslizumab, benralizumab

Komparator:

- Placebo als Brückenkomparator

Endpunkte:

- Clinically significant exacerbations, defined as an exacerbation requiring treatment with OCSs/systemic corticosteroids (for patients on maintenance OCSs, a >2-fold increase in dose was required) or requiring an emergency department (ED) visit or hospitalization; exacerbations requiring an ED visit/hospitalization; ACQ score (any version); and change from baseline prebronchodilator FEV1. Finally, all included studies had a randomized, double-blind, controlled study design.

Recherche/Suchzeitraum:

- Primary data source for this ITC was the published Cochrane by Farne et al. → siehe oben Reference [10]. Additional search on January 2018.

Qualitätsbewertung der Studien:

- Vermutlich analog Cochrane Publikation [10].

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Eleven studies were included: Results of the systematic literature search have previously been reported. From the Cochrane review, 9 studies were identified as eligible for inclusion in this ITC. Additional searches identified 11 further articles, 2 of which presented subgroup analyses relevant for this ITC that were not reported in the primary publications.

Charakteristika der Population:

- Across all studies, 3723 patients received either 100 mg of mepolizumab administered subcutaneously Q4W, 3 mg/kg reslizumab Q4W, 30 mg of benralizumab Q8W or placebo. Of the 385 and 551 patients in MENSA and MUSCA, respectively, who received either 100 mg of mepolizumab administered subcutaneously Q4W or placebo.

Qualität der Studien:

- K.A.

Studienergebnisse:

- All treatments significantly reduced the rate of clinically significant exacerbations and improved asthma control versus placebo in all blood eosinophil count subgroups.
- Mepolizumab reduced clinically significant exacerbations by 34% to 45% versus benralizumab across subgroups (rate ratio >400 cells/mL: 0.55 [95% CI, 0.35-0.87]; >300 cells/mL: 0.61 [95% CI, 0.37-0.99]; and >150 cells/mL: 0.66 [95% CI, 0.49-0.89]; all P < .05) and by 45% versus reslizumab in the 400 cells/mL or greater subgroup (rate ratio, 0.55 [95% CI, 0.36-0.85]; P 5.007).
- Asthma control was significantly improved with mepolizumab versus benralizumab (all subgroups: P < .05) and versus reslizumab in the 400 cells/mL or greater subgroup (P 5 .004).
- Benralizumab significantly improved lung function versus reslizumab in the 400 cells/mL or greater subgroup (P 5 .025).

**Anmerkung/Fazit der Autoren**

This ITC of the licensed doses suggests that mepolizumab was associated with significantly greater improvements in clinically significant exacerbations and asthma control compared with reslizumab or benralizumab in patients with similar blood eosinophil counts.

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**Xiong XF et al., 2019 [36].**

Efficacy and safety of dupilumab for the treatment of uncontrolled asthma: a metaanalysis of randomized clinical trials.

**Fragestellung**

to evaluate the overall efficacy and safety of dupilumab for the treatment of uncontrolled asthma.

**Methodik**

Population:

- adults/adolescents (≥ 12 years old) diagnosed with uncontrolled asthma
  - Uncontrolled asthma was defined based on current treatment with a medium-to-high-dose inhaled glucocorticoid (fluticasone propionate at a total daily dose of ≥500 μg or equipotent equivalent), plus up to 2 additional controllers (e.g., a long-acting β2-agonist or leukotriene receptor antagonist);

Intervention:

- dupilumab

Komparator:

- placebo

Endpunkte:

- lung function (FEV1), he 5-item Asthma Control Questionnaire (ACQ-5) score, fractional exhaled nitric oxide (FENO), AM and PM asthma symptom scores, quality of life (AQLQ), severe exacerbation rate, or adverse events

Recherche/Suchzeitraum:

- PubMed, Embase, the Cochrane Library and Chinese Biological Medicine (CBM) databases for articles published up to June 30, 2018

Qualitätsbewertung der Studien:

- Cochrane approach

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Five studies involving 3369 patients

Charakteristika der Population:

- A single intervention group (dupilumab 300 mg qw and 300 mg q2w) was presented in 2 trials, and the remaining studies included 2 or more interventions (dupilumab 200 mg q2w, 200 mg q4w, 300 mg q2w, 300 mg q4w).
- Outcome reporting varied among the trials. FEV1 was reported in 5 studies
- Severe asthma exacerbations rate was reported in 4 trials. ACQ-5 scores, FENO, and AM and PM asthma symptom scores were reported in 3 trials. AQLQ was reported in 2 trials.

Qualität der Studien:

- All trials had a low risk of bias in terms of the 6 domains

Studienergebnisse:

- significant improvements with dupilumab in the first-second forced expiratory volume (FEV1) (SMD = 4.29, 95% CI: 2.78–5.81) and Asthma Quality of Life Questionnaire scores (SMD = 4.39, 95% CI: 1.44–7.34).
- Dupilumab treatments were also associated with significantly decreased 5-item Asthma Control Questionnaire scores (SMD = − 4.95, 95% CI: − 7.30 to − 2.60), AM and PM asthma
- symptom scores (SMD = − 5.09, 95% CI: − 6.40 to − 3.77; SMD = − 4.92, 95% CI: − 5.98 to − 3.86, respectively), and severe exacerbation risk (RR = 0.73; 95% CI: 0.67–0.79) compared with placebo, with similar incidence of adverse events.

**Anmerkung/Fazit der Autoren**

Dupilumab treatment is relatively well-tolerated and could significantly improve FEV1, symptoms, asthma control, and quality of life, and reduced severe exacerbation risk in patients with uncontrolled asthma.

*Kommentare zum Review*

- Siehe auch Zayed Y et al. 2018 [38].

**Casale TB et al., 2019 [9].**

Reslizumab Compared with Benralizumab in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis

**Fragestellung**

To indirectly compare reslizumab with benralizumab in similar patient populations using a network meta-analysis.

**Methodik**

Population:

- Patients with severe eosinophilic asthma

Intervention:

- Reslizumab (in addition to best standard of care)

Komparator:

- Best standard of care and/or placebo
- Benralizumab (in addition to best standard of care)

Endpunkte:

- Incidence of exacerbations and clinically significant exacerbations
- Asthma control (ie, overall change from baseline in FEV1, change from baseline in FVC, change in ACQ score from baseline)
- Quality of life (change in AQLQ score from baseline, change in ASUI score)
- Use of oral corticosteroids; patient and clinical evaluation of response; lung function; mortality; time to discontinuation; adverse effects of treatment

Recherche/Suchzeitraum:

- on August 12, 2016, using Medline (PubMED), Embase, and the Cochrane library. Additional hand searches were performed on June 1, 2017

Qualitätsbewertung der Studien:

Quality criteria published by the Centre for Reviews and Dissemination

- o

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 11 randomized controlled clinical studies; All studies evaluated reslizumab or benralizumab as add-on therapy. Concomitant maintenance therapy, such as the administration of ICSs and/or long-acting b2-antagonists, was allowed.

Charakteristika der Population:

- Studies were generally balanced with respect to age, sex, baseline FEV1 levels, and baseline AQLQ scores; however, differences in inclusion criteria resulted in imbalances between the patient populations in which reslizumab and benralizumab were assessed. The reslizumab trials enrolled patients with blood eosinophil levels of greater than or equal to 400 cells/mL who experienced at least 1 previous exacerbation, whereas benralizumab studies enrolled patients who had a lower blood eosinophil threshold of greater than or equal to 150 cells/mL and who had experienced at least 2 previous exacerbations. In addition, reslizumab trials included patients in GINA steps 3 through 5; whereas benralizumab trials did not report GINA stage, but baseline medications suggest patients were in GINA step 4/5.

Qualität der Studien:

- All studies identified were of high quality according to criteria published by the Centre for Reviews and Dissemination

Studienergebnisse:

- Reslizumab produced significantly greater improvement in asthma control, as measured by the 6-item ACQ, compared with benralizumab 30 mg Q4W (D = -0.37; CrI, -0.63 to -0.10; Pr = 100%); statistical significance compared with benralizumab 30 mg Q8W was not reached. A sensitivity analysis using the 7-item ACQ had results that were similar to the base-case analysis.
- AQLQ scores increased (indicating greater health-related quality of life) significantly more with reslizumab than with benralizumab 30 mg Q4W (D = 0.32; CrI, 0.03 to 0.60; Pr = 99%).
- In the FEV1 analysis, Pr was 92% that reslizumab would improve FEV1 more than benralizumab Q8W and 96% compared with benralizumab Q4W with a magnitude of difference ranging from 0.09 to 0.11 L; these differences were not significant. Heterogeneity assessment of the inputs used in the analysis of FEV1 revealed important differences among the studies with respect to change in FEV1. In the 2 benralizumab studies, FEV1 increased by 0.22 L and 0.24 L in the placebo arms. In the reslizumab studies, FEV1 increased by 0.05 L and 0.18 L in the placebo arms.
- There was no significant difference between reslizumab and benralizumab 30 mg Q4W or Q8W for clinical asthma exacerbations; the model estimated a Pr of 86% that reslizumab is superior to benralizumab 30 mg Q4W and Q8W. In the sensitivity analysis for efficacy using the overall study populations instead of subgroups, reslizumab was associated with a significantly greater reduction in clinically significant asthma exacerbations compared with either benralizumab dose. The rate ratio for reslizumab compared with benralizumab 30 mg Q4W was 0.73 (95% CI, 0.62-0.85) and compared with benralizumab 30 mg Q8W was 0.72 (95% CI, 0.61-0.84); Pr was 100% for both comparisons. Results for the other efficacy outcome measures were directionally consistent with the base-case efficacy analysis and the overall conclusions were not changed.

**TABLE III.** Treatment rankings for efficacy outcomes based on SUCRA*

| Regimen | Reduce clinical asthma exacerbations | Improve $FEV_1$ | Improve ACQ score | Improve AQLQ score |
|---|---|---|---|---|
| Reslizumab 3.0 mg/kg Q4W | First | First | First | First |
| Benralizumab 30 mg Q4W | Second | Second | Second | Second |
| Benralizumab 30 mg Q8W | Second | Third | Third | Third |
| Placebo | Fourth | Fourth | Fourth | Fourth |

*SUCRA*, Surface under the cumulative ranking.
*Because this analysis involved indirect comparisons between individual studies, these results may have been influenced by differences in study populations and methodologies.

- Adverse Events: Adverse events leading to discontinuation were significantly less frequent with reslizumab than with either benralizumab dose (Pr = 99%). No significant difference was observed in the frequency of adverse events, treatment-related adverse events, or serious adverse events for reslizumab compared with either benralizumab regimen. For treatment-related and all-cause adverse events, Pr was 83% to 92% for a lower rate of adverse events with reslizumab compared with benralizumab Q4W or Q8W.

**Anmerkung/Fazit der Autoren**

In conclusion, although analyses are limited by differences in study designs, this indirect comparison of reslizumab with benralizumab suggests that reslizumab may be more efficacious in patients with eosinophilic asthma in GINA step 4/5 with elevated blood eosinophil levels (≥300 cells/mL for benralizumab and ≥400 cells/mL for reslizumab) and 2 or more exacerbations in the previous year, and has similar tolerability. Further study is needed to confirm these results and to explain the observed differences in efficacy and tolerability.

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**Liu W et al., 2019 [23].**

Adverse events of benralizumab in moderate to severe eosinophilic asthma: A meta-analysis.

**Fragestellung**

to assess the incidence of these AEs in published randomized controlled trials (RCTs)

**Methodik**

Population:

- patients recruited into these studies were diagnosed with moderate to severe eosinophilic asthma; ≥12 years old

Intervention:

- intervention must include benralizumab

Komparator:

- placebo

Endpunkte:

- AEs

Recherche/Suchzeitraum:

- Embase, PubMed and Cochrane from inception to September 2018

Qualitätsbewertung der Studien:

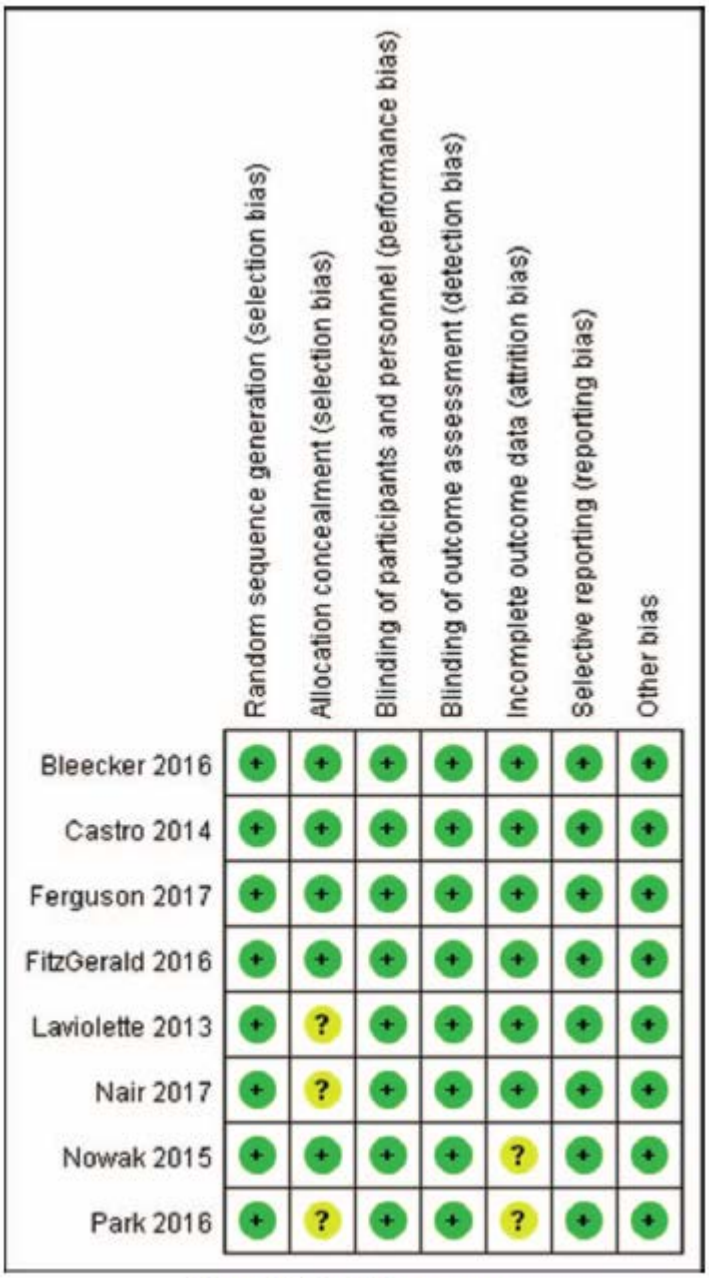


Figure 2. Risk-of-bias summary.

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Eight RCTs with 3788 patients

Charakteristika der Population:

- Of these 3788 patients, 2277 received benralizumab treatment and the remaining 1511 received placebo, and a comparative analysis of different dose groups was included. All patients enrolled in the trials were from various experimental centers in a number of countries. All patients had a history of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS or ICS/LABA for at least 1 year or 2 years prior to screening, and post-bronchodilator reversibility of airflow obstruction ≥12%.

Qualität der Studien:

- Cochrane Collaboration's tool

Studienergebnisse:

- Overall AEs (6 trials):
  - 7.61% (1448/2008) of patients in the benralizumab group developed bronchitis as compared to 10.04% (799/1063) of patients in the placebo group.
  - Fewer patients treated with benralizumab vs placebo experienced overall AEs (RR 0.94, 95% CI 0.90–0.98, P=.03, I2=14%).
- Serious AEs (SAEs) (7 trials):
  - benralizumab had a lower chance of suffering SAEs than patients in the placebo group (RR 0.82, 95% CI 0.68–0.98, P=.03, I2= 0%)
- Asthma (7 trials):
  - A statistically significant difference in worsening asthma between the patients receiving benralizumab and patients receiving placebo was observed (RR 0.72, 95% CI 0.61–0.85, P=.0001, I2=30%). Thus, the benralizumab group had a lower risk of worsening asthma than the placebo group
- Bronchitis (5 trials):
  - The benralizumab group had a lower probability of bronchitis than the placebo group (RR 0.76, 95% CI 0.59–0.96, P=.02, I2=0%)
- Sinusitis (5 trials):
  - benralizumab group had a lower probability of experiencing sinusitis than the placebo group (RR 0.65, 95% CI 0.49–0.86, P=.002, I2=0%)
- Headache (7 trials):
  - The benralizumab group was more likely to suffer headache than the placebo group (RR 1.42, 95% CI 1.07–1.87, P=.01, I2=0%)
- Pyrexia (4 trials):
  - a higher odds of pyrexia in the benralizumab group as compared to the placebo group (RR 2.26, 95% CI 1.32–3.87, P=.003, I2=0%)
- Other AEs: No increased incidence of death, hypersensitivity, injection-site reactions, nasopharyngitis, rhinitis, upper respiratory tract infection, influenza, cough, nausea, back pain or arthralgia was observed with benralizumab compared with placebo.

**Anmerkung/Fazit der Autoren**

Benralizumab reduced the risk of SAEs, asthma exacerbation, bronchitis and sinusitis, and aggravated the risk of headache and pyrexia. Other AEs were comparable between the benralizumab group and placebo group. Therefore, benralizumab is a relatively safe drug, but vigilance regarding AEs is imperative during long-term treatment.

**Meng JF et al., 2019 [24].**

Efficacy of tiotropium in treating patients with moderate-to-severe asthma: A meta-analysis and systematic review based on 14 randomized controlled trials

**Fragestellung**

To explore the clinical efficacy of tiotropium in treating patients suffering from moderate-to-severe asthma.

**Methodik**

Population:

- patients with moderate-to-severe asthma

Intervention:

- tiotropium

Komparator:

- standard therapy or ICS or LABA

Endpunkte:

- morning peak expiratory flow (PEF), evening PEF, peak forced expiratory volume (FEV), trough FEV, peak forced vital capacity (FVC), trough FVC
- adverse event (AE), and serious AE

Recherche/Suchzeitraum:

- Embase, Cochrane, and PubMed was conducted up to January 2019

Qualitätsbewertung der Studien:

- Jadad Score

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 14 RCTs; 4998 patients in the tiotropium group and 5074 patients in the control group.

Charakteristika der Population:

**The basic characteristics description of included studies.**

| Study | Treatment | | No. of patients | | Gender (M: male) | Age (mean±SD) | The severity of asthma | The Jadad score |
|---|---|---|---|---|---|---|---|---|
| | Tiotropium group | Control group | Tiotropium group | Control group | | | | |
| Tom Fardon 2007 | ICS+LABA+Tiotropium, 4 weeks | ICS+LABA, 4 weeks | 25 | 25 | 11M | 54±2.44 | severe | 4 |
| Stephen P. Peters 2010 | ICS+LABA+Tiotropium, 14 weeks | ICS, 14 weeks | 203 | 196 | 69M | 42.2±12.3 | moderate | 4 |
| Eric D. Bateman 2011 | ICS+Tiotropium, 16 weeks | ICS, 16 weeks | 128 | 126 | 97M | 43.3±12.3 | moderate | 6 |
| Huib A. M. Kerstipens 2011 | ICS+Tiotropium5 μg, 8 weeks | ICS, 8 weeks | 104 | 103 | 46M | 54.8±11.7 | severe | 4 |
| Wolfgang Timmer 2015 a | ICS+LABA+once-daily Tiotropium5 μg, 4 weeks | ICS+LABA, 4 weeks | 94 | 94 | 39M | 44.3±13.2 | moderate | 4 |
| Wolfgang Timmer 2015 b | ICS+LABA+twice daily Tiotropium2.5 μg, 4 weeks | ICS+LABA, 4 weeks | 94 | 94 | 39M | 44.3±13.2 | moderate | 4 |
| Kai-Michael Beeh 2014 a | ICS+LABA+Tiotropium5 μg, 4 weeks | ICS+LABA, 4 weeks | 146 | 144 | 67M | 49.3±13.3 | moderate | 4 |
| Kai-Michael Beeh 2014 b | ICS+LABA+Tiotropium2.5 μg, 4 weeks | ICS+LABA, 4 weeks | 147 | 144 | 67M | 49.3±13.3 | moderate | 4 |
| Kai-Michael Beeh 2014 c | ICS+LABA+Tiotropium1.25 μg, 4 weeks | ICS+LABA, 4 weeks | 146 | 144 | 67M | 49.3±13.3 | moderate | 4 |
| Huib A. M. Kerstipens 2015 a | ICS+LABA+Tiotropium5 μg, 24 weeks | ICS+LABA, 24 weeks | 517 | 523 | 632M | 43.1±12.9 | moderate | 6 |
| Huib A. M. Kerstipens 2015 b | ICS+LABA+Tiotropium2.5 μg, 24 weeks | ICS+LABA, 24 weeks | 519 | 523 | 632M | 43.1±12.9 | moderate | 6 |
| Elianne J L E Vrijlandt 2018 a | ICS+LABA+Tiotropium5 μg, 12 weeks | ICS+LABA, 12 weeks | 31 | 34 | 61M | - | severe | 6 |
| Elianne J L E Vrijlandt 2018 b | ICS+LABA+Tiotropium2.5 μg, 12 weeks | ICS+LABA, 12 weeks | 36 | 34 | 61M | - | severe | 6 |
| Huib A. M. Kerstijens 2012 a | ICS+LABA+Tiotropium, 48 weeks | ICS+LABA, 48 weeks | 237 | 222 | 170M | 53±12.4 | severe | 6 |
| Huib A. M. Kerstijens 2012 b | ICS+LABA+Tiotropium, 48 weeks | ICS+LABA, 48 weeks | 219 | 234 | 191M | 53±12.4 | severe | 6 |
| Stanley J. Szefler 2016 a | ICS+LABA+Tiotropium5 μg, 12 weeks | ICS+LABA, 12 weeks | 130 | 134 | 183M | 9.2±1.6 | severe | 6 |
| Stanley J. Szefler 2016 b | ICS+LABA+Tiotropium2.5 μg, 12 weeks | ICS+LABA, 12 weeks | 136 | 134 | 189M | 8.8±1.7 | severe | 6 |
| Eckard Hamelmann 2017 a | ICS+LABA+Tiotropium5 μg, 12 weeks | ICS+LABA, 12 weeks | 130 | 135 | 162M | - | severe | 6 |
| Eckard Hamelmann 2017 b | ICS+LABA+Tiotropium2.5 μg, 12 weeks | ICS+LABA, 12 weeks | 127 | 135 | 159M | - | severe | 6 |
| Eckard Hamelmann 2016 a | ICS+LABA+Tiotropium5 μg, 48 weeks | ICS+LABA, 48 weeks | 134 | 138 | 177M | 14.5±1.6 | moderate | 6 |
| Eckard Hamelmann 2016 b | ICS+LABA+Tiotropium2.5 μg, 48 weeks | ICS+LABA, 48 weeks | 125 | 138 | 169M | 14.2±1.8 | moderate | 6 |
| Pierluigi Paggiaro 2015 a | ICS+LABA+Tiotropium5 μg, 12 weeks | ICS+LABA, 12 weeks | 155 | 155 | 111M | 41.9±13 | moderate | 6 |
| Pierluigi Paggiaro 2015 b | ICS+LABA+Tiotropium2.5 μg, 12 weeks | ICS+LABA, 12 weeks | 154 | 155 | 124M | 43.8±14 | moderate | 6 |
| Christian Vogelberg 2015 a | ICS+LABA+Tiotropium5 μg, 12 weeks | ICS+LABA, 12 weeks | 76 | 76 | 69M | 8.8±1.7 | moderate | 6 |
| Christian Vogelberg 2015 b | ICS+LABA+Tiotropium2.5 μg, 12 weeks | ICS+LABA, 12 weeks | 74 | 76 | 69M | 8.8±1.7 | moderate | 6 |
| Christian Vogelberg 2015 c | ICS+LABA+Tiotropium1.25 μg, 12 weeks | ICS+LABA, 12 weeks | 75 | 76 | 69M | 8.8±1.7 | moderate | 6 |
| Huib A M Kerstjens 2015 a | ICS+LABA+Tiotropium5 μg, 24 weeks | ICS+LABA, 24 weeks | 517 | 541 | 446M | 44.3±12.6 | moderate | 6 |
| Huib A M Kerstjens 2015 b | ICS+LABA+Tiotropium2.5 μg, 24 weeks | ICS+LABA, 24 weeks | 519 | 541 | 432M | 43.4±12.9 | moderate | 6 |

*ICS = inhaled corticosteroids, LABA = long-acting beta-agonist.

Qualität der Studien:

- The main Jadad score of the included studies was 5.43 which was greater than 3; thus, all the included studies were of high quality.

Studienergebnisse:

- PEF: Seven trials with 2146 patients in the tiotropium group and 2197 patients in the control group studied morning PEF. On the basis of the I2 test-value (99.6%>50%) and Chi-squared test P value (.000<.05), the random effects model was selected for analysis of morning PEF. The pooled result showed that the tiotropium group was associated with significant effect in improving morning PEF vs the control group (SMD: 3.29, 95%CI: 2.03–4.55). Eight trials with 2412 patients in the tiotropium and 2465 patients in the control group reported evening PEF. On the basis of the I2 test-value (99.5%>50%) and Chi-squared test P value (.000<.05), the random effects model was applied to analyze evening PEF. Based on the pooled results, evening PEF was remarkably improved in the tiotropium group vs the control group (SMD: 3.36, 95%CI: 2.24–4.48)
- AE: Thirteen trials with 4973 patients in the tiotropium and 5049 patients in the control group reported AE. On the basis of the I2 test value (0.0%<50%) and Chi-squared test P value (.817>.05), the fixed effects model was selected for analysis of AE. According to the pooled result, no significant difference in the incidence of AE was observed between the 2 groups (RR: 0.98, 95%CI: 0.94–1.02). Nine trials with 2212 patients in the tiotropium and 2234 patients in the control group reported serious AE. On the basis of the I2 test value (0.0%<50%) and Chi-squared test P value (.967>.05), the fixed effects model was selected for analysis of serious AE. Based on the pooled result, no significant difference in the incidence of serious AE was found between the two groups (RR: 1.08, 95%CI: 0.77–1.52)

**Anmerkung/Fazit der Autoren**

Considering the limitation of number among included studies based on earlier meta-analyses, we conduct a new and more comprehensive meta-analysis to further explore the accurate efficacy of tiotropium in treating moderate-to-severe asthma. Based on the available evidence, tiotropium could increase morning PEF, evening PEF, peak FEV and trough FEV vs the control group based on high-quality RCTs. Besides, there was no significant difference in peak FVC, trough FVC, AE and serious AE between the 2 groups. Given that there was no

significant publication bias and the main Jadad score of included studies was 5.43, high quality of all the included studies should be confirmed. Furthermore high-quality, larger-sample RCTs are warranted to gather more solid evidence of the safety profile of tiotropium in clinical practice.

*Kommentare zum Review*

Siehe auch Murphy KR et al., 2020 [25]

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**Bourdin A et al., 2018 [5].**

Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review.

**Fragestellung**

to perform a MAIC of benralizumab versus IL-5-directed monoclonal antibodies for the treatment of patients with severe, uncontrolled asthma and with an eosinophilic phenotype.

**Methodik**

Population:

- patients with severe, uncontrolled asthma receiving medium- or high-dosage ICS plus an additional controller medication

Intervention/Komparator

- Indirekter Vergleich
  - IL-5Rα/anti-IL-5 treatments with placebo

Endpunkte:

- annual rate of clinically significant exacerbations, annual rate of exacerbations requiring emergency department (ED) visit or hospitalisation, and pre-bronchodilator forced expiratory volume in 1 s (FEV1)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, MEDLINE In-Process and CENTRAL databases from inception to August 2016

Qualitätsbewertung der Studien:

- risk of bias was assessed using a NICE checklist

**Ergebnisse**

Anzahl eingeschlossener Studien:

- In total identified: 32. For analysis:
  - The evidence networks generated for the placebo-anchored comparison of benralizumab versus mepolizumab included the benralizumab SIROCCO and CALIMA trials and the mepolizumab MENSA and DREAM trials (siehe Studiencharakteristika unten).
  - The evidence network for the placebo-anchored comparison of benralizumab versus reslizumab included the benralizumab SIROCCO and CALIMA trials and the reslizumab Study 3082 and Study 3083 trials.
  - In studies with several treatment arms, only active treatment arms that used licenced (European and USA) dosages were included.

## Charakteristika der Population:

**Table S4. Summary of study characteristics of benralizumab, mepolizumab, and reslizumab studies**

| Study characteristics | Benralizumab | | Mepolizumab | | Reslizumab | |
|---|---|---|---|---|---|---|
| | SIROCCO [3] | CALIMA [5] | MENSA [16] | DREAM [18] | Study 3082 [26] | Study 3083 [26] |
| Publication type | Journal and CSR | Journal and CSR | Journal and CSR | Journal and CSR | Journal | Journal |
| Interventions | Benralizumab 30 mg Q4W SC | Benralizumab 30 mg Q4W SC | Mepolizumab 75 mg Q4W IV | Mepolizumab 75 mg Q4W IV | Reslizumab 3.0 mg/kg IV | Reslizumab 3.0 mg/kg IV |
| | Benralizumab 30 mg Q8W SC | Benralizumab 30 mg Q8W SC | Mepolizumab 100 mg Q4W SC | Mepolizumab 250 mg Q4W IV | Placebo | Placebo |
| | Placebo | Placebo | Placebo | Mepolizumab 750 mg Q4W IV | - | - |
| | - | - | - | Placebo | - | - |
| Phase | III | III | III | IIb | III | III |
| Sample size | 1205 (805)[a] | 1306 (734)[a] | 580 | 308 | 489 | 464 |
| Method of randomisation | Adequate | Adequate | Adequate | Adequate | Adequate | Adequate |
| Blinding status | Double-blind | Double-blind | Double-blind | Double-blind | Double-blind | Double-blind |
| Treatment duration | 48 weeks | 56 weeks | 32 weeks | 52 weeks | 52 weeks | 52 weeks |
| Primary outcome | • Annual rate ratio of asthma exacerbations for patients receiving high-dose ICS + LABA vs placebo with baseline blood EOS ≥300 cells/μL | • Annual rate ratio of asthma exacerbations for patients receiving high-dose ICS + LABA vs placebo with baseline blood EOS ≥300 cells/μL | • Rate of clinically significant exacerbations | • Rate of clinically significant exacerbations | • The frequency of clinical asthma exacerbations per patient during the 52 week treatment period, with events adjudicated by an independent review committee | • The frequency of clinical asthma exacerbations per patient during the 52 week treatment period, with events adjudicated by an independent review committee |

The highlighted cells indicate differences across the trials.

*Number in parenthesis represents patients for benralizumab Q8W and placebo arms.

TABLE 1 Comparison of baseline characteristics of patients included in benralizumab (SIROCCO, CALIMA) and mepolizumab (MENSA, DREAM) studies

| Characteristics | SIROCCO | | CALIMA (only high-dosage ICS subgroup) | | MENSA | | | DREAM | |
|---|---|---|---|---|---|---|---|---|---|
| | Benralizumab Q8W | Placebo | Benralizumab Q8W | Placebo | Mepolizumab 100 mg SC | Mepolizumab 75 mg IV | Placebo | Mepolizumab 75 mg IV | Placebo |
| Patients n | 398 | 407 | 364 | 370 | 194 | 191 | 191 | 153 | 155 |
| Age mean±SD years | 47.6±14.5 | 48.7±14.9 | 50.1±13.3 | 49.8±14.3 | 51.2±14.55 | 50.0±14.03 | 49.2±14.26 | 50.2±11.3 | 46.4±10.8 |
| Male sex % | 36.7 | 33.9 | 38.2 | 40.3 | 40.0 | 45.0 | 44.0 | 32.0 | 37.0 |
| Race % | | | | | | | | | |
| White | 72.1 | 74.2 | 85.2 | 86.8 | 77.0 | 79.0 | 77.0 | 91.0 | 90.0 |
| Black | 3.8 | 3.9 | 3.6 | 3.2 | 4.0 | 3.0 | 2.0 | 3.0 | 4.0 |
| Asian | 12.6 | 12.3 | 11.0 | 10.0 | 18.0 | 17.0 | 20.0 | 5.0 | 6.0 |
| Other | 11.6 | 9.6 | 0.3 | 0.0 | 1.0 | 1.0 | 1.0 | 1.0 | 0.0 |
| BMI mean±SD kg·m$^{-2}$ | 28.21±6.18 | 28.93±7.07 | 29.0±6.5 | 29.25±6.54 | 27.60±5.58 | 27.68±5.68 | 28.04±5.58 | 28.4±6.0 | 28.3±6.1 |
| FEV$_1$ % pred mean | 56.1[#] | 56.6[#] | 56.9 | 57.5 | 59.3 | 61.4 | 62.4 | 60[#] | 59[#] |
| Morning PEF mean L·min$^{-1}$ | 233.12 | 230.83 | 241.85 | 242.16 | 255.3 | 268.6 | 277 | - | - |
| FEV$_1$/FVC % | 65 | 66 | 64 | 65 | 63 | 64 | 64 | 68 | 67 |
| FEV$_1$ pre-bronchodilator L | 1.68 | 1.66 | 1.72 | 1.76 | 1.73 | 1.85 | 1.86 | 1.81[#] | 1.90[#] |
| Reversibility % | 27.2 | 25.5 | 25.1 | 27.2 | 27.9[#] | 25.4[#] | 27.4[#] | 22.6[¶] | 26.8[¶] |
| ACQ score[+] | 2.8 | 2.87 | 2.82 | 2.73 | 2.26 | 2.12 | 2.28 | 2.2 | 2.5 |
| Exacerbations in previous year | | | | | | | | | |
| Mean n | **2.8** | **3** | **2.7** | **2.8** | **3.8** | **3.5** | **3.6** | **>3[§]** | **>3[§]** |
| 2 exacerbations % | **63.3** | **60** | **62.9** | **63.5** | **38** | **43** | **47** | **46** | **42** |
| ⩾3 exacerbations % | **36.68** | **40** | **36.81** | **36.49** | **61.86** | **57.07** | **52.88** | **54** | **57** |
| Never smokers % | 82.2 | 80.6 | 78.02[#] | 78.92[#,f] | 74[#,f] | 73[#] | 70[#] | 80[#] | 78[#] |
| OCS use % | **17.8** | **16.2** | **10.71[#]** | **11.08[#,f]** | **27[#,f]** | **25[#]** | **23[#]** | **30.07[#]** | **29.03[#]** |
| EOS ⩾300 cells·μL$^{-1}$ % | **67.08** | **65.6** | **65.6** | **67.02** | **51.5** | **53.4** | **55.4** | **56.2** | **45.16** |
| EOS <300 cells·μL$^{-1}$ % | **32.9** | **34.3** | **34.3** | **32.9** | **47.4** | **45.02** | **43.4** | **43.7** | **54.8** | |
| EOS count mean cells·μL$^{-1}$ | 469.8 | 456.5 | 463.4 | 490.8 | 290[##] | 280[##] | 320[##] | 250[##] | 280[##] |
| IgE concentration IU·mL$^{-1}$ | - | - | - | - | 149.72[##] | 180.32[##] | 150.12[##] | - | - |
| Atopic status % | 61.3 | 56.5 | 61.5 | 63.0 | - | - | - | 51.0 | 52.0 |
| Nasal polyps % | 19.0 | 19.0 | 16.8 | 18.1 | 14.4 | 16.7 | 17.2 | 7.0 | 10.0 |

Data in bold indicate differences across benralizumab and mepolizumab trials. For cells with no data listed, none were available. ICS: inhaled corticosteroid; Q8W: every 8 weeks (first three doses every 4 weeks); SC: subcutaneous; IV: intravenous; BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; PEF: peak expiratory flow; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; OCS: oral corticosteroid; EOS: eosinophil. [#]: data extracted from publications rather than clinical study reports; [¶]: data reported at screening visit; [+]: ACQ-6 in SIROCCO, CALIMA and DREAM, and ACQ-5 in MENSA; [§]: calculated from the reported frequency of exacerbations; [f]: calculated from the reported subgroup data; [##]: geometric means.

## Qualität der Studien:

- ‘‘ Only phase 3 studies were included‘‘

Studienergebnisse:

- After matching adjustment, benralizumab and mepolizumab reduced exacerbations versus placebo by 52% and 49%, respectively (rate ratio [RR] 0.94, 95% CI 0.78–1.13; n=1524) and reduced the rate of exacerbations requiring hospitalisation/emergency department visit by 52% and 52%, respectively (RR 1.00, 95% CI 0.57–1.75; n=1524).
- Benralizumab and mepolizumab similarly improved pre-bronchodilator forced expiratory volume in 1 s at 32 weeks (difference 0.03 L, 95% CI −0.06–0.12; n=1443).
- Benralizumab and reslizumab patient populations were too dissimilar to generate a sufficient effective sample size to produce a reliable estimate for MAIC.

**Anmerkung/Fazit der Autoren**

MAIC is an accepted method for comparing treatments in lieu of head-to-head trials and is less subject to biases than standard ITC. To our knowledge, this is the first MAIC comparing monoclonal antibodies for the treatment of severe asthma. The MAIC demonstrated that, after adjustment for baseline population characteristics that differed across benralizumab versus mepolizumab trials, reductions in asthma exacerbation rates were similar, and improvements in FEV1 were slightly better but not statistically significant at all time points tested. Comparisons with reslizumab could not be performed because of insufficient ESS.

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**Sobieraj DM et al., 2018 [32].**

Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

Siehe auch: **Sobieraj DM et al., 2018 [31].**

**Fragestellung**

To conduct a systematic review and meta-analysis of the effects associated with LAMA vs placebo or vs other controllers as an add-on therapy to inhaled corticosteroids and the use of a LAMA as add-on therapy to inhaled corticosteroids and long-acting β-agonists (LABAs; hereafter referred to as triple therapy) vs inhaled corticosteroids and LABA in patients with uncontrolled, persistent asthma

**Methodik**

Population:

- patients 12 years and older with uncontrolled, persistent asthma

Intervention vs Komparator:

- LAMA vs placebo or vs another controller as an add-on therapy to inhaled corticosteroids or that compared triple therapy vs inhaled corticosteroids and LABA

Endpunkte:

- asthma exacerbations (systemic corticosteroid use, hospitalization, emergency department visits, intensive care or intubation, or as defined by the study)
- mortality (all cause or asthma-specific),
- spirometry (measuredas peak, trough,andarea under the curve [AUC] values for forced expiratory volume in the first second [FEV1], forced vital capacity [FVC], and FEV1/FVC);
- asthma control (Asthma Control Test [ACT] or Asthma Control Questionnaires [ACQs; 5-,6-, or 7-item]), asthma-related quality of life (Asthma Quality of Life Questionnaire [AQLQ], MiniAQLQ,and AQLQ for 12 y and older [AQLQ +12]),
- health care utilization (additional medication use, additional health resource use related to the intervention)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Cochrane databases, and clinical trial registries (earliest date through November 28, 2017).

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of BiasTool forRCTs

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 15 RCTs (n=7122)

Charakteristika der Population:

- All trials enrolled adults 18 years or older with the exception of 2 trials22,28 that were exclusively focused on children and adolescents aged 12 to 17 years.
- Sample sizes for individual studies ranged from 21029 to 1071 participants.18 Eight RCTs compared LAMA vs placebo as add-on therapy to inhaled corticosteroids.17-22,29
- Five of these trials17-19,29 also included a LABA group andwere also used to evaluate the effect of LAMA vs LABA as add-on therapy to inhaled corticosteroids. An additional 3 trials23-25 compared LAMA with another controller, including LABA, doxofylline, and montelukast. Four RCTs evaluated triple therapy vs inhaled corticosteroids and LABA. Trials ranged from15 days19 to 18 months25 in duration.
- Trials included in this systematic review defined uncontrolled asthma based on the ACQ score. However, this is only 1 of many criteria recommended for assessment.1 Likewise, although all patients were considered to have persistent asthma given their use of inhaled corticosteroids maintenance therapy, whether patients had mild, moderate, or severe persistent asthma was left to the reporting of the study authors.

Qualität der Studien:

- Most RCTs had a low risk of bias for random sequence generation (13 [86.7%]), allocation concealment (12 [80%]), incomplete data reporting (14 [93.3%]), selective reporting (12 [80%]), and other types of bias (15 [100%]). Three studies (20%) had a high risk of bias for blinding of participants and personnel and 2 studies (13.3%) for blinding of study outcomes.

**Studienergebnisse:**

LAMA vs Other Controllers as Add-on Therapy to Inhaled Corticosteroids

- Comparing LAMA with LABAas add-on therapy to inhaled corticosteroids, there was no statistically significant association of LAMA with
  - the risk of exacerbation requiring systemic corticosteroid (RR,0.87 [95% CI, 0.53 to 1.42]; RD, 0.00 [95% CI, −0.02 to 0.02])
  - in asthma worsening (RR, 1.00 [95% CI, 0.84 to 1.20]; RD, 0.00 [95% CI, −0.05 to 0.04]), or in the composite outcome including oral steroid use or increase in asthma medication (RR,0.60[95%CI,0.15 to2.42];RD,−0.03 [95%CI,−0.12 to 0.06]).
- No deaths occurred in 3 RCTs and in the fourth trial 3 of 532 participants (0.6%) died in the LAMAgroup, 2 of these deaths were considered asthma-related (0.4%) whereas no deaths occurred in the LABA group.
- LAMA had no significant associations with ACQ scores with 1 trial reportingACQ-6score, 2 trials reportingACQ-7 scores, and 2 trials reportingACQ-7 responder analysis.
- No significant associations were found in measures of spirometry including the most frequently reported lung function measures of FEV1 trough, FEV1% predicted, and FVC trough with LAMA use
- No significant associations were found for AQLQ score

Triple Therapy vs Inhaled Corticosteroids and LABA

- Triple therapy was not significantly associated with the risk of exacerbation requiring systemic corticosteroids vs inhaled corticosteroidsandLABAwhenthe inhaled corticosteroid dose remained the same (RR, 0.84 [95%CI, 0.57 to 1.22];RD, −0.01[95% CI, −0.08 to 0.07]) (Figure 2A)
- it was significantly associated with a lower risk of asthma worsening (RR, 0.78 [95%CI, 0.72 to 0.86];RD, −0.01 [95%CI, −0.22 to 0.01])
- (eFigure 3 in the Supplement) (Table 3).
- Two studies reported exacerbations requiring hospitalization and neither found a significant association at 48 weeks.
- No deaths occurred in the 3 trials included in this analysis, 2 of which were 48 weeks in duration and the third being 12weeks in duration.
- No significant associations with ACQ-7 scores were found with triple therapy vs inhaled corticosteroids and LABA (Figure 2B). No consistent association for triple therapy on ACQ response was mseen across studies (Table 3).
- Triple therapy was associated with improvements in some measures of spirometry, including FEV1 trough (MD, 0.07 [95%CI, 0.01 to 0.14]) and measures of FVC (peak MD, 0.11 [95% CI, 0.05 to 0.17]; trough MD, 0.09 [95% CI, 0.03 to 0.15]; AUC MD, 0.10 [95% CI, 0.04 to 0.17]) (Figure 3A, eFigures 6-10 in the Supplement).
- No significant association with AQLQ score or AQLQ score response was seen with triple therapy.
- Triple therapy was not significantly associated with improvements in rescue medication use vs combined inhaled corticosteroids and LABA therapy (Figure 3B).


1) Referenzen
2) 17.
3) Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. J Allergy Clin Immunol. 2011;128(2):315-322.PubMedGoogle ScholarCrossref
4) 18.
5) Kerstjens HA, Casale TB, Bleecker ER, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. Lancet Respir Med. 2015;3(5):367-376.PubMedGoogle ScholarCrossref
6) 19.
7) Lee LA, Yang S, Kerwin E, Trivedi R, Edwards LD, Pascoe S. The effect of fluticasone furoate/umeclidinium in adult patients with asthma: a randomized, dose-ranging study. Respir Med. 2015;109(1):54-62.PubMedGoogle ScholarCrossref
8) 20.
9) Ohta K, Ichinose M, Tohda Y, et al. Long-term once-daily tiotropium Respimat is well tolerated and maintains efficacy over 52 weeks in patients with symptomatic asthma in Japan: a randomised, placebo-controlled study. PLoS One. 2015;10(4):e0124109.PubMedGoogle ScholarCrossref
10) 21.
11) Paggiaro P, Halpin DM, Buhl R, et al. The effect of tiotropium in symptomatic asthma despite low- to medium-dose inhaled corticosteroids: a randomized controlled trial. J Allergy Clin Immunol Pract. 2016;4(1):104-13.e2.PubMedGoogle ScholarCrossref
12) 22.
13) Hamelmann E, Bateman ED, Vogelberg C, et al. Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial. J Allergy Clin Immunol. 2016;138(2):441-450.e8.PubMedGoogle ScholarCrossref
14) 23.
15) Rajanandh MG, Nageswari AD, Ilango K. Pulmonary function assessment in mild to moderate persistent asthma patients receiving montelukast, doxofylline, and tiotropium with budesonide: a randomized controlled study. Clin Ther. 2014;36(4):526-533.PubMedGoogle ScholarCrossref
16) 24.
17) Rajanandh MG, Nageswari AD, Ilango K. Assessment of montelukast, doxofylline, and tiotropium with budesonide for the treatment of asthma: which is the best among the second-line treatment? a randomized trial. Clin Ther. 2015;37(2):418-426.PubMedGoogle ScholarCrossref
18) 25.
19) Wechsler ME, Yawn BP, Fuhlbrigge AL, et al; BELT Investigators. Anticholinergic vs long-acting β-agonist in combination with inhaled corticosteroids in black adults with asthma: the BELT randomized clinical trial. JAMA. 2015;314(16):1720-1730.ArticlePubMedGoogle ScholarCrossref
20) 26.
21) Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012;367(13):1198-1207.PubMedGoogle ScholarCrossref
22) 27.
23) Wang K, Tian P, Fan Y, Wang Y, Liu C. Assessment of second-line treatments for patients with uncontrolled moderate asthma. Int J Clin Exp Med. 2015;8(10):19476-19480.PubMedGoogle Scholar
24) 28.
25) Hamelmann E, Bernstein JA, Vandewalker M, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. Eur Respir J. 2017;49(1):1601100.PubMedGoogle ScholarCrossref

26) 29.
27) Peters SP, Kunselman SJ, Icitovic N, et al; National Heart, Lung, and Blood Institute Asthma Clinical Research Network. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010;363(18):1715-1726.PubMedGoogle ScholarCrossref

**Anmerkung/Fazit der Autoren**

The association of LAMA with benefit may not be greater than that with LABA. Triple therapy was not associated with a lower risk of exacerbations.

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**Tian BP et al., 2018 [33].**

Efficacy and safety of benralizumab for eosinophilic asthma: A systematic review and meta-analysis of randomized controlled trials

**Fragestellung**

We conducted a systematic review of the literatures to provide a summary of the relevant studies and to assess the efficacy and safety of administering benralizumab on clinical exacerbation, lung function, life quality, and adverse events (AEs) in asthma patients.

**Methodik**

Population:

- Eosinophilic asthma patients

Intervention:

- benralizumab

Komparator:

- placebo

Endpunkte:

- symptom control, lung function or AEs

Recherche/Suchzeitraum:

- PubMed» Embase, and Cochrane Controlled Trials Register databases until May 31, 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 7 articles on 9 RCTs (n=2321 patients)

Charakteristika der Population:

- The subjects were patients with uncontrolled severe or severe asthma in five articles [21, 29-32], asthma exacerbation in one article 119], and eosinophilic asthma in two studies from one article [20].
- Participants received intravenous benralizumab in two studies [20, 2I], and the others received subcutaneous injections.

Qualität der Studien:

Table 2. Risk of bias of the included studies.

| Source | Random sequence generation | Allocation concealment | Blinding of participants & personal | Blinding of outcomes assessment | Incomplete outcome data | Selective reporting |
|---|---|---|---|---|---|---|
| Laviolette (2013) | | | | | | |
| Cohort 1 | Yes | Yes | Yes | Yes | Yes | Yes |
| Cohort 2 | Yes | Yes | Yes | Yes | Yes | Yes |
| Castro (2014) | Yes | Yes | Yes | Yes | Yes | Yes |
| Nowak (2015) | Yes | Unclear | Yes | Yes | Yes | Yes |
| Park (2016) | Yes | Unclear | Yes | Yes | Yes | Yes |
| FitzGerald (2016) | Yes | Yes | Yes | Yes | Yes | Yes |
| Bleecker (2016) | Yes | Yes | Yes | Yes | Yes | Yes |
| Nair (2017) | Yes | Yes | Yes | Yes | Yes | Yes |

**Studienergebnisse:**

Asthma Exacerbations.

- All six studies defined asthma exacerbation based on the unscheduled use of rescue medication.
- Among them, five studies defined asthma exacerbation äs the use or increase dose ofsystemic steroids for at least three days [28-32], and one defined the criterion äs an uncontrolled Symptom after the use ofrescue albuterol or corticosteroids within 2 h, and required a visit to the emergency room [19].

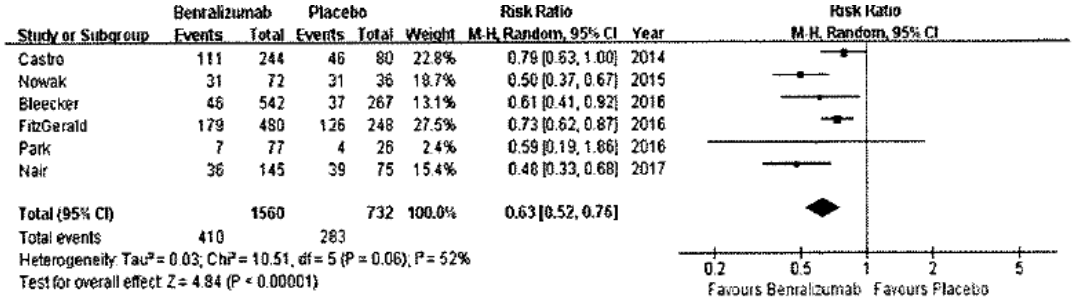


Figure 2. The effect of benralizumab versus placebo on exacerbations.

FEV1% changes from basefine

- Three studies assessed the responsiveness ofFEVl (forced expiratory volume in l sec) % of predicted value
- No significant difFercnce was observed between the benralizumab and placebo groups in changes from baseline of FEV1% of the predicted value (SMD: -0. 10, 95% CI: -0.31 to 0. 10, p = 0. 33). No statistical heterogeneity was observed {I == 0%, p == 0.38).
- Notably, two phase 3 studies (FitzGerald, CALIMA & Bleecker, SIROCCO) suggested that eosinophilic asthma subjects who were treated with benralizumab exhibited significant increases in the pre-bronchodilator FEV1 compared to placebo for patients receiving high-dosage ICSs plus LABA with baseline blood eosinophil counts of at least 300 cells//xL on both the Q4W (30 mg, every 4 weeks) and Q8W (30 mg, every 8 weeks) therapeutic schedules [29,30].
- For patients with baseline eosinophil counts lower than 300 cells/^L, an improvement in FEV1 after benralizumab treatment was noted in Castro et al.s study (100 mg) bu£ not in the trials conducted by FitzGerald elal. And Bleecker et al. [21, 29, 30].
- For the severe asthma, benralizumab treatment significantly increased the FEV1 at 20 weeks but not at aver the entire 28-week trial period versus placebo [31 ].

Asthma Control Questionnaire IACQ) score

- Although several trials described the ACQ scores, the ACQ data of four RCTs with 755 participants (544 in the benralizumab treatment group and 217 in the placebo-control group) could be analyzed together [19, 21, 31, 32].

- The findings from the meta-analysis suggested similar outcomes for the ACQ changes from baseüne between the benralizumab and control groups (SMD: -0. 10, 95% CI: -0.26 to 0. 06, p = 0.22) in eosinophilic asthmatics.
- No significan£ heterogeneity was observed among the studies (I2 = 32%, f = 0.22) (Figure S2).

Asthma control and Quality ofLife Assessment (AQLQ)

- In the eosinophilic asthma subpopulations, life quaäity was assessed using the AQLQ questionnaire [19, 21].
- The results from the pooled statistical analysis from these two studies showed no obvious improvement for the AQLQ score in the benralizumab arm compared to the placebo arm (SMD: -0. 11, 95% CI:-0.32 to 0. 10, p == 0. 3), and statistical heterogeneity was not found (/2 0%, p == 0. 58).
- However, äs reported by three phase three dinical trials [29-31], health-related quality oflife benefited from benralizumab treatment for the 30 mg Q8 schedule but not for the 30 mg Q4W schedule.

Adverse events

- Although seven studies included AEs, six studies reported total AEs that could be analyzed [20, 21, 29-32).
- A total of 1,216 of l ,646 patients suffered AEs in the benralizumab arms compared to 622 ofthe 847 controls in asthmatics who had a peripheral blood eosinophil count of at least 300 cells/ytL, with a RR of 1.00 (95% CI: 0. 95-1.05, p = 0.96).
- Statistical heterogeneity was not observed among the studies (/ ^ 40%, p == 0. 13).


28) 18. Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K, et ai. A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. Interna Arch Aller Immunol. 2016, 169(3);135-145.

29) 19. NowakRM, ParkerJM, SilvermanRA, RoweBH, Smithline H, Khan F, et a!, A randomized trial of benralixumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after aculc aslhma. Am ) Emerg Med. 2015;33(1):14-20.

30) 20. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et ai. Effecls of benralixumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol. 2013, 132(5):1086-1096. el085.

31) 28. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusseile GG, Bardin P, et ai. Reslizumab for inadequateiy controlled asthma with etevated blood eosinophil counts: resuks from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3(5):355-366.

32) 29. Bleecker ER, FitzGerald ;M, Chane?. P, Papi A, Weinstein SF, Barker P, et ai, Ef&cacy and safely of benralizumab for patients with severe asthma uncontrolied with high-dosage inhaled corticosteroids and iong-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 tnal. Lancet. 2016; 388(10056); 2115-2127.

33) 30. FitzGerald )M, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M> et ai. Benratizumab, aii anti-interleukin-5 receptor alpha monoclonal antibody, äs add-on treatment for patients with severe, uncontrolled, eosinophiiic asthma (CALIMA): a randomised, double-blind, placebocontrolled phase 3 trial. Lanccl. 2016; 388(10056); 2128-2141.

34) 31. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et ai. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl) Med. 2017; 376 (25):2448-2458.


**Anmerkung/Fazit der Autoren**

In summary, we found that the use of benralizumab, a humanized monoclonal antibody against IL-5Ro', appears to be safe for controlling exacerbations but may not improve the lung function, ACQ or AQLQ score. These findings provided a foundation for the reasonable use of benralizumab for asthma patients. Additionally, larger samples and more high-quality studies are required to further investigate the efficacy and safety of benralizumab in asthma.

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**Wang FP et al., 2018 [35].**

Anti-interleukin 5 Therapy for Eosinophilic Asthma: a Meta-analysis of Randomized Clinical Trials

**Fragestellung**

We conducted a meta-analysis of randomized controlled trials (RCTs) to assess the overall efficacy and safety of anti-interleukin 5 treatments on eosinophilic asthma.

**Methodik**

Population:

- adults/ adolescents (12 years or older) with a diagnosis of eosinophilic asthma,
- eosinophilic inflammation was shown by one or more criteria at study entry or in the previous year: a sputum eosinophil count ≥2.5 % or the eosinophil/lymphocyte and eosinophil/neutrophil (ELEN; a surrogate blood-based marker of sputum eosinophilia) index was positive, an exhaled nitric oxide concentration (FENO) ≥50 ppb, and an asthma-related peripheral blood eosinophil count ≥300 μL

Intervention:

anti-interleukin 5 therapy at any dose

Komparator:

others

Endpunkte:

lung function, asthma exacerbations, asthma control and quality-of-life scores, and adverse events

Recherche/Suchzeitraum:

PubMed, Embase, the Cochrane Library, and the Chinese Biological Medicine (CBM) database for articles published up to June 2016

Qualitätsbewertung der Studien:

Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

12 RCTs (3340 patients)

Charakteristika der Population:

- The sample sizes ranged from 20 to 621 subjects.
- Of these, five studies used mepolizumab [7–11], four reslizumab [19–22], and three benralizumab [12, 23, 24].
- Treatment duration ranged from 1 day to 52weeks and follow-up ranged from 12 to 52 weeks.
- The mean age of patients was 46.8 years old. […]
- Five studies included severe eosinophilic asthmatics [8–11, 19], three studies included refractory or uncontrolled eosinophilic asthmatics [7, 20, 22], and the remaining studies did not specify asthma severity [12, 21, 23, 24].

Qualität der Studien:

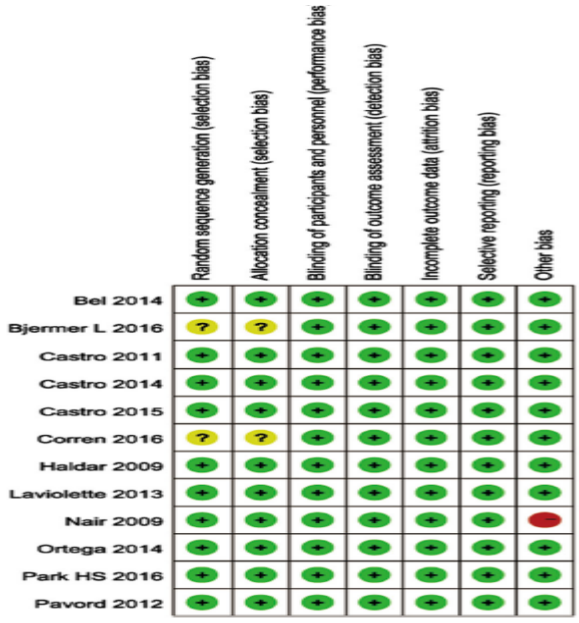


Fig. 8 Risk of bias summary of included studies

**Studienergebnisse:**

FEV1

- Nine trials reported the data on FEV1.
- Mepolizumab was used in four studies showed significant effect on FEV1 (MD = 0.09; 95 % CI, 0.03 to 0.14; P = 0.002).
- Reslizumab was reported in four studies, also could significantly improve FEV1 (MD=0.15, 95 % CI, 0.09 to 0.22; P < 0.001).
- Benralizumab was used in only one study (MD = 0.14, 95 % CI, 0.02 to 0.26; P = 0.02).
- Overall, anti-interleukin 5 treatment were associated with significant improvements in FEV1 (MD = 0.12; 95 % CI, 0.08 to 0.16; P < 0.001) (Fig. 2), with minimal heterogeneity (I2 = 15 %, P = 0.3),

Asthma Quality-of-Life Questionnaire (AQLQ)

- Five trials provided data about AQLQ scores.
- The pooled analysis showed anti-interleukin 5 treatment was associated with a significant increase in AQLQ scores (MD = 0.23; 95 % CI, 0.13–0.34; P < 0.001), with no significant heterogeneity (I2 = 0 %; P = 0.81).
- AQLQ scores improved both in
  - mepolizumab treatment (MD = 0.18; 95 % CI, 0.01–0.36; P = 0.04)
  - reslizumab (MD = 0.27; 95 % CI, 0.13–0.42; P < 0.001).
  - Benralizumab only used in one study (MD = 0.21; 95 % CI, −0.12–0.54; P = 0.22).

Asthma Exacerbations

- Six studies were included.
- Overall, compared with placebo, asthma exacerbations risk was significantly decreased with anti-interleukin 5 treatment (RR = 0.52; 95 % CI, 0.46 to 0.59; P < 0.001), and there was no heterogeneity among studies (I2 = 0 %, P = 0.5).
- When looking at subgroups, mepolizumab (RR = 0.55; 95 % CI, 0.47 to 0.64; P < 0.001) and reslizumab (RR = 0.46; 95 % CI, 0.37 to 0.58; P < 0.001) were also linked to markedly lower asthma exacerbations.

Adverse Events

- Eight studies mentioned adverse events.
- Anti-interleukin 5 treatment was associated with a trend of lower adverse events incidence (RR = 0.93; 95 % CI, 0.89 to 0.97; P = 0.001), with no heterogeneity (I2 = 0 %, P = 0.55).
- In subgroup analysis, however, we found no significant differences in both mepolizumab (RR = 0.96; 95 % CI, 0.9–1.03; P = 0.3) and benralizumab treatment groups (RR = 0.91; 95 % CI, 0.81–1.02; P = 0.09).
- Only treatment with reslizumab was associated with a trend of lower adverse events incidence (RR = 0.92; 95 % CI, 0.87–0.97; P = 0.003)
- The incidence of serious adverse events was low in the antiinterleukin 5 treatment group (1–16 %). Common adverse events were nasopharyngitis, headache, asthma worsening, injection-site reactions and upper respiratory tract infection


35) 7.
36) Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID (2009) Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 360(10):973–984CrossRefPubMedPubMedCentralGoogle Scholar
37) 8.
38) Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, O'Byrne PM (2009) Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 360(10):985–993CrossRefPubMedGoogle Scholar
39) 9.
40) Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID (2014) Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 371(13):1189–1197. doi: 10.1056/NEJMoa1403291 CrossRefPubMedGoogle Scholar
41) 10.
42) Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P, Investigators M (2014) Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 371(13):1198–1207CrossRefPubMedGoogle Scholar
43) 11.
44) Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P (2012) Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet (London, England) 380(9842):651–659. doi: 10.1016/s0140-6736(12)60988-x CrossRefGoogle Scholar
45) 12.
46) Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, Ward CK, Wu Y, Wang B, Khatry DB, Merwe R, Kolbeck R, Molfino NA, Raible DG (2014) Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2(11):878–890. doi: 10.1016/S2213-2600%2814%2970201-2 CrossRefGoogle Scholar
47) 19.
48) Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P (2011) Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 184(10):1125–1132. doi: 10.1164/rccm.201103-0396OC CrossRefPubMedGoogle Scholar
49) 20.
50) Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P (2015) Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 3(5):355–366. doi: 10.1016/S2213-2600(15)00042-9 CrossRefPubMedGoogle Scholar
51) 21.
52) Corren J, Weinstein S, Janka L, Zangrilli J, Garin M (2016) Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest. doi: 10.1016/j.chest.2016.03.018 PubMedCrossRefGoogle Scholar
53) 22.
54) Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M (2016) Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. Chest. doi: 10.1016/j.chest.2016.03.032 PubMedCrossRefGoogle Scholar
55) 23.
56) Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, Busse WW, Wenzel S, Wu Y, Datta V, Kolbeck R, Molfino NA (2013) Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol 132(5):1086–1096.e1085. doi: 10.1016/j.jaci.2013.05.020 CrossRefPubMedPubMedCentralGoogle Scholar
57) 24.
58) Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K (2016) A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. Int Arch Allergy Immunol 169(3):135–145. doi: 10.1159/000444799


**Anmerkung/Fazit der Autoren**

In summary, the current meta-analysis indicated that antiinterleukin 5 treatment was well tolerated and could significantly improve FEV1, quality of life, and reduced asthma exacerbation risk in patients with eosinophilic asthma. Therefore, the humanized anti-interleukin 5 monoclonal antibodies may be effective and safe for eosinophilic asthma. The

results highlight the importance of selection asthma phenotypes could derive clinical benefit from anti-interleukin 5 therapy. Nasopharyngitis was the most frequently reported adverse event in either study involving anti-interleukin 5 treatments, and benralizumab needs more data to support its safety profile.

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**Li J et al., 2017 [22].**

**Fragestellung**

The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: A systematic review and meta-analysis

**Methodik**

Population:

inadequately controlled, eosinophilic asthma

Intervention vs Komparator:

Reslizumab vs. others

Endpunkte:

Asthma exacerbation, a forced expiratory volume in 1 s (FEV1), Asthma Control Questionnaire (ACQ) score, blood eosinophil counts, the proportion of individuals who withdrawn due to adverse event (AE) and Upper respiratory AEs.

Recherche/Suchzeitraum:

Medline, Embase and Cochrane Controlled Trials Register databases until May 2016

Qualitätsbewertung der Studien:

Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

4 articles [16–19], reporting data from a total of 5 RCTs that compared reslizumab with placebo

## Charakteristika der Population:

**Table 1.** Study and patient characteristics.

| Study | Therapy in experimental group | Therapy in control group | Country | Sample size | | Administration method | Duration of treatment | Dosage (mg) | Inclusion population |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Experimental | Control | | | | |
| Castro M 2015 [16] | Reslizumab | Placebo | Asia, Australia, North America, South America, South Africa, and Europe | 245/232 | 244/232 | intravenous | 16 weeks | (3.0 mg/kg) | Patients aged 12–75 with at least one blood eosinophil count of 400 cells per μL or higher and inadequately controlled asthma |
| Castro M 2011 [17] | Reslizumab | Placebo | United States and Canada | 53 | 53 | intravenous | 15 weeks | (3.0 mg/kg) | Patients aged 18–75 with asthma was poorly controlled associated with induced sputum eosinophils of 3% or more |
| Corren J 2016 [18] | Reslizumab | Placebo | United States | 77 | 19 | intravenous | 16 weeks | (3.0 mg/kg) | Patients aged 18–65 years with asthma inadequately controlled |
| Bjermer L 2016 [19] | Reslizumab | Placebo | Sweden | 106 | 105 | Intravenous | 16 weeks | (3.0 mg/kg) | Patients aged 12–75 years with inadequately controlled asthma and had at least one blood eosinophil count of ≥400 cells/μL |

## Qualität der Studien:

**Table 2.** Quality assessment of individual study.

| Study | Allocation sequence generation | Allocation concealment | Blinding | Loss to follow-up | Calculation of sample size | Statistical analysis | ITT analysis | Level of quality |
|---|---|---|---|---|---|---|---|---|
| Castro M 2015 [16] | A | A | A | 7 | YES | analysis of covariance | YES | A |
| Castro M 2011 [17] | A | A | A | 0 | YES | analysis of covariance | YES | A |
| Corren J 2016 [18] | A | A | A | 1 | YES | linear regression analysis | NO | A |
| Bjermer L 2016 [19] | A | A | A | 3 | YES | stratified Cochran-Mantel-Haenszel test | NO | A |

*Note.* A - all quality criteria met (adequate): low risk of bias. B - one or more of the quality criteria only partly met (unclear): moderate risk of bias.
C - one or more criteria not met (inadequate or not used): high risk of bias.

Studienergebnisse:

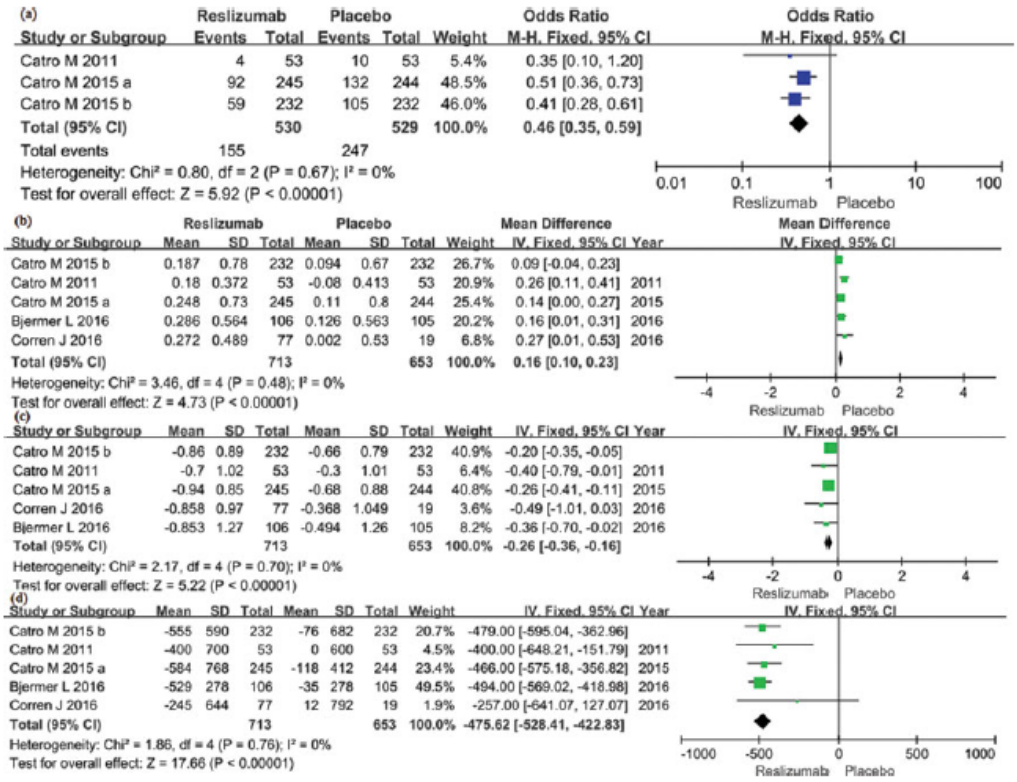


**Figure 3.** Forest plots showing changes in (a) asthma exacerbation, (b) $FEV_1$, (c) ACQ score and (d) blood eosinophil counts in the treatment studies. FEV1: a forced expiratory volume in 1 second; ACQ: Asthma Control Questionnaire; SD: standard deviation, IV: inverse variance; CI: confidence interval, MH: mantel haenszel.

The proportion of individuals who withdrawn due to AE

- Five RCTs included the proportion of individuals who withdrawn due to AE data representing a cohort of 1365 participants (713 in the reslizumab group and 652 in the placebo group)
- The fixed-effects estimate of the OR was 0.86, and the 95% CI was 0.68 to 1.10 (p= 0.24). The result suggests that reslizumab and placebo were similar in terms of the incidence of withdrawn due to AE.

Upper respiratory AEs

- Five RCTs included the upper respiratory AEs data representing a cohort of 1365 participants (713 in the reslizumab group and 652 in the placebo group).
- The heterogeneity test showed P = 0.94, so we adopted the fixed-effects model (Figure 4), the OR was 0.67, and the 95% CI was 0.38 to 1.17 (p = 0.16).
- The result suggests that reslizumab and placebo were similar in terms of the incidence of upper respiratory AEs.

16. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3(5):355–66.
17. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am Respir Crit Care Med 2011;184(10):1125-32.
18. Corren J,Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest. in press.
19. Bjermer L, Lemiere C,Maspero J,Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: A randomized phase 3 study. Chest. in press.

**Anmerkung/Fazit der Autoren**

This meta-analysis indicates reslizumab to be an effective and safe treatment for eosinophilic asthma.

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**Rodrigo GJ et al., 2017 [28].**

Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review

**Fragestellung**

The aim of this systematic review was to perform the first assessment of the efficacy, safety, and tolerability of tiotropium delivered through Respimat® inhaler in children aged 6-11 years with symptomatic asthma.

**Methodik**

Population:

- school-agechildren (6-11 years old) with symptomatic stable asthma receiving maintenance therapy with ICS alone or ICS plus one or more controller medications (eg, LABAs or leukotriene receptor antagonists [LTRAs])

Intervention:

- Tiotropium

Komparator:

- Placebo

Endpunkte:

- pulmonary function ([FEV1] within 3 h after dosing [FEV1 (0-3 h)] or trough FEV1 measured at the end of the dosing interval), rescue medication use (puffs/day/ night), asthma control (Asthma Control Questionnaire 7 [ACQ-7] total score,13) or ACQ-7 responder rate, asthma, and withdrawals (total and due to adverse events [AEs]), and
- safety (AEs and serious AEs [SAEs]) as secondary outcomes.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, CINAHL, SCOPUS, and the Cochrane Controlled Trials Register (CENTRAL) (until April 2017)

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 3 RCTs including around 900 Patients
- included RCTs were all three arm trials with two different doses of tiotropium compared with placebo (OD tiotropium 2.5 and 5 µg) and were therefore included in the treated set for pooled efficacy and safety analysis.

| Study | Design | Duration (weeks) | Randomized patients, n (% female) | Mean Age (range), years | Mean baseline $FEV_1$, %predicted | Concomitant medications | Primary outcome | Comparisons of interest |
|---|---|---|---|---|---|---|---|---|
| Vogelberg[20] | Phase II, R, DB, PC, incomplete CO | 4 | 101 (32) | 8.8 (6-11) | 80 | ICS (medium dose) (100% patients) LTRA (46%) | FEV1 peak | OD TIO 5 µg Respimat® vs PL, OD TIO 2.5 µg Respimat® vs PL |
| Szefler[21] | Phase III, R, DB, PC, PG | 12 | 401 (30) | 9.0 (6-11) | 80 | ICS (high dose) (100% patients) LABA (78% patients) LTRA (85%) | FEV1 peak | OD TIO 5 µg Respimat® vs PL, OD TIO 2.5 µg Respimat® vs PL |
| NCT01634139[22] | Phase III, R, DB, PC, PG | 48 | 401 (34) | 8.9 (6-11) | 78 | ICS (medium dose) (100% patients) LABA or LTRA | FEV1 peak | OD TIO 5 µg Respimat® vs PL, OD TIO 2.5 µg Respimat® vs PL |

CO, crossover; ICS, inhaled corticosteroids; DB, double-blinded; $FEV_1$, forced volume in the first second; LTRA, leukotriene receptor antagonist; OD, once daily; PC, placebo-controlled; PG, parallel group; PL, placebo; R, randomized; TIO, tiotropium; LABA, long-acting beta-agonist.

Charakteristika der Population:

- The three studies included moderate-to- severe asthmatics receiving OD tiotropium added to ICS (medium or high dose) plus one or two controllers (LABAs or LTRAs) vs placebo

Qualität der Studien:

**TABLE 2** Risk of bias of the eligible studies

| Source | Sequence generation | Allocation concealment | Data collection blinded | Complete outcome data | Selective outcome reporting |
|---|---|---|---|---|---|
| Vogelberg[20] | Low risk | Low risk | Low risk | Low risk | Low risk |
| Szefler[21] | Low risk | Low risk | Low risk | Low risk | Low risk |
| NCT01634139[22] | Low risk | Unclear risk | Low risk | Low risk | Low risk |

- Two of three studies had low risk of bias across the five domains of the Cochrane instrument

Studienergebnisse:

- FEV1: The analysis of data indicated that tiotropium was associated with significant improvements in FEV1 peak (mean change from baseline) by 102 mL (P<.0001) and FEV1 trough by 82 mL (P<.0001) compared with placebo
- ACQ-7: Tiotropium significantly increase the rate of ACQ-7 responders (defined as a change from trial baseline ≥0.5 points) compared with placebo (82.2% vs 75.4%, NNTB=15, P=.04)
- Asthma exazerbations: tiotropium treatment was associated with a significantly decreased risk of exacerbation (number of patients with at least one episode of asthma exacerbation) in comparison with placebo (29.1% vs 39.8%, with a NNTB of 10, P=.002).
- Finally, there were no significant differences in rescue medication use (day and night-time), withdrawals, withdrawals due to AEs, AEs (43.3% vs 47.5%), and SAEs (1.4% vs 2.3%). None of the three studies showed an increase in the rate of AEs or SAEs compared to placebo. Again, both doses of tiotropium resulted in equivalent effects on different outcomes.

**Anmerkung/Fazit der Autoren**

In conclusion, this systematic review suggests that OD tiotropium Respimat® is efficacious and well tolerated as an add-on to ICS plus one or more controller medications for school-age children with symptomatic asthma. Major benefits are concentrated in lung function, and available data suggest a possible advantage of the OD 5 µg dose over OD 2.5 µg.

**Wang FP et al., 2016 [34].**

Efficacy and Safety of Anti-Interleukin- Therapy in Patients with Asthma A Systematic Review and Meta-Analysis

**Fragestellung**

We conducted a meta-analysis of randomized, controlled trials (RCTs) to assess whether anti-IL-5 monoclonal antibodies therapy is safe and effective in patients (more than 12 years) with asthma.

**Methodik**

Population:

adults/adolescents (12 years) with diagnosis of asthma

Intervention:

anti-interleukin-5 monoclonal antibody therapy at any dose

Komparator:

placebo-controlled or standard therapy

Endpunkte:

Primary outcomes: lung function [first second forced expiratory volume (FEV1), FEV1% of predicted value, peak expiratory flow (PEF), histamine PC20], the Asthma Quality of Life Questionnaire (AQLQ) scores, and asthma exacerbation

Secondary outcomes: adverse events and efficacy outcomes [blood eosinophil count, sputum eosinophils (%), short-acting β-agonist (SABA) rescue use].

Recherche/Suchzeitraum:

PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles published from 1946 to October 2016

Qualitätsbewertung der Studien:

Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

20 RCTs

Charakteristika der Population:

Sample sizes ranged from 19 to 1306 subjects.

Nine, five, and six trials used mepolizumab [18-26], reslizumab [27-31], and benralizumab [32-37], respectively.

Treatment duration ranged from 1 day to 56 weeks and follow-up ranged from 12 to 56 weeks.

Nine studies involved patients with severe/refractory asthma [22-28, 36, 37]; four studies included patients with mild, mild to moderate, or moderate asthma [18-21]; the remaining studies did not specify asthma severity [29±35]. Corren et al. [30] and Castro et al. [33] studied patients with noneosinophilic asthma.

Qualität der Studien:

Most trials had low risk of bias across the six domains. The allocation sequence was adequately generated and concealed in fourteen trials, [22±29, 32±37]. The randomization techniques included computer generated randomization codes and minimization. The remaining trials did not report the method used, and we were unable to obtain this information. All but one study was described as double-blinded [20]. Almost all RCTs reported complete outcome data, only one trial reported on attrition insufficiently [27].

Studienergebnisse:

Subgroup analysis of asthma exacerbation and FEV1 in RCTs.

| Stratification | asthma exacerbation | | | | $FEV_1$ | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of Patients (Studies) | RR(95% CI) | *P* Value | $I^2$, % | No. of Patients (Studies) | MD(95% CI) | *P* Value | $I^2$, % |
| **Subgroup analysis** | | | | | | | | |
| **Effects model** | | | | | | | | |
| random-effects model | 6072(13) | 0.66(0.59–0.73) | <0.001 | 51 | 6725(14) | 0.09(0.06–0.12) | <0.001 | 10 |
| fixed effects model | 6072(13) | 0.63(0.59–0.67) | <0.001 | 51 | 6725(14) | 0.09(0.06–0.12) | <0.001 | 10 |
| **Asthma severity** | | | | | | | | |
| mild or moderate asthma | 362(1) | 0.85(0.51–1.43) | 0.55 | ... | 365(2) | -0.02(-0.2–0.15) | 0.8 | 0 |
| severe asthma | 4090(8) | 0.59(0.53–0.65) | <0.001 | 23 | 3901(7) | 0.11(0.07–0.14) | <0.001 | 35 |
| mixed asthma | 1620(4) | 0.73(0.65–0.82) | <0.001 | 18 | 2459(5) | 0.08(0.04–0.12) | <0.001 | 0 |

59) Studies including patients with severe/referactory asthma


60) **22.** Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009; 360(10):973±84. doi: 10.1056/ NEJMoa0808991

61) **23.** Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009; 360(10):985±93. doi: 10. 1056/NEJMoa0805435

62) **24.** Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. The Lancet. 2012; 380 (9842):651±9. doi: 10.1016/S0140-6736(12)60988-X

63) **25.** Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoidsparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014; 371(13):1189±97. doi: 10. 1056/NEJMoa1403291

64) **26.** Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371(13):1198±207. doi: 10.1056/ NEJMoa1403290 PMID: 25199059.

65) **27.** Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. Am J Respir Crit Care Med. 2003; 167(12):1655±9. Epub 2003/03/22. doi: 10.1164/rccm.200206-525OC PMID: 12649124.

66) **28.** Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011; 184 (10):1125±32. Epub 2011/08/20. doi: 10.1164/rccm.201103-0396OC PMID: 21852542.

67) Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety o benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroid Anti-Interleukin-5 Therapy for Asthma and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3

68) trial. Lancet. 2016. doi: 10.1016/S0140-6736(16)31324-1 PMID: 27609408.

69) **37.** FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin- 5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016. doi: 10.1016/S0140-6736(16)31322-8 PMID: 27609406.


**Anmerkung/Fazit der Autoren**

Our study indicates that anti-interleukin-5 therapy is safe and may reduce asthma exacerbation risk, slightly improve FEV1, FEV1%, and quality of life; and decrease blood and sputum eosinophil levels, although PEF, PC20 were not improved or SABA rescue use reduced. Antiinterleukin-5 therapy may therefore be beneficial as adjunct asthma therapy, particularly in severe and eosinophilic asthma.

## 3.4 Leitlinien

**Bundesärztekammer (BÄK), 2020 [6].**

Leitlinienreport. 2020 [7].

Nationale VersorgungsLeitlinie 4. Auflage, 2020 Asthma – Langfassung

**Leitlinienorganisation/Fragestellung**

Sicherung der bestmöglichen Lebensqualität und sozialen Teilhabe für Betroffene durch eine individuell optimierte medikamentöse und nicht-medikamentöse Therapie unter Berücksichtigung von Komorbiditäten mit dem Ziel des Erhalts der bestmöglichen Lungenfunktion, der Minimierung von Nebenwirkungen und Langzeitfolgen und der Förderung der Adhärenz

**Methodik**

Grundlage der Leitlinie

Diese Leitlinie wurde am 7. September 2020 durch die Träger des NVL-Programms verabschiedet und ist bis zur nächsten Überarbeitung bzw. spätestens bis 7. September 2025 gültig.

Nationale VersorgungsLeitlinien erfüllen alle Anforderungen an S3-Leitlinien gemäß AWMF-Regelwerk.

Dazu gehören ein multidisziplinäres Gremium, in dem alle an der Versorgung beteiligten Fachgruppen und -disziplinen vertreten sind, ein transparentes Management von Interessenkonflikten, die systematische Recherche und Bewertung der Evidenz zu allen relevanten Fragestellungen sowie ein strukturierter, formaler Konsensprozess. Detaillierte Angaben zu dem methodischen Vorgehen sowie zu der Organisation des NVL-Programms sind im Leitlinienreport zur 4. Auflage der NVL Asthma beschrieben [7].

Leitliniengruppe: Primäre Ansprechpartner bei der Benennung von Leitlinienautoren sind die Mitgliedsgesellschaften der AWMF sowie die Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ). Die an der Versorgung von Patienten mit Asthma maßgeblich beteiligten Fachgesellschaften wurden durch das ÄZQ angesprochen und um Entsendung von Mandatsträgern in die Leitliniengruppe gebeten. Die Nominierung liegt im Verantwortungsbereich der angesprochenen medizinischen wissenschaftlichen Fachgesellschaften. Die Leitliniengruppe wurde multidisziplinär zusammengesetzt.

Strukturierter und detailliert beschriebener Konsentierungsprozess. Nominaler Gruppenprozess bei der Konsensuskonferenz.

Für die Fälle, in denen Interessenkonflikte durch bezahlte Berater- oder Gutachtertätigkeit, bezahlte Vortragstätigkeit, Geschäftsanteile und Aktien oder Drittmittel durch die Industrie bezüglich eines Themas vorlagen, wurden Enthaltungen beschlossen

Recherche/Suchzeitraum:

Grundlegend

- Reviews: 18.08.2016
- Cochrane Reviews bis 2012
- Leitlinien: bis 29.01.2016

Eine zusätzliche systematische Recherche erfolgte:

- bei weit zurückliegenden Suchzeiträumen in den identifizierten systematischen Übersichtsarbeiten (z. B. komplementäre und alternative Therapie);

- bei Fehlen thematisch passender Übersichtsarbeiten von IQWiG, NICE, AHRQ und Cochrane (z. B. Sicherheits-aspekte von Sedativa bei einem Asthmaanfall);
- bei Fehlen wichtiger Aspekte in den primär identifizierten Übersichtsarbeiten (z. B. Wirksamkeit und Sicherheit von Terbutalin s.c und Reproterol i.v.);
- bei nicht-etablierten Therapieverfahren mit hoher Dynamik (z. B. monoklonale Antikörper), um einen möglichst aktuellen Erkenntnisstand wiederzugeben
  - o Wirksamkeit und Sicherheit von Anti-IL-5-Antikörpern bei Patienten mit Asthma 15.05.2019
  - o Wirksamkeit und Sicherheit von Benralizumab 26.04.2018
  - o Wirksamkeit und Sicherheit von Dupilumab bei Patienten mit Asthma 29.04.2019

LoE

- Die methodische Bewertung der recherchierten Übersichtsarbeiten erfolgte mit dem AMSTAR-2-Tool.
- Die methodische Bewertung der randomisierten kontrollierten Studien erfolgte in Anlehnung an das Cochrane Risk of Bias Tool
- Die Bewertung von nicht randomisierten Studien erfolgte entsprechend den Empfehlungen zur „Bewertung des Biasrisikos (Risiko systematischer Fehler) in klinischen Studien: ein Manual für die Leitlinienerstellung“

GoR

Tabelle 1: Einstufung von Leitlinien-Empfehlungen in Empfehlungsgrade (Grades of Recommendation) [4]

| Empfehlungsgrad | Beschreibung | Formulierung | Symbol |
|---|---|---|---|
| A | Starke Positiv-Empfehlung | soll | ⇑⇑ |
| B | Abgeschwächte Positiv-Empfehlung | sollte | ⇑ |
| 0 | Offene Empfehlung | kann | ⇔ |
| B | Abgeschwächte Negativ-Empfehlung | sollte nicht | ⇓ |
| A | Starke Negativ-Empfehlung | soll nicht | ⇓⇓ |

**Empfehlungen**

Definition schweres Asthma

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **1-1 \| Erwachsene**<br>Bei Erwachsenen liegt ein schweres Asthma vor, wenn unter Therapie mit inhalativen Corticosteroiden (ICS) in Höchstdosis (siehe Tabelle 6) und mindestens einem zusätzlichen Langzeitmedikament (Langwirkendes Beta-2-Sympathomimetikum oder Montelukast) oder oralen Corticosteroiden (OCS) > 6 Monate/Jahr mindestens einer der folgenden Punkte zutrifft bzw. bei Reduktion der Therapie zutreffen würde:<br>• Atemwegsobstruktion: FEV1 < 80% des Sollwertes (FEV1/FVC < LLN);<br>• häufige Exazerbationen: ≥ 2 corticoidsteroidpflichtige Exazerbationen in den letzten 12 Monaten;<br>• schwere Exazerbationen: ≥ 1 Exazerbation mit stationärer Behandlung oder Beatmung in den letzten 12 Monaten;<br>• teilweise kontrolliertes oder unkontrolliertes Asthma (siehe Abbildung 2). | **Statement** |

**Stufenschema**

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-2**<br>Patienten mit diagnostiziertem Asthma sollen gemäß Stufenschema (siehe Abbildung 4 und Abbildung 5) behandelt werden. | ⇑⇑ |

### 4.5.1 Therapieintensivierung

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-8**<br>Falls keine Asthmakontrolle mit der Therapie erzielt wird, sollen zunächst verschiedene Aspekte berücksichtigt werden, bevor die Therapie intensiviert wird:<br>• Überprüfung der Inhalationstechnik (Vorführung durch den Patienten);<br>• Überprüfung des Schulungsbedarfes;<br>• Kontrolle der Therapieadhärenz;<br>• Allergie- und Umweltkontrolle;<br>• Beachtung von Komorbiditäten;<br>• Beachtung aggravierender Faktoren;<br>• Überprüfung der Diagnose Asthma.<br>(siehe Abbildung 6) | ⇑⇑ |
| **4-9**<br>Bei unkontrolliertem Asthma soll eine Intensivierung der Therapie den Stufenschemata folgend empfohlen werden. | ⇑⇑ |
| **4-10**<br>Bei teilweise kontrolliertem Asthma sollte eine Intensivierung der Therapie den Stufenschemata folgend erwogen werden. | ⇑ |
| **4-11**<br>Nach einer Intensivierung der Langzeittherapie gemäß Stufenschemata soll die Asthmakontrolle innerhalb von drei Monaten überprüft werden. | ⇑⇑ |

**Abbildung 4: Medikamentöses Stufenschema | ERWACHSENE**

| Stufe 1 | Stufe 2 | Stufe 3 | Stufe 4 | Stufe 5 |
|---|---|---|---|---|
| Bedarfstherapie:<br>Fixkombination aus ICS niedrigdosiert + Formoterol[1]<br>oder<br>SABA | Langzeittherapie mit ICS niedrigdosiert + Bedarfstherapie mit SABA<br>oder<br>ausschließlich Bedarfstherapie mit Fixkombination aus ICS niedrigdosiert + Formoterol[1] | Langzeittherapie:<br>ICS niedrigdosiert + LABA (bevorzugt)<br>oder<br>ICS mitteldosiert | Langzeittherapie:<br>ICS mittel- bis hochdosiert + LABA (bevorzugt)<br>oder<br>ICS mittel- bis hochdosiert + LABA + LAMA[2] | Langzeittherapie:<br>ICS in Höchstdosis + LABA + LAMA[2]<br>Vorstellung bei einem in der Behandlung von schwerem Asthma erfahrenen Pneumologen<br>und<br>Anti-IgE- oder Anti-IL-5-(R)- oder Anti-IL-4-R-Antikörper |
| | | *Alternativen zur Langzeittherapie in begründeten Fällen:* | | |
| | | ICS niedrigdosiert + LAMA[2]<br>oder<br>ICS niedrigdosiert + LTRA | ICS mittel- bis hochdosiert + LABA + LTRA<br>oder<br>ICS mittel- bis hochdosiert + LAMA[2] | OCS (zusätzlich oder alternativ) |
| *Alternative in begründeten Fällen:*<br>Langzeittherapie mit ICS niedrigdosiert + Bedarfstherapie mit SABA | *Alternative in begründeten Fällen:*<br>Langzeittherapie mit LTRA + Bedarfstherapie mit SABA | Zusätzlich Bedarfstherapie:<br>SABA<br>oder<br>Fixkombination aus ICS + Formoterol, wenn diese auch die Langzeittherapie darstellt | | |
| Asthmaschulung, Allergie-/Umweltkontrolle, Beachtung von Komorbiditäten | | | | |
| Spezifische Immuntherapie (bei gegebener Indikation) | | | | |

Im Stufenschema werden zur besseren Übersicht übergeordnete Arzneimittelkategorien und keine einzelnen Präparate genannt. Nicht alle Präparate und Kombinationen sind für die jeweilige Indikation zugelassen (siehe Fachinformationen), teilweise handelt es sich um einen Off-Label-Use (siehe Kapitel 4.2 Hinweis zum Off-Label-Use)

[1] Fixkombination (ICS niedrigdosiert + Formoterol) bedarfsorientiert in Stufe 1 und 2 nicht zugelassen. (Stand: August 2020)

[2] aus der Gruppe der LAMA ist Tiotropium für die Behandlung des Asthmas zugelassen (Stand: August 2020)

ICS: Inhalative Corticosteroide, IgE: Immunglobulin E, IL: Interleukin, LABA: Langwirkende Beta-2-Sympathomimetika, LAMA: Langwirkende Anticholinergika, LTRA: Leukotrienrezeptorantagonisten, OCS: Orale Corticosteroide, R: Rezeptor, SABA: Kurzwirkende Beta-2-Sympathomimetika

### 4.8.4 Stufe 4 | ERWACHSENE

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-29 | ERWACHSENE**<br>Bei Erwachsenen soll in Stufe 4 bevorzugt die Kombination aus einem ICS im mittleren oder hohen Dosisbereich und einem LABA angewandt werden. | ⇑⇑ |

Die Leitliniengruppe sieht eine additive Behandlung mit LAMA zu einer bereits bestehenden Medikation aus ICS in mittlerer oder hoher Dosis plus LABA als Therapiealternative für Patienten mit Asthma in Stufe 4. Wichtig ist, dass in der Stufe 4 alle verfügbaren Therapieoptionen ausgereizt werden, bevor die Therapie zur Stufe 5 eskaliert wird. Dabei entscheidet der Arzt individuell mit dem Patienten (siehe Kapitel 3.2 Gemeinsame Entscheidungsfindung), ob er zunächst die ICS-Dosis erhöht oder zu einer Dreifachkombination übergeht.

**Alternative in begründeten Fällen in Stufe 4 bei Erwachsenen**

In begründeten Fällen, insbesondere, wenn Kontraindikationen gegen die bisher verwendeten Medikamente vorliegen oder unerwünschte Wirkungen bei deren Anwendung auftreten, empfiehlt die Leitliniengruppe auch die Kombination aus ICS mittel- bis hochdosiert, LABA und LTRA oder ICS mittel- bis hochdosiert und LAMA. In der systematischen Recherche wurden keine Metaanalysen identifiziert, die die Wirksamkeit und Sicherheit der Dreifachkombination evaluierten.

Die Ergebnisse der systematischen Übersichtsarbeiten, die die Kombinationstherapien von ICS plus LAMA im Vergleich zu einer höheren ICS-Dosis [99] oder im Vergleich zur Kombination aus ICS plus LABA [67] untersuchten, sind bereits im Hintergrundtext der Therapiealternativen in begründeten Fällen der Stufe 3 zitiert (siehe Kapitel 4.8.2 Stufe 3 | ERWACHSENE). Diese können auch hier nur indirekt herangezogen werden, weil für die Vergleiche keine Subgruppenanalysen für die verschiedenen ICS-Dosierungen vorgenommen wurden.

### 4.8.6 Stufe 5 | ERWACHSENE

| Empfehlungen/Statements | Empfehlungsgrad |
|---|---|
| **4-33 \| ERWACHSENE**<br>Die Indikation zur Therapie mit monoklonalen Antikörpern sollte erst gestellt werden, wenn selbst unter dreimonatiger maximaler inhalativer Kombinationstherapie mit einem ICS in Höchstdosis, einem LABA und einem LAMA (Tiotropium) keine Asthmakontrolle erreicht wird. | ⇑ |

Die allgemeinen Prinzipien der Intensivierung der Therapie sind in den Empfehlungen 4-8 bis 4-11 dargestellt. Darüber hinaus weist die Leitliniengruppe darauf hin, dass die Therapie mit monoklonalen Antikörpern in Stufe 5 sehr aufwändig und über einen längeren Zeitraum mit hohen Kosten verbunden ist. Vor diesem Hintergrund erachtet sie es auf Basis eines Expertenkonsenses als notwendig, dass die in der Empfehlung 4-33 genannte Dreifachkombination mit ICS höchstdosiert (siehe Tabelle 6) über drei Monate evaluiert wird, bevor die Therapie mit monoklonalen Antikörpern initiiert wird. Der Eindruck aus der Versorgungssituation ist, dass die Kombination ICS plus LABA plus LAMA vor einer weiteren Therapieeskalation häufig nicht ausgeschöpft wird, da es sich um ein eher neueres Therapiekonzept handelt.

#### 4.8.6.2 Omalizumab

| Empfehlungen/Statements | Empfehlungsgrad |
|---|---|
| **4-34 \| ERWACHSENE**<br>Ein Therapieversuch mit Omalizumab für mindestens vier Monate soll bei Erwachsenen in Stufe 5 empfohlen werden, wenn folgende Kriterien vorliegen:<br>• schweres IgE-vermitteltes allergisches Asthma und<br>• positiver Hauttest oder in-vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen und<br>• IgE-Serumkonzentration unter Berücksichtigung des Körpergewichts im therapierbaren Bereich und<br>• erfolgte Eliminierung vermeidbarer Allergenexpositionen. | ⇑⇑ |

Die Leitliniengruppe empfiehlt einen Therapieversuch mit Omalizumab, wenn die in Empfehlung 4-34 genannten eng umschriebenen Kriterien erfüllt sind. Entscheidend ist, vor Initiierung der Therapie alle vermeidbaren Allergene zu eliminieren (siehe Kapitel 6.8

Verminderung der Allergenexposition) und die Möglichkeiten der Tabakentwöh-nung vor Therapiebeginn auszuschöpfen

#### 4.8.6.3 Mepolizumab, Reslizumab und Benralizumab

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-35 \| ERWACHSENE**<br>Ein Therapieversuch mit Mepolizumab, Reslizumab oder Benralizumab für mindestens vier Monate sollte bei Erwachsenen in Stufe 5 erwogen werden, wenn folgende Kriterien vorliegen:<br>• schweres eosinophiles Asthma und<br>• zweimaliger Nachweis einer Konzentration von > 300 Eosinophilen pro µl Blut außerhalb von Exazerbationen in den vergangenen zwei Jahren. | ⇑ |

Basierend auf diesen Daten empfehlen die Autoren einen Therapieversuch mit den Wirkstoffen Mepolizumab, Reslizumab und Benralizumab für eine eng definierte Patientengruppe (siehe Empfehlung 4-35). Studien, die die Wirksamkeit und Sicherheit der monoklonalen Antikörper untereinander vergleichen, wurden nicht identifiziert. Die Patientengruppe ergibt sich durch die Einschlusskriterien und Ergebnisse der zitierten Zulassungsstudien. Die Behandlung mit Anti-IL-5-(R)-Antikörpern ermöglicht aus Sicht der Autoren, die Therapie mit OCS zu reduzieren und ggf. zu beenden. Die Autoren der Leitlinie sprechen eine abgeschwächte Empfehlung aus, da zur Beurteilung der Langzeitverträglichkeit der Anti-IL-5-(R)-Antikörper zu wenige Daten vorliegen.

#### 4.8.6.4 Dupilumab

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-36 \| ERWACHSENE**<br>Ein Therapieversuch mit Dupilumab für mindestens vier Monate sollte bei Erwachsenen in Stufe 5 erwogen werden, wenn folgende Kriterien vorliegen:<br>• schweres eosinophiles Asthma und zweimaliger Nachweis einer Konzentration von > 300 Eosinophilen pro µl Blut außerhalb von Exazerbationen in den vergangenen zwei Jahren oder<br>• zweimaliger Nachweis einer erhöhten FeNO-Konzentration (> 25 ppb). | ⇑ |

Wegen der postivien Effekte auf die Rate schwerer Exazerbationen und der Möglichkeit der Reduktion von OCS sieht die Leitliniengruppe eine Option für einen Therapieversuch mit Dupilumab in Stufe 5 für die in Empfehlung 4-36 eng umschriebene Patientengruppe, die nach Ausschöpfen der inhalativen Therapie keine Asthmakontrolle erreichte. Gleichzeitig stellt sie fest, dass in den Studien keine Vergleiche zu den anderen – schon länger zugelassenen – monoklonalen Antikörpern erfolgten, wodurch eine vergleichende Beurteilung erschwert ist. Die Leitlinienautoren weisen darauf hin, dass die Ergebnisse der FeNO-Messung und der Bestimmung von Eosinophilen im Blut durch die Gabe von systemischen Corticosteroiden beeinflusst sein kann.

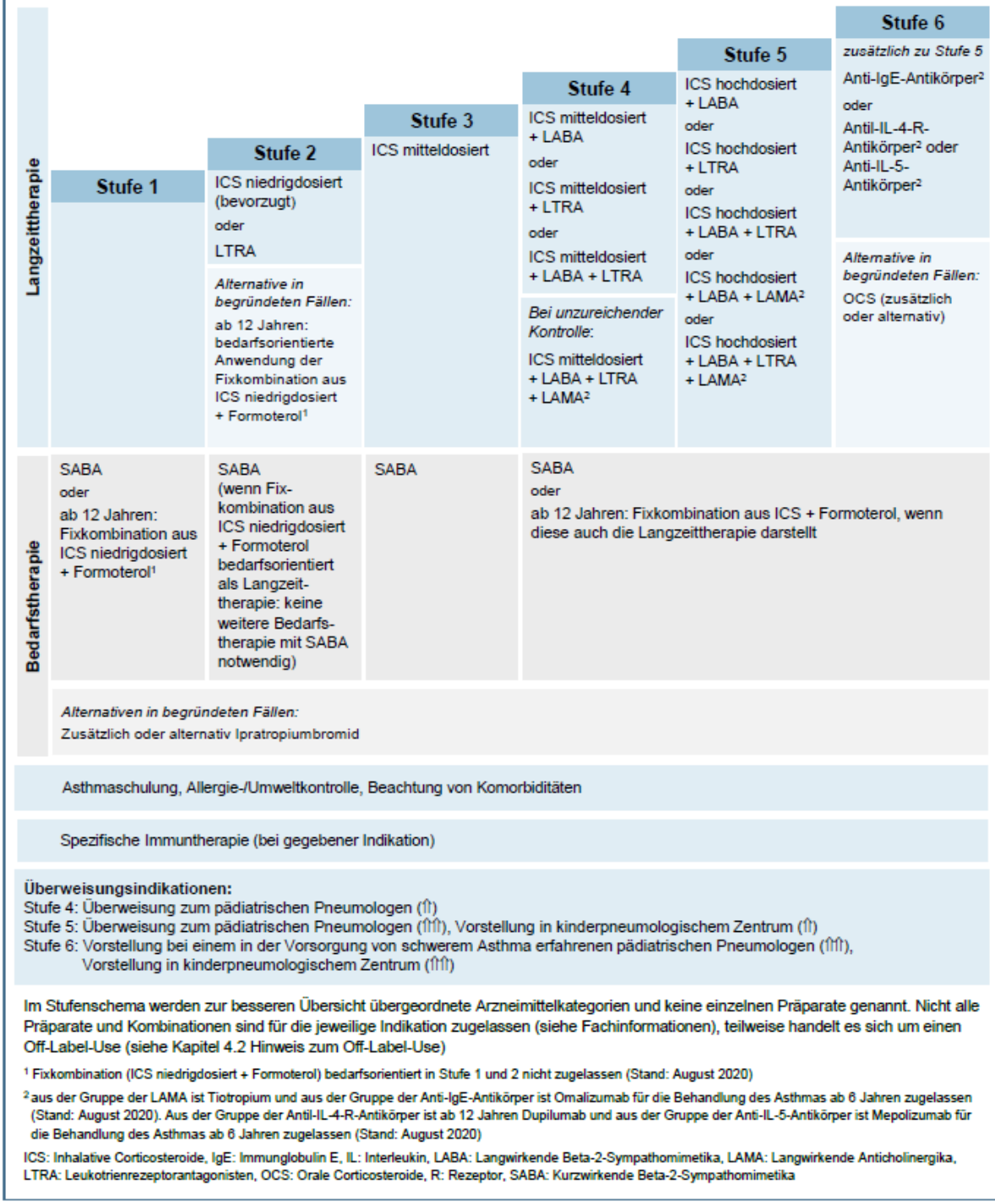
#### 4.8.6.6 Orale Corticosteroide

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-40 \| ERWACHSENE**<br>Die Langzeittherapie mit systemischen Corticosteroiden soll bei Erwachsenen in Stufe 5 wegen der Gefahr schwerer Nebenwirkungen nicht empfohlen werden, es sei denn, die Asthmakontrolle ist trotz des kombinierten Einsatzes der verschiedenen Therapieoptionen der vorherigen Stufe sowie zusätzlich monoklonaler Antikörper (sofern indiziert und wirksam) unzureichend. | ⇓⇓ |

Systemische Corticosteroide werden seit langem in der Praxis eingesetzt. Neue Erkenntnisse zu Wirksamkeit und Sicherheit wurden in der systematischen Recherche nicht identifiziert.

Sie werden in der geringstmöglichen Dosis empfohlen, um das Risiko für unerwünschte Wirkungen zu minimieren. Bei erwachsenen Patienten sind insbesondere das Risiko für eine Blutdrucksteigerung und die Entwicklung eines Diabetes mellitus sowie einer Osteoporose zu beachten. Auch wenn zum aktuellen Zeitpunkt nur begrenzte Langzeiterhebungen für die Sicherheit der verschiedenen monoklonalen Antikörper vorliegen (siehe Empfehlungen 4-34, 4-35 bis 4-39), werden die unerwünschten Langzeitwirkungen von systemischen Corticosteroiden als so erheblich eingeschätzt, dass die Leitliniengruppe OCS als nachrangige Therapieoption für die Langzeittherapie in Stufe 5 einordnen.

**Abbildung 5: Medikamentöses Stufenschema | KINDER UND JUGENDLICHE**




### 4.8.5 Stufe 4 | KINDER UND JUGENDLICHE

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-30 | KINDER UND JUGENDLICHE**<br>Bei Kindern und Jugendlichen soll in Stufe 4 eine Kombinationstherapie aus einem mitteldosierten ICS mit einem LABA oder/und einem LTRA empfohlen werden. | ⇑⇑ |

### 4.8.7 Stufe 5 | KINDER UND JUGENDLICHE

Die Autoren der NVL Asthma entschließen sich, eine zusätzliche Stufe in das Stufenschema für Kinder und Jugendliche einzufügen, die zwischen dem Einsatz von mittel- und hochdosierten ICS differenziert.

| Empfehlungen/Statements | Empfehlungsgrad |
|---|---|
| **4-41 \| KINDER UND JUGENDLICHE**<br>Bevor bei Kindern und Jugendlichen die Eskalation der Therapie zur Stufe 5 erfolgt, soll die Wirksamkeit der verschiedenen möglichen Therapieoptionen der Stufe 4 evaluiert werden. | ⇑⇑ |
| **4-45 \| KINDER UND JUGENDLICHE**<br>Bei Kindern und Jugendlichen soll in Stufe 5 eine Kombinationstherapie aus einem hochdosierten ICS mit einem LABA oder/und einem LTRA empfohlen werden. | ⇑⇑ |

#### 4.8.8.2 Omalizumab

| Empfehlungen/Statements | Empfehlungsgrad |
|---|---|
| **4-49 \| KINDER UND JUGENDLICHE**<br>Ein Therapieversuch mit Omalizumab für mindestens vier Monate soll bei Kindern ab sechs Jahren sowie Jugendlichen ab Stufe 6 empfohlen werden, wenn folgende Kriterien vorliegen:<br>• schweres IgE-vermitteltes allergisches Asthma und<br>• positiver Hauttest oder in-vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen und<br>• IgE-Serumkonzentration unter Berücksichtigung des Körpergewichts im therapierbaren Bereich und<br>• erfolgte Eliminierung vermeidbarer Allergenexpositionen. | ⇑⇑ |

#### 4.8.8.3 Mepolizumab

Für die 3. Auflage der NVL Asthma wurde eine systematische Recherche zur Wirksamkeit und Sicherheit von Anti-IL5-(R)-Antikörpern durchgeführt. Diese wurde aktualisiert, um zu prüfen, ob in der Zwischenzeit Studien für die Anwendung bei Kindern und Jugendlichen vorliegen. Identifiziert wurden jedoch nur die Verlängerungsstudien der im Kapitel 4.8.6.3 Mepolizumab, Reslizumab und Benralizumab beschriebenen RCTs. Die Verlängerungsstudien wurden teilweise verblindet [137] und teilweise unverblindet [135,136,138] durchgeführt.

Im aktualisierten Cochrane-Review [145] und in den identifizierten Primärstudien zur Wirksamkeit und Sicherheit von Anti-IL5-(R)-Antikörpern [118,131,136] konnte anhand der Baseline-Charakteristika nicht ermittelt werden, wieviele Patienten unter 18 Jahren eingeschlossen wurden. Darüber hinaus wurden keine Subgruppenanalysen für die primären Endpunkte für diese Altersgruppe identifiziert [118,131,136,145].

Die EMA begründet eine partielle Extrapolation der Daten im Assessment Report [146] damit, dass schweres eosiniphiles Asthma bei Kindern und Jugendlichen selten auftritt und Studien schwer umsetzbar sind. Sie berechnet den Endpunkt klinisch bedeutsame Exazerbationen auf Basis der Daten der zur Verfügung stehenden Primärstudien altersgruppenspezifisch. Bei einer geringen Anzahl von jugendlichen Patienten ergibt sich laut EMA ein weites Konfidenzintervall, das den Nullwert schneidet, der Effektschätzer weist jedoch in die gleiche Richtung wie in der Gesamtbetrachung der Altersgruppen. [146]

Für Kinder zwischen 6 bis 11 Jahren lag der EMA eine unverblindete, nicht kontrollierte Studie mit geringer Teilnehmerzahl vor (n = 26), in der sich Hinweise für eine Besserung der Asthmakontrolle nach einem Zeitraum von 12 Wochen ergaben [146].

Das Sicherheitsprofil wird von der EMA [146] für Kinder und Jugendliche ähnlich eingeschätzt wie das der Erwachsenen, wobei Kopfschmerzen und Reaktionen an der Injektionsstelle die häufigsten unerwünschten Wirkungen darstellten. Der prozentuale Anteil von Kindern mit nicht-tödlichen schweren unerwünschten Wirkungen war höher der als bei Jugendlichen und Erwachsenen. Die EMA weist jedoch auf die Unsicherheiten dieser Einschätzungen aufgrund der geringen Fallzahlen bzw. der kurzen Behandlungsdauer (12 Wochen) bei Kindern hin. [146]

Das IQWiG schätzt die verfügbaren Daten als nicht geeignet bzw. als nicht ausreichend für einen Evidenztransfer ein [147].

Die Leitliniengruppe sieht seit der Zulassung von Mepolizumab bei Kindern ab 6 Jahren die Möglichkeit für einen Therapieversuch zur Behandlung des schweren Asthmas in Stufe 6, jedoch – sofern bei Vorliegen entsprechender Indikationskriterien beide monoklonalen Antikörper eingesetzt werden könnten – nachrangig zur Therapie mit Omalizumab (siehe Abbildung 5).

#### 4.8.8.4 Dupilumab

In der systematischen Recherche wurde zwei Phase-III-Studien identifiziert, die Patienten ab einem Alter von 12 Jahren einschlossen [139,140]. In der Studie Asthma Liberty Quest waren 5,6% der eingeschlossenen Patienten zwischen 12 und 18 Jahre alt [139]. Subgruppenanalysen für die Effektivität und Sicherheit von Dupilumab bei der Altergruppe der 12 bis 18-Jährigen wurden in den Studien nicht identifiziert [139,140].

Die EMA schildert in ihrem Assessment Report [141], dass das mittlere Alter der 107 eingeschlossenen Jugendlichen in der Studie Asthma Liberty Quest 14,2 Jahre bei einer Spanne von 12 bis17 Jahren betrug. Darüber hinaus berichtet sie, dass die adjustierte jährliche Rate schwerer Exazerbationen bei Anwendung von 200 mg Dupilumab geringer war als unter Placebo (0,191 vs. 0,356). Im Vergleich der Gruppen 300 mg Dupilumab vs. Placebo habe sich kein Unterschied ergeben. Sie zeigt auf, dass in der Studie Asthma Liberty Venture lediglich drei Patienten unter 18 Jahren eingeschlossen wurden. [141]

Die EMA berichtet zudem die unerwünschten (Dupilumab 200 mg: 70,6%; Dupilumab 300 mg: 76,5%; Placebo: 76,2% bzw. 88,9%) und schweren unerwünschten Effekte jeglicher Art (Dupilumab 200 mg: 8,8%; Dupilumab 300 mg: 2,9%; Placebo: 0 bzw. 11,1%) bei Jugendlichen in der Studie Asthma Liberty Quest [141]. Der eine Jugendliche, der in der Studie Asthma Liberty Venture zur Verumgruppe randomisiert wurde, habe keine unerwünschten Wirkungen gezeigt [141].

Die Leitliniengruppe schätzt die oben beschriebenen Daten als einen Hinweis für positive Effekte auf die Rate schwerer Exazerbationen ein. Sie sieht eine Option für einen Therapieversuch mit Dupilumab in Stufe 6 für Patienten ab 12 Jahren, jedoch – sofern bei Vorliegen entsprechender Indikationskriterien beide monoklonalen Antikörper eingesetzt werden könnten – nachrangig zur Therapie mit Omalizumab (siehe Abbildung 5).

Gleichzeitig stellt sie fest, dass in den Studien keine Vergleiche zu den anderen – schon länger zugelassenen – monoklonalen Antikörpern erfolgten, wodurch eine vergleichende Beurteilung erschwert ist. Die Leitliniengruppe weist darauf hin, dass die Ergebnisse der FeNO-Messung und der Bestimmung von Eosinophilen im Blut durch die Gabe von systemischen Corticosteroiden beeinflusst sein kann.

#### 4.8.8.6 Systemische Corticosteroide

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-51 \| KINDER UND JUGENDLICHE**<br>Die Langzeittherapie mit systemischen Corticosteroiden soll bei Kindern und Jugendlichen in Stufe 6 wegen der Gefahr schwerer Nebenwirkungen nicht empfohlen werden, es sei denn, die Asthmakontrolle ist trotz des kombinierten Einsatzes der verschiedenen Therapieoptionen der vorherigen Stufe sowie zusätzlich monoklonaler Antikörper (sofern indiziert und wirksam) unzureichend. | ⇓⇓ |

Die Langzeittherapie mit systemischen Corticosteroiden bildet bei Kindern und Jugendlichen in Stufe 6 wegen der Langzeitfolgen eine nachrangige Therapiealternative in begründeten Fällen. In der Empfehlung 4-25 empfehlen die Leitlinienautoren gezielte Maßnahmen zur Vermeidung bzw. Früherkennung von unerwünschten Wirkungen für Kinder und Jugendliche durch Corticosteroide.

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**National Institute for Health and Care Excellence (NICE), 2017 [26].**

Asthma: diagnosis, monitoring and chronic asthma management.

**Leitlinienorganisation/Fragestellung**

NICE has produced guidance on the components of good patient experience in adult NHS services.

**Methodik**

Grundlage der Leitlinie

This guideline will contain recommendations for the management of symptoms in adults, young people and children who have been diagnosed with asthma. Specific consideration will be given to subgroups based on age: children under 5 years; children aged 5–16 years; and adults and young people over 16 years of age.

Update: Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

In February 2020, this guideline was updated by an expert committee. They reviewed the evidence on increasing ICS treatment within supported self-management for children and young people.

Recherche/Suchzeitraum:

- 09/2016

LoE/GoR

Overall quality of outcome evidence in GRADE

| Level | Description |
|---|---|
| High | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low | Any estimate of effect is very uncertain |

**Empfehlungen**

Pharmacological treatment pathway for adults (aged 17 and over)

This section is for people with newly diagnosed asthma or asthma that is uncontrolled on their current treatment. Where the recommendations represent a change from traditional clinical practice, people whose asthma is well controlled on their current treatment should not have their treatment changed purely to follow this guidance.

1.6.4 If asthma is uncontrolled in adults (aged 17 and over) on a low dose of ICS as maintenance therapy, offer a leukotriene receptor antagonist (LTRA) in addition to the ICS and review the response to treatment in 4 to 8 weeks. [2017]

1.6.5 If asthma is uncontrolled in adults (aged 17 and over) on a low dose of ICS and an LTRA as maintenance therapy, offer a long-acting beta2 agonist (LABA) in combination with the ICS, and review LTRA treatment as follows:

- discuss with the person whether or not to continue LTRA treatment
- take into account the degree of response to LTRA treatment. [2017]

1.6.6 If asthma is uncontrolled in adults (aged 17 and over) on a low dose of ICS and a LABA, with or without an LTRA, as maintenance therapy, offer to change the person's ICS and LABA maintenance therapy to a MART regimen with a low maintenance ICS dose. [2017]

1.6.7 If asthma is uncontrolled in adults (aged 17 and over) on a MART regimen with a low maintenance ICS dose, with or without an LTRA, consider increasing the ICS to a moderate maintenance dose (either continuing on a MART regimen or changing to a fixed dose of an ICS and a LABA, with a SABA as a reliever therapy). [2017]

1.6.8 If asthma is uncontrolled in adults (aged 17 and over) on a moderate maintenance ICS dose with a LABA (either as MART or a fixed-dose regimen), with or without an LTRA, consider:

- increasing the ICS to a high maintenance dose (this should only be offered as part of a fixed-dose regimen, with a SABA used as a reliever therapy) or

- a trial of an additional drug (for example, a long-acting muscarinic receptor antagonist or theophylline) or
- seeking advice from a healthcare professional with expertise in asthma. [2017]

Pharmacological treatment pathway for children and young people aged 5 to 16

This section is for children and young people with newly diagnosed asthma or asthma that is uncontrolled on their current treatment. Where the recommendations represent a change from traditional clinical practice, children and young people whose asthma is well controlled on their current treatment should not have their treatment changed purely to follow guidance.

1.7.4 If asthma is uncontrolled in children and young people (aged 5 to 16) on a paediatric low dose of ICS as maintenance therapy, consider an LTRA in addition to the ICS and review the response to treatment in 4 to 8 weeks. [2017]

1.7.5 If asthma is uncontrolled in children and young people (aged 5 to 16) on a paediatric low dose of ICS and an LTRA as maintenance therapy, consider stopping the LTRA and starting a LABA in combination with the ICS. [2017]

1.7.6 If asthma is uncontrolled in children and young people (aged 5 to 16) on a paediatric low dose of ICS and a LABA as maintenance therapy, consider changing their ICS and LABA maintenance therapy to a MART regimen with a paediatric low maintenance ICS dose. Ensure that the child or young person is able to understand and comply with the MART regimen. [2017]

1.7.7 If asthma is uncontrolled in children and young people (aged 5 to 16) on a MART regimen with a paediatric low maintenance ICS dose, consider increasing the ICS to a paediatric moderate maintenance dose (either continuing on a MART regimen or changing to a fixed dose of an ICS and a LABA, with a SABA as a reliever therapy). [2017]

1.7.8 If asthma is uncontrolled in children and young people (aged 5 to 16) on a paediatric moderate maintenance ICS dose with LABA (either as MART or a fixed-dose regimen), consider seeking advice from a healthcare professional with expertise in asthma and consider either:

- increasing the ICS dose to paediatric high maintenance dose (only as part of a fixed-dose regimen, with a SABA used as a reliever therapy) or
- a trial of an additional drug (for example, theophylline). [2017]

MART

Maintenance and reliever therapy (MART) is a form of combined ICS and LABA treatment in which a single inhaler, containing both ICS and a fast-acting LABA, is used for both daily maintenance therapy and the relief of symptoms as required. MART is only available for ICS and LABA combinations in which the LABA has a fast-acting component (for example, formoterol).

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**Global Initiative for Asthma (GINA), 2020 [19].**

*GINA – Global Initiative for Asthma*

Global strategy for asthma management and prevention (2020 update)

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- For each meeting of the GINA Science Committee, a rolling PubMed search is performed covering approximately 10 months.
- The GINA report has been updated in 2020 following the routine twice-yearly review of the literature by the GINA Science Committee.
- The literature searches for 'clinical trial' publication types (see above) and meta-analyses identified a total of 2,420 publications, of which 1,860 were screened out for duplicates, relevance and/or quality.
- The remaining 560 publications (377 'clinical trials' and 183 meta-analyses) were reviewed by at least two members of the Science Committee; a total of 89 were subsequently discussed at face-to-face meetings in May 2019 in Dallas, USA and in September 2019 in Madrid, Spain.

LoE

| Evidence level | Sources of evidence | Definition |
|---|---|---|
| A | Randomized controlled trials (RCTs) and meta-analyses. Rich body of data. | Evidence is from endpoints of well designed RCTs, meta-analyses of relevant studies, or strong observational evidence that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants. |
| B | Randomized controlled trials (RCTs) and meta-analyses. Limited body of data. | Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or meta-analysis of such RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were under-taken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent. |
| C | Nonrandomized trials. Observational studies. | Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies. |
| D | Panel consensus judgment. | This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above listed criteria. |



GoR

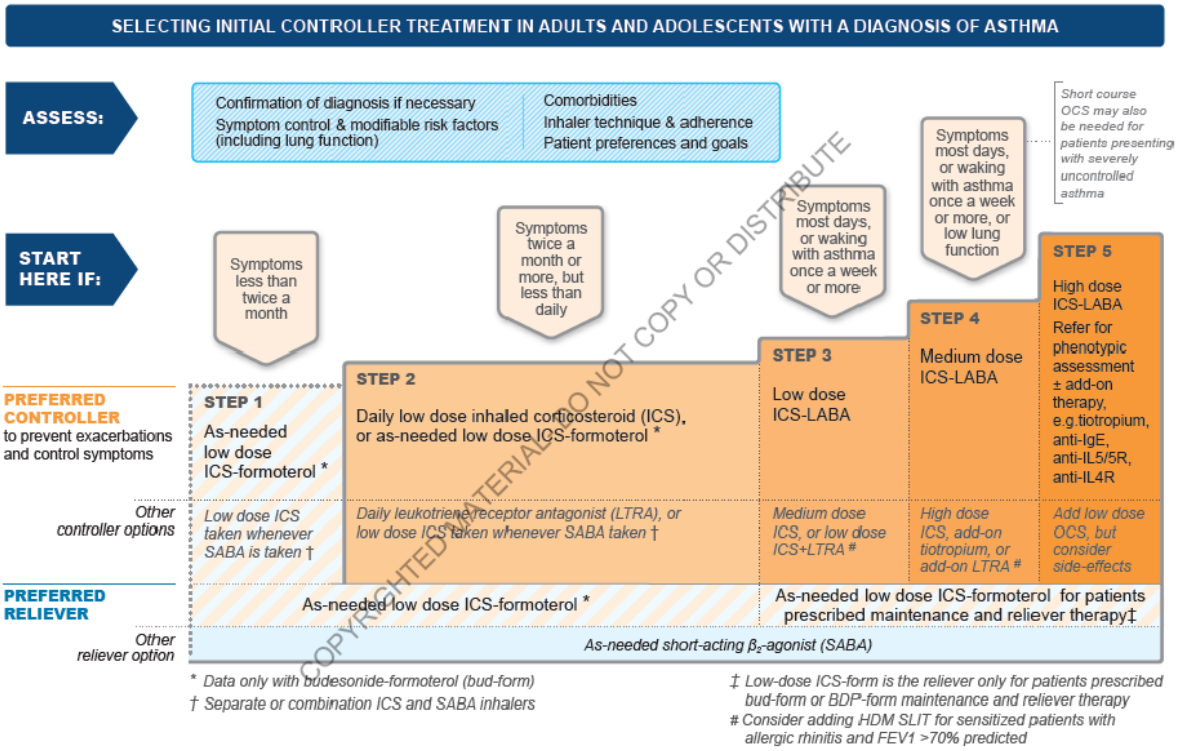
- keine Angabe des GoR.

Sonstige methodische Hinweise

/

## Empfehlungen

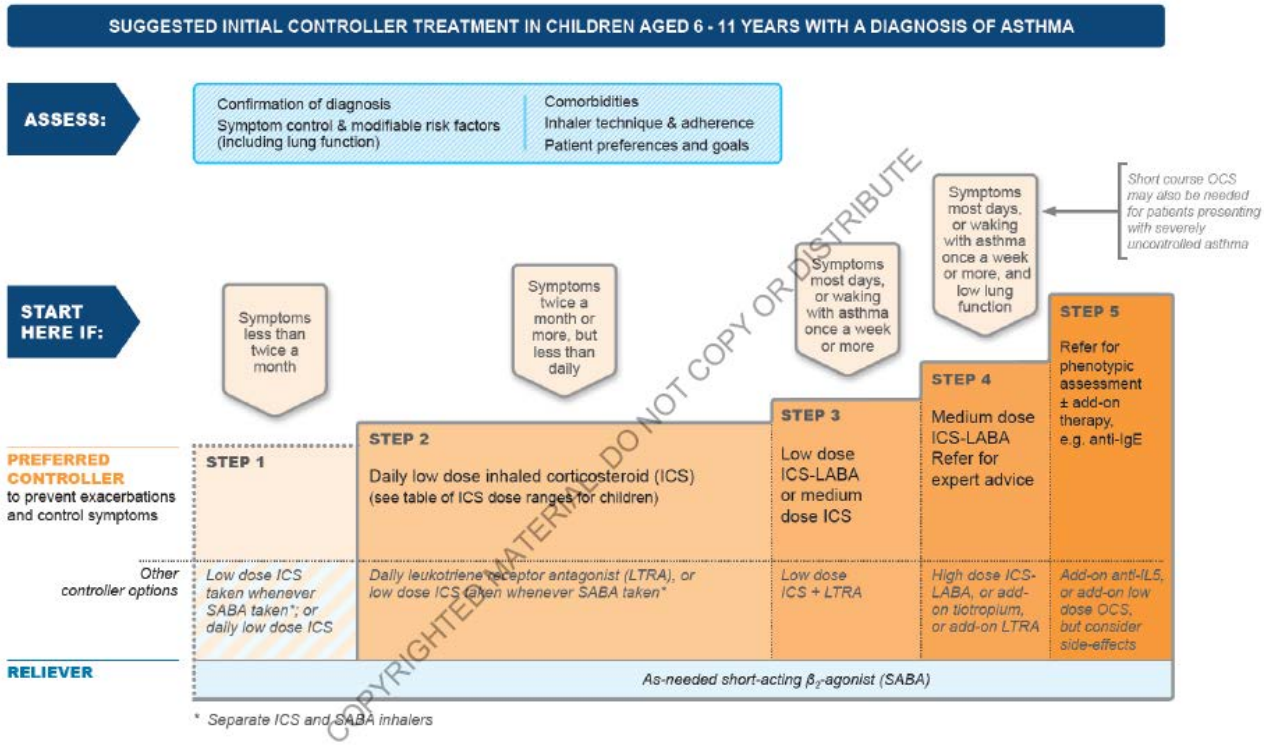
**Box 3-4B. Selecting initial controller treatment in adults and adolescents with a diagnosis of asthma**






HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist; SLIT: sublingual immunotherapy

**Box 3-4D. Selecting initial controller treatment in children aged 6–11 years with a diagnosis of asthma**






ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist

STEP 4: Preferred controller: Low dose ICS-formoterol as maintenance and reliever therapy (adults and adolescents), OR medium dose ICS-LABA maintenance plus as-needed SABA (adults, adolescents and children)

- Although at a group level most benefit from ICS is obtained at low dose, individual ICS responsiveness varies, and some patients whose asthma is uncontrolled on low dose ICS-LABA despite good adherence and correct inhaler technique may benefit from increasing the maintenance dose to medium. High dose ICS is no longer recommended at Step 4.

Preferred Step 4 controller options for adults and adolescents

- The selection of Step 4 treatment depends on the prior selection at Step 3. Before stepping up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p.40).
- For adult and adolescent patients with ≥1 exacerbations in the previous year, combination low dose ICS-formoterol as maintenance and reliever treatment is more effective in reducing exacerbations than the same dose of maintenance ICS-LABA or higher doses of ICS223 (Evidence A). This regimen can be prescribed with low dose budesonide-formoterol or beclometasone-formoterol as in Step 3; the maintenance dose may be increased to medium if necessary. Based on product information, the maximum recommended total dose of formoterol in a single day is 48mcg (for beclometasoneformoterol) or 72mcg (for budesonide-formoterol).
- Alternatively, for patients taking low dose maintenance ICS-LABA with as-needed SABA, whose asthma is not adequately controlled, treatment may be increased to medium dose ICS-LABA158 (Evidence B); combination ICS-LABA medications are as for Step 3.

Other Step 4 controller options for adults and adolescents

- Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy in patients aged 6 years and older; it modestly improves lung function235,236 (Evidence A) and modestly reduces exacerbations.235-237 In Step 4, there is insufficient evidence to support ICS+tiotropium over ICS-LABA combination.[237]
- For adult patients with allergic rhinitis and sensitization to house dust mite, with suboptimally controlled asthma despite low-high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV1 is >70% predicted.225,226 (see p.68).
- For medium or high dose budesonide, efficacy may be improved with dosing four times daily[238,239] (Evidence B), but adherence may be an issue. For other ICS, twice-daily dosing is appropriate (Evidence D). Other options for adults or adolescents that can be added to a medium or high dose ICS, but that are less efficacious than adding LABA, include [LTRA240-244] (Evidence A), or low dose sustained-release theophylline208 (Evidence B). See note above about the FDA warning for montelukast.[205]

STEP 5: Preferred option: Refer for phenotypic assessment and consideration of add-on treatment (adults, adolescents and children)

- Patients of any age with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in investigation and management of severe asthma[138] (Evidence D).
- In severe asthma, as in mild-moderate asthma,[245] participants in randomized controlled trials may not be representative of patients seen in clinical practice. For example, a registry study found that over 80% of patients with severe asthma would have been excluded from recent studies evaluating biologic therapy.[246]
- The GINA Pocket Guide and decision tree on Diagnosis and Management of difficult-to-treat and severe asthma in adolescent and adult patients are included in Chapter 3E (p.94). Treatment options that may be considered after optimization of existing therapy may include the following (always check local eligibility and payer criteria):
- Combination high dose ICS-LABA: this may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit122,130,228 (Evidence A), and there is an increased risk of side-effects, including adrenal suppression.247 A high dose is recommended only on a trial basis for 3–6 months when good asthma control

cannot be achieved with medium dose ICS plus LABA and/or a third controller (e.g. LTRA or sustained-release theophylline208,243 Evidence B).

- Add-on tiotropium (long-acting muscarinic antagonist) in patients aged ≥6 years whose asthma is not wellcontrolled with ICS-LABA. Add-on tiotropium (mostly 5µg once daily by mist inhaler) modestly improves lung function (Evidence A) and modestly increases the time to severe exacerbation requiring oral corticosteroids (Evidence B).236,237 Results with other LAMA preparations are awaited.236
- Add-on azithromycin (three times a week) for adult patients with persistent symptomatic asthma despite moderate-high dose ICS and LABA reduced asthma exacerbations in eosinophilic248 and non-eosinophilic asthma248,249 (Evidence B) and improved asthma-related quality of life248,249 (Evidence B). Diarrhea was more common.248 Since macrolides such as azithromycin can cause ototoxicity and cardiac arrhythmia, asthma patients with hearing impairment248 or abnormal prolongation of the corrected QT interval[248,249] were excluded from the studies. Before considering add-on therapy with azithromycin in adult patients with uncontrolled or severe asthma, ECG should be checked for long QTc, sputum should be checked for atypical mycobacteria, and the risk of increasing antimicrobial resistance at the patient and the population level should be taken into account. Treatment for at least 6 months is suggested, as a clear benefit was not seen by 3 months. There is no clear evidence about how long treatment should be continued.
- Add-on anti-immunoglobulin E (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4–5 treatment[250,251] (Evidence A).
- Add-on anti-interleukin-5/5R treatment (subcutaneous mepolizumab for patients aged ≥6 years; intravenous reslizumab for ages ≥18 years) or anti-interleukin 5 receptor treatment (subcutaneous benralizumab for ages ≥12 years), with severe eosinophilic asthma that is uncontrolled on Step 4–5 treatment (Evidence A).252-256 Efficacy data for mepolizumab in children 6–11 years are limited to one very small open label uncontrolled study.[257]
- Add-on anti-interleukin-4R α treatment (subcutaneous dupilumab) for patients aged ≥12 years with severe Type 2 asthma, or requiring treatment with maintenance OCS (Evidence A).[258-260]}
- Sputum-guided treatment: for adults with persisting symptoms and/or exacerbations despite high dose ICS or ICS-LABA, treatment may be adjusted based on eosinophilia (>3%) in induced sputum. In severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS161 (Evidence A).
- Add-on treatment with bronchial thermoplasty: may be considered for some adult patients with severe asthma[138,261] (Evidence B). Evidence is limited and in selected patients (see p.69). The long-term effects compared with control patients, including for lung function, are not known.
- Add-on low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma138 (Evidence D), but are often associated with substantial side effects262,263 (Evidence A). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors and other add-on treatments including biologics where available and affordable. Patients should be counseled about potential side-effects.263 They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[264]

PART E. DIFFICULT-TO-TREAT AND SEVERE ASTHMA IN ADULTS AND ADOLESCENTS

## KEY POINTS

### What are difficult to treat and severe asthma?

- Difficult-to-treat asthma is asthma that is uncontrolled despite GINA Step 4 or 5 treatment or that requires such treatment to maintain good symptom control and reduce exacerbations. It does not mean a 'difficult patient'.
- Severe asthma is asthma that is uncontrolled despite adherence with maximal optimized Step 4 or Step 5 therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased. Approximately 3–10% of people with asthma have severe asthma.
- Severe asthma places a large physical, mental, emotional, social and economic burden on patients.

### How should these patients be assessed?

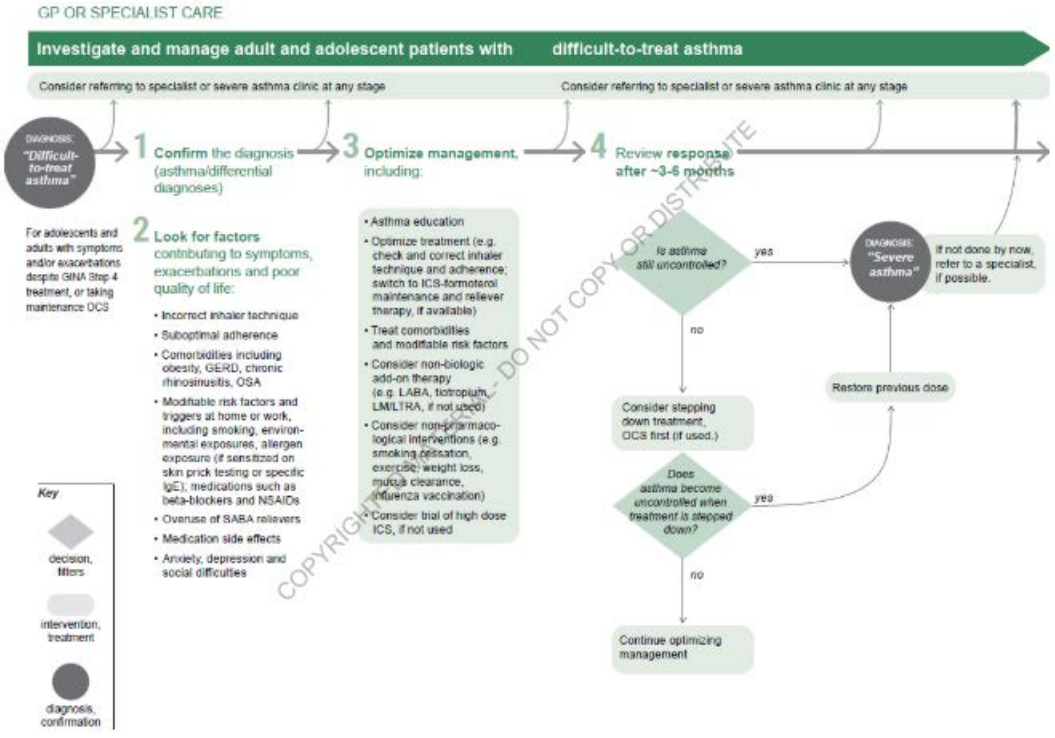
- Assess all patients with difficult to treat asthma to confirm the diagnosis of asthma, and to identify and manage factors that may be contributing to symptoms, poor quality of life, or exacerbations.
- Refer for expert advice at any stage, or if asthma does not improve in response to optimizing treatment.
- For patients with persistent symptoms and/or exacerbations despite high dose ICS, the clinical or inflammatory phenotype should be assessed, as this may guide the selection of add-on treatment.

### Management of severe asthma

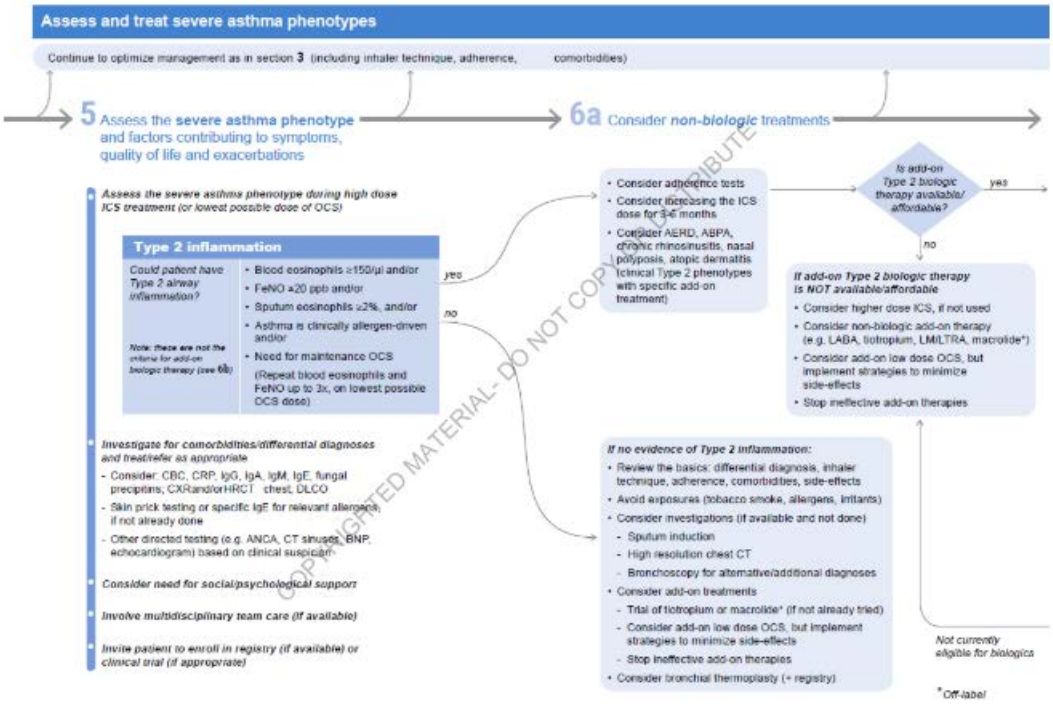
- Add-on treatments for severe asthma include tiotropium, LTRA and low dose macrolides, and biologic agents for severe allergic or severe Type 2 asthma. Maintenance OCS should be avoided if other options are available, because of its serious side-effects.
- Assess the response to any add-on treatment, stop ineffective treatments, and consider other options.
- Utilize specialist multidisciplinary team care for severe asthma, if available.
- For patients with severe asthma, continue to optimize patient care in collaboration with the primary care clinician, and taking into account the patient's social and emotional needs.
- Invite patients with severe asthma to enrol in a registry or clinical trial, if available and relevant, to help fill evidence gaps.



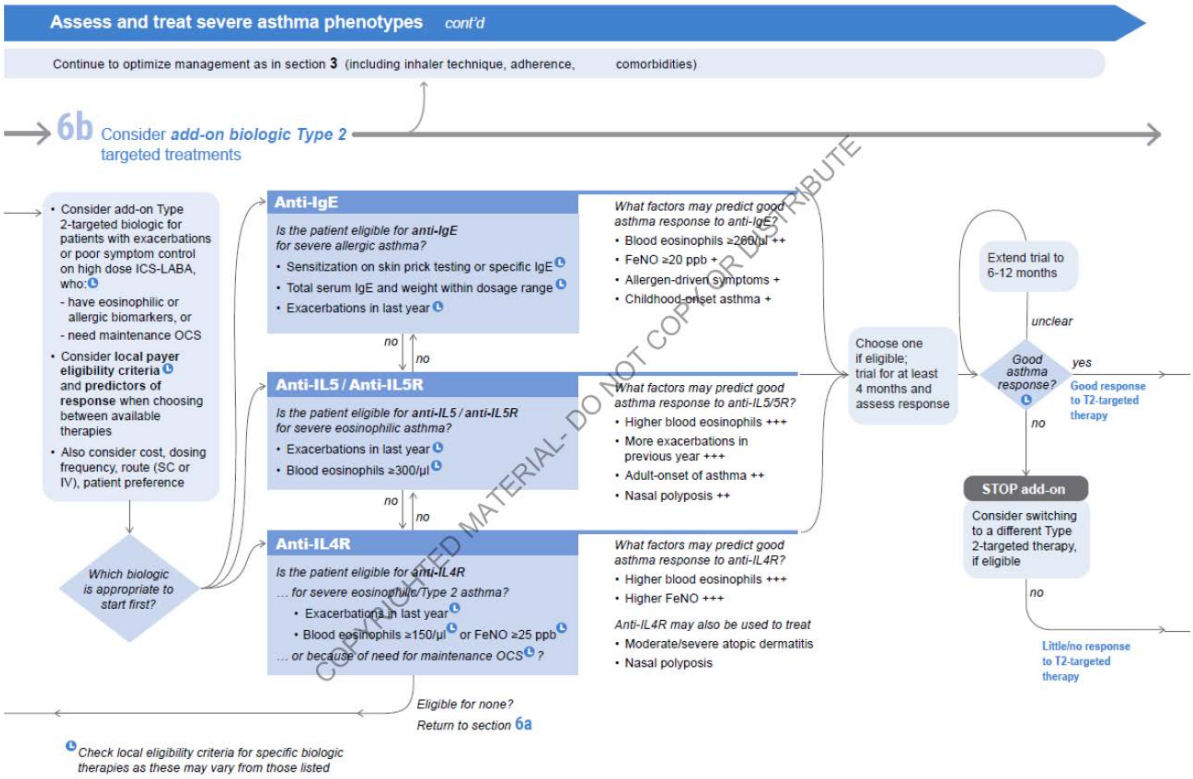
**Box 3-16A. Decision tree – investigate and manage adult and adolescent patients with difficult-to-treat asthma**

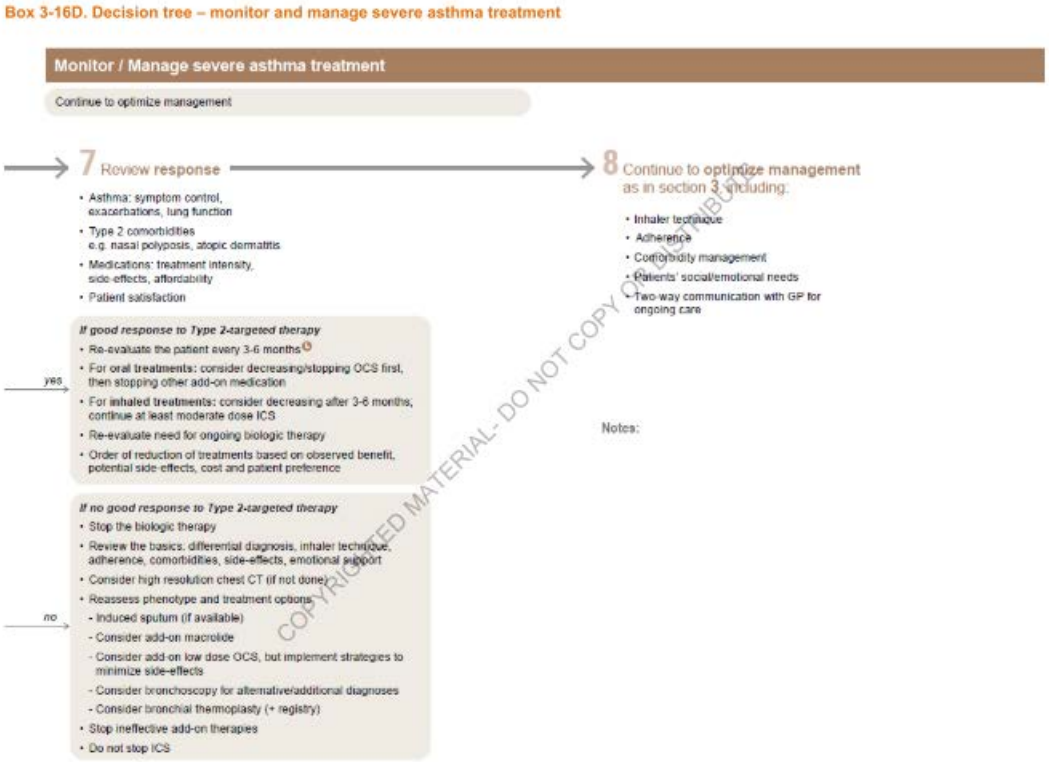


**Box 3-16B. Decision tree – assess and treat severe asthma phenotypes**




**Box 3-16C. Decision tree – consider add-on biologic Type 2 targeted treatments**



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**SIGN, 2019 [30].**

*Scottish Intercollegiate Guidelines Network (SIGN) in Kooperation mit British Thoracic Society*

British guideline on the management of asthma

**Leitlinienorganisation/Fragestellung**

The guideline considers asthma management in all patients with a diagnosis of asthma, although there is less evidence available for people at either age extreme.

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; The evidence base for this guideline was synthesised in accordance with SIGN methodology.
- Regelmäßige Überprüfung der Aktualität gesichert.

Update: Between 2004 and 2012 sections within the guideline were updated annually. Subsequently, updating moved to a biennial basis, beginning with the 2014 update. This edition of the guideline was issued in 2019. All updates were published on the BTS and SIGN websites. A list of the key questions addressed in this update is given in Annex 1. Any updates to the guideline in the period between scheduled updates will be noted on the SIGN and BTS websites.

Recherche/Suchzeitraum:

Section 7 Pharmacological management

The 2019 revision updated searches for inhaled steroids, long-acting β2 agonists, theophyllines, leukotriene receptor antagonists, frequency and dose of inhaled steroids, monoclonal antibodies, sublingual immunotherapy and bronchial thermoplasty. The Cochrane Library, Medline and Embase were searched from 2012–2018. SIGN systematic review and RCT filters were applied.

Loe/GoE:

**Key to evidence statements and recommendations**

Levels of evidence

| | |
|---|---|
| 1++ | High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias |
| 1− | Meta-analyses, systematic reviews, or RCTs with a high risk of bias |
| 2++ | High-quality systematic reviews of case-control or cohort studies<br>High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal |
| 2+ | Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal |
| 2− | Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal |
| 3 | Non-analytic studies, eg case reports, case series |
| 4 | Expert opinion |

Grades of recommendation

Note: The grade of recommendation relates to the strength of the supporting evidence on which the evidence is based. It does not reflect the clinical importance of the recommendation.

| | |
|---|---|
| A | At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*<br>A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results |
| B | A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*<br>Extrapolated evidence from studies rated as 1++ or 1+ |
| C | A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*<br>Extrapolated evidence from studies rated as 2++ |
| D | Evidence level 3 or 4; *or*<br>Extrapolated evidence from studies rated as 2+ |

Good-practice points

| | |
|---|---|
| ✓ | Recommended best practice based on the clinical experience of the guideline development group. |

**Emfehlungen**

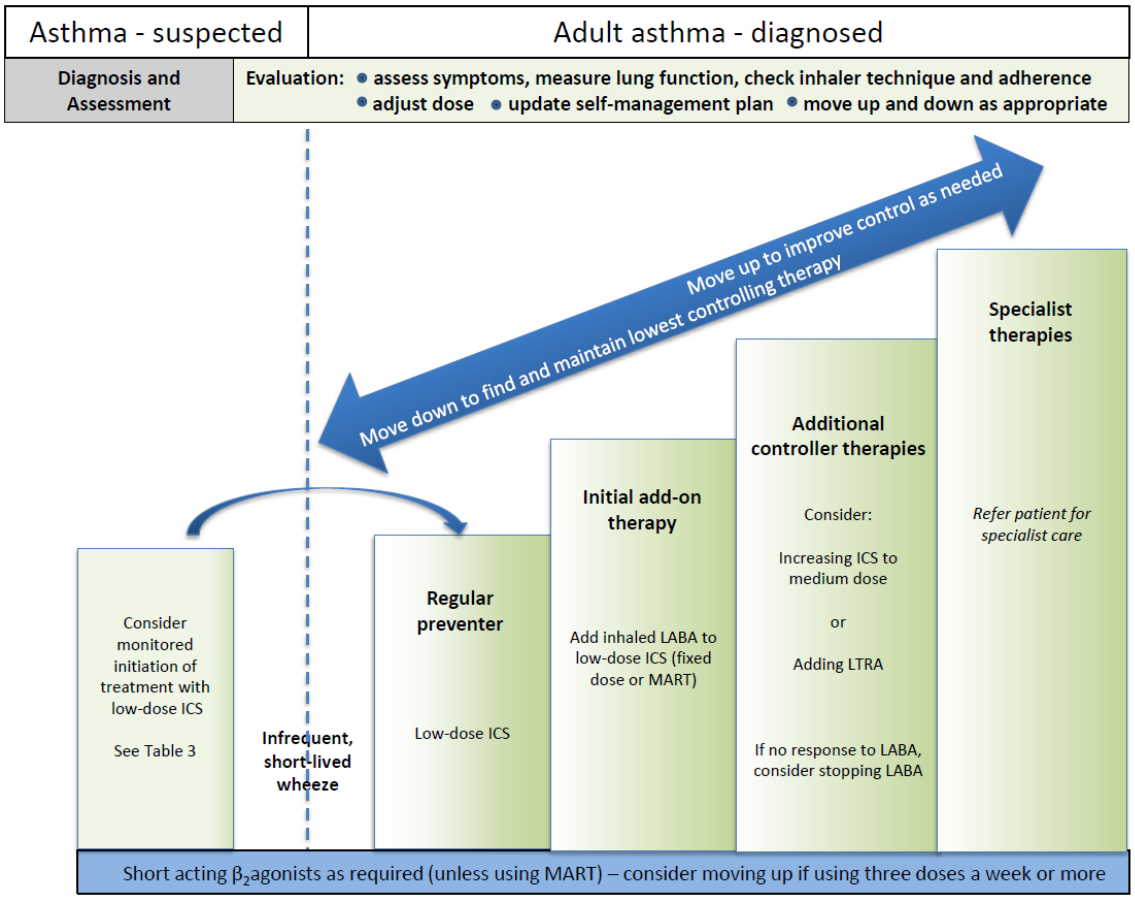
Recommendations in sections 7 and 8 have been graded and the supporting evidence assessed for adults and adolescents over 12 years old, children aged 5–12 years, and children aged under 5 years. The evidence is less clear in children under two and the threshold for seeking an expert opinion should be lowest in these children.

1 2 3

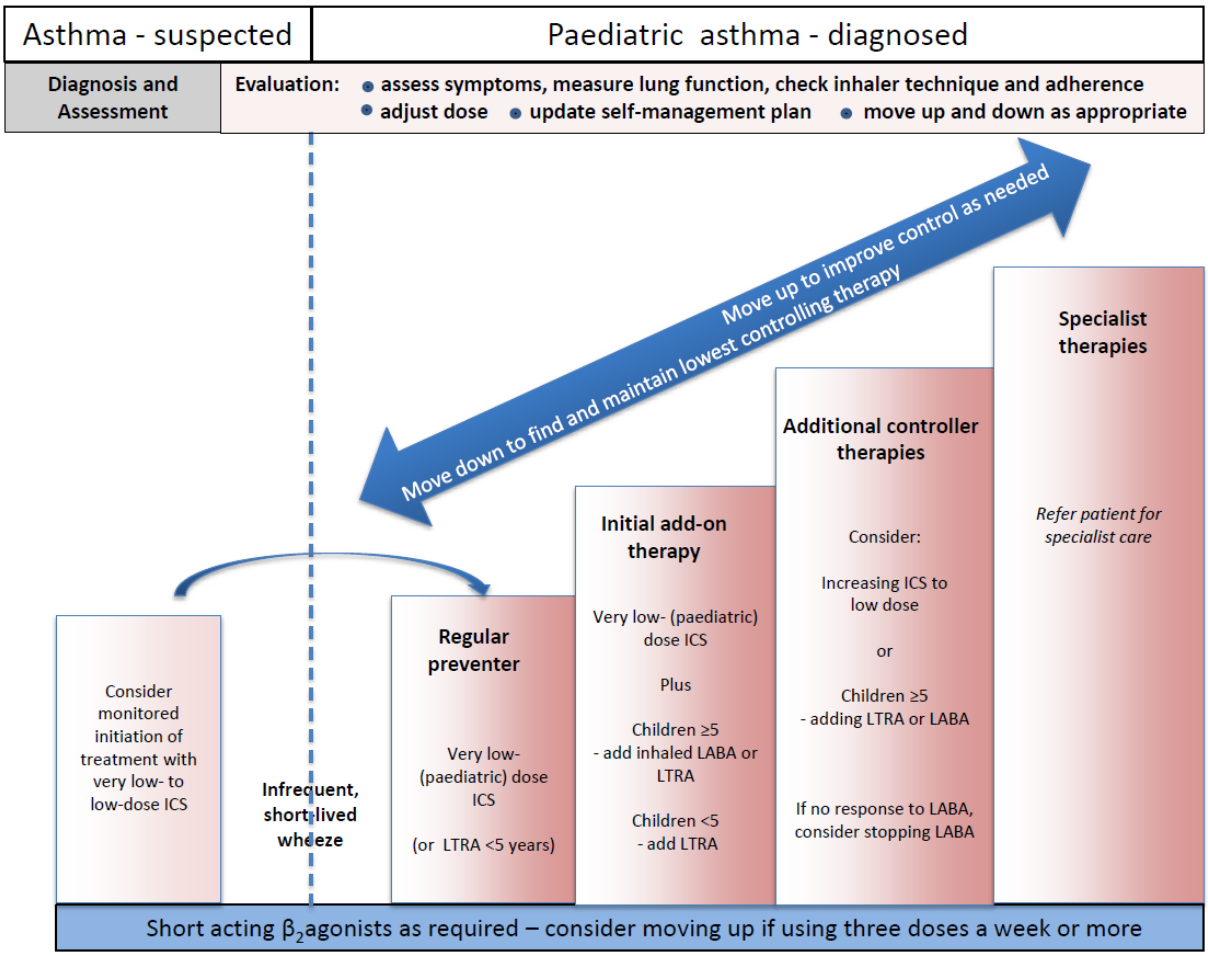
1 Adults and adolescents aged over 12
2 Children aged 5–12 years
3 Children under 5 years

Recommendation does not apply to this age group.

Summary of management in adults



Summary of management in children




## 2.5 Pharmacological management

✓ Before initiating a new drug therapy practitioners should check adherence with existing therapies, check inhaler technique, and eliminate trigger factors.

A A A **Inhaled corticosteroids are the recommended preventer drug for adults and children for achieving overall treatment goals.**

A **The first choice as add-on therapy to inhaled corticosteroids in adults is an inhaled long-acting $\beta_2$ agonist, which should be considered before increasing the dose of inhaled corticosteroids.**

D D **If asthma control remains suboptimal after the addition of an inhaled long-acting $\beta_2$ agonist then:**

- **increase the dose of inhaled corticosteroids from low dose to medium dose in adults or from very low dose to low dose in children (5–12 years), if not already on these doses.**
- **consider adding a leukotriene receptor antagonist.**

## 7.4 Additional controller therapies

If control remains poor on low-dose (adults) or very low-dose (children aged five and over) ICS plus a LABA, recheck the diagnosis, assess adherence to existing medication and check inhaler technique before increasing therapy. If more intense treatment is appropriate, then the following options can be considered.

### 7.4.1 Increased dose of inhaled corticosteroids

| >12 years | 5–12 years | <5 years |
|---|---|---|
| 4 | 4 | |

If there is an improvement when LABA is added, but control remains suboptimal, continue with the LABA and increase the dose of ICS to medium (adults) or low dose (children 5–12 years). If there is no improvement when a LABA is added, consider stopping the LABA before increasing the dose of ICS.[475]

### 7.4.2 Leukotriene receptor antagonists

| >12 years | 5–12 years | <5 years |
|---|---|---|
| 1++ | 1++ | |

Evidence to support the use of LTRA as an add-on therapy to ICS plus LABA is lacking and evidence for their use is largely based on extrapolation from trials of LTRA as add-on therapy to ICS alone. The addition of LTRA to ICS may provide improvement in lung function, a decrease in asthma attacks, and an improvement in symptoms in adults and children over five years of age, although reported benefits differ between studies and evidence is limited in children.[454, 478, 479]

| | | |
|---|---|---|
| 1++ | 1++ | |

A systematic review of studies comparing the addition of LTRA to ICS with the addition of LABA to ICS showed that the addition of LABA to ICS was more effective at reducing asthma attacks (the primary outcome) and improving secondary outcomes including SABA use, symptoms and quality of life in adults, although differences were generally small. There was insufficient evidence on which to base conclusions regarding which add-on therapy is more effective in children.[472]

| | | |
|---|---|---|
| 1+ | | |

In adults, the addition of LTRA to ICS is superior to ICS alone and has a similar effect on asthma control to high-dose ICS. High-dose ICS, however, appears superior to ICS-LTRA for some pulmonary function indices, although further studies to investigate this are required.[480]

In adults, if there is no improvement following addition of a LABA, consider stopping the LABA and initiating a trial of LTRA.

D D

**If asthma control remains suboptimal after the addition of an inhaled long-acting $\beta_2$ agonist then:**

- **increase the dose of inhaled corticosteroids from low dose to medium dose in adults or from very low dose to low dose in children (5–12 years), if not already on these doses.**

  ***or***

- **consider adding a leukotriene receptor antagonist.**

## 7.5 Specialist therapies

In a small proportion of patients asthma is not adequately controlled on the recommended initial or additional controller therapies *(see sections 7.3 and 7.4)*. There are very few clinical trials in this specific patient group to guide management. For this reason, these patients should be referred for specialist care.

✓ All patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care.

### 7.5.1 Tiotropium bromide

| | >12 years | 5–12 years | <5 years |
|---|---|---|---|
| A review of RCTs in adults taking tiotropium bromide, a long-acting muscarinic antagonist (LAMA), in addition to ICS plus LABA compared with ICS plus LABA, reported fewer asthma exacerbations (although results were inconclusive), improved lung function and some benefits relating to asthma control in those taking tiotropium, but no improvement in quality of life. Evidence relating to serious adverse effects was inconclusive but fewer non-serious adverse events were reported in those taking tiotropium. In two of the three trials included in the review patients were taking high-dose ICS.[481] The addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit although results are currently inconclusive. Further research is needed to confirm possible benefits or harms of tiotropium in combination with different doses of ICS/LABA.[481] | 1++ | | |
| There is insufficient evidence to suggest that addition of tiotropium to ICS in patients inadequately controlled on ICS alone has any benefit over addition of LABA to ICS.[482] The addition of LABA to ICS remains the first choice for add-on treatment in adults. In adults with asthma who do not respond to ICS plus LABA, the addition of tiotropium to ICS is a possible, although 'off-label' alternative.[483, 484] | 1++<br>1+ | | |
| A review comparing the addition of tiotropium to ICS with increased dose of ICS in adults found only one study suitable for inclusion and insufficient evidence to determine if adding tiotropium to ICS ('off-label' use) is safer or more effective than increasing the dose of ICS.[485] | 1+ | | |

### 7.5.2 Other approaches

| | >12 years | 5–12 years | <5 years |
|---|---|---|---|
| Theophyllines may improve lung function and symptoms, but are associated with an increase in adverse events.[463] | 1+ | 1− | |
| Addition of short-acting anticholinergics is generally of no value.[464, 486] Addition of nedocromil to ICS is of marginal benefit.[457, 465] | 1+ | | |

✓ If control remains inadequate after stopping a LABA and increasing the dose of inhaled corticosteroid, consider sequential trials of add-on therapy, ie leukotriene receptor antagonists or theophyllines.

The following recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone *(see sections 7.3 and 7.4)*.

**If asthma control remains inadequate on medium-dose (adults) or low-dose (children) of inhaled corticosteroid plus a long-acting $\beta_2$ agonist or a leukotriene receptor antagonist, the following interventions can be considered:**

- **increase the inhaled corticosteroids to high dose (adults)/ medium dose (children 5–12 years)* *or***
- **add a leukotriene receptor antagonist (if not already trialled) *or***
- **add tiotropium (adults) *or***
- **add a theophylline.**

*at high doses of inhaled corticosteroid via a pMDI, a spacer should be used.

There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines.

✓ If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose).

✓ Although there are no controlled trials, children (all ages) who are under specialist care may benefit from a trial of higher doses ICS (greater than 800 micrograms/day) before moving to use of oral steroids.

### 7.5.3 Continuous or frequent use of oral steroids

The aim of treatment is to control asthma using the lowest possible doses of medication.

Some patients with very severe asthma not controlled with high-dose ICS, and who have also been tried on or are still taking LABA, LTRA, tiotropium (adults only) or theophyllines, may require regular long-term steroid tablets. These patients should already be under the care of a specialist asthma service.

✓ For the small number of patients not controlled on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control.

✓ Patients requiring frequent or continuous use of oral corticosteroids should be under the care of a specialist asthma service.

### 7.5.4 Monoclonal antibody

***Anti-IgE monoclonal antibody***

| >12 years | 5–12 years | <5 years |
|---|---|---|
| 1++<br>2++ | 1++<br>2++ | |

Omalizumab given by subcutaneous injection can reduce the steroid burden for the patient without increasing the risk of adverse events.[489-491] Three systematic reviews reported reductions in asthma exacerbations in patients with moderate or severe allergic asthma receiving omalizumab compared with placebo in addition to oral corticosteroids or ICS.[489-491] These studies all reported that more patients on omalizumab compared with placebo withdrew steroids.

Omalizumab is given as a subcutaneous injection every two or four weeks depending on the patient's IgE level and weight. Local skin reactions may occur. Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue have been reported after administration of omalizumab occurring as early as the first dose, and as late as one year. Due to concerns about anaphylaxis, the first three doses of omalizumab should only be administered to patients in a healthcare setting under direct medical supervision.

Guidance on when to consider treatment can be found in NICE technology appraisal guidance TA278.[489]

***Anti-IL-5 monoclonal antibody***

| >12 years | 5–12 years | <5 years |
|---|---|---|
| 1++ | | |

A systematic review of anti-interleukin-5 (IL-5) monoclonal antibody therapies including trials of mepolizumab (four trials; two intravenous, one subcutaneous, one mixed), reslizumab (four trials intravenous) and benralizumab (five trials subcutaneous), and 6,000 patients aged 12 years and over, most of whom had severe eosinophilic asthma, reported reduced asthma exacerbation rates and emergency department/unscheduled care visits with mepolizumab and benralizumab, and reduced asthma exacerbation rates with reslizumab compared with placebo. No serious excess adverse events were reported although significantly more patients receiving benralizumab than placebo discontinued treatment due to adverse events and this requires further investigation.[492] The review did not look at the potential steroid-sparing effect of anti-IL5 therapies. Use of intravenous mepolizumab is not currently licensed.

| >12 years | 5–12 years | <5 years |
|---|---|---|
| 1++ | | |

An RCT of 135 patients with severe eosinophilic asthma receiving 100 mg of mepolizumab subcutaneously or placebo every four weeks, reported a significant glucocorticoid-sparing effect with mepolizumab (28% *v* 11%, respectively), improved secondary outcomes including fewer exacerbations and improved ACQ-5 scores, and a similar safety profile.[493]

| >12 years | 5–12 years | <5 years |
|---|---|---|
| 1+ | | |

No studies were found that directly compared omalizumab with mepolizumab. A systematic review and meta-analysis, however, concluded that mepolizumab was of equivalent benefit compared to omalizumab in patients eligible for both treatments.[494] A network meta-analysis comparing omalizumab with mepolizumab showed similar adverse event rates for omalizumab and intravenous mepolizumab (not a licensed route of administration) and a reduction in adverse events compared with placebo and/or baseline therapy (mean annualised asthma exacerbation rate 1.22 *v* 2.29 omalizumab; 1.28 *v* 2.56 mepolizumab).[495]

Head-to-head trials comparing omalizumab with mepolizumab and other IL-5 therapies and of different IL-5 therapies are needed to confirm the relative clinical and cost effectiveness of each approach.

Guidance on use of mepolizumab, reslizumab and benralizumab differs in England/ Wales and Scotland and the relevant NICE or SMC advice should, therefore, be checked prior to considering these treatment approaches.

| | |
|---|---|
| B B | **Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden.** |
| A | **Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden.** |
| ✓ | • Patients being considered for monoclonal antibody treatment should be assessed to confirm the diagnosis of asthma, that uncontrolled asthma is the cause of their ongoing symptoms, and that they are adherent with current treatment.<br>• An asthma specialist with expertise in monoclonal antibody treatment should assess patients prior to undergoing treatment, and treatment should take place in a specialist centre with the appropriate resources and training, including access to an intensive care unit.<br>• Patients undergoing monoclonal antibody treatment should have their details entered onto the UK Severe Asthma Registry. |

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**Holguin F et al., 2020 [21].**

Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium: 23 clinicians and researchers with experience in severe asthma and two severe asthma patient representatives; 3 methodologists;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz:
- Evidence profiles and Evidence to Decision tables (supplementary material) developed with the GRADEpro Guideline Development Tool
- iterative consensus process conducted face-to-face and also via teleconference and e-mail, and finally a vote by all members of the Task Force who had no relevant conflicts
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- MEDLINE, Embase and Cochrane Central Register of Controlled Trials, beginning in 2008 and ending with a final update on September 27, 2018

LoE

Evidence was appraised using the GRADE

GoR

- A strong recommendation was made for or against an intervention when the panel was certain that the desirable consequences outweighed the undesirable consequences (or the converse for a recommendation against). A strong recommendation is one that most well-informed patients would follow.
- A conditional recommendation was made for or against an intervention when the panel was uncertain that the desirable consequences of the intervention outweighed the undesirable consequences (or the converse for a recommendation against). Reasons for uncertainty included low or very low quality of evidence, the desirable and undesirable consequences being finely balanced, the population in reviewed studies not uniformly meeting ERS/ATS severe asthma criteria, or the underlying values and preferences playing an important role. A conditional recommendation indicates that well-informed patients may make different choices regarding whether to have or not have the intervention.keine Angabe des GoR.

Sonstige methodische Hinweise

/

**Empfehlungen**

Severe asthma was defined as:

When a diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as “asthma that requires treatment with high dose inhaled corticosteroids […] plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy”.

TABLE 2 European Respiratory Society (ERS)/American Thoracic Society (ATS) Severe Asthma Task Force recommendations for the management of severe asthma

| Question | Recommendation | Strength | Quality of evidence |
|---|---|---|---|
| 1 | We suggest an anti-IL-5 strategy as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma | Conditional | Low |
| 2 | We suggest that a blood eosinophil cut-point $\geqslant 150\ \mu L^{-1}$ can be used to guide anti-IL-5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations | Conditional | Low |
| 3 | We suggest using a blood eosinophil cut-off $\geqslant 260\ \mu L^{-1}$ to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment | Conditional | Low |
| | We suggest using a $F_{ENO}$ cut-off $\geqslant 19.5$ ppb to identify adolescents (>12 years) and adults with severe allergic asthma more likely to benefit from anti-IgE treatment | Conditional | Low |
| 4 | For children, adolescents and adults with severe asthma uncontrolled despite GINA step 4–5 or NAEPP step 5 therapies, we recommend the addition of tiotropium | Strong | Moderate |
| 5 | We suggest a trial of macrolide treatment to reduce asthma exacerbations in adult asthma subjects on GINA/NAEPP step 5 therapy that remain persistently symptomatic or uncontrolled | Conditional | Low |
| | We suggest against the use of chronic macrolide treatment in children and adolescents with severe uncontrolled asthma | Conditional | Low |
| 6 | We suggest dupilumab as add-on therapy for adult patients with severe eosinophilic asthma and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels | Conditional | Low |

IL: interleukin; R: receptor; $F_{ENO}$: exhaled nitric oxide fraction; GINA: Global Initiative for Asthma; NAEPP: National Asthma Education and Prevention Program.

# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 3 of 12, March 2021) am 18.03.2021**

| # | Suchfrage |
|---|---|
| 1 | [mh Asthma] |
| 2 | asthma*:ti |
| 3 | #1 OR #2 |
| 4 | #3 with Cochrane Library publication date from Mar 2016 to present, in Cochrane Reviews |

**Systematic Reviews in Medline (PubMed) am 18.03.2021**

| # | Suchfrage |
|---|---|
| 1 | „asthma/therapy"[mh] |
| 2 | asthma*[ti] |
| 3 | (#2) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])) |
| 4 | #1 OR #3 |
| 5 | (#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab])))))) |

| # | Suchfrage |
|---|---|
| 6 | (#5) AND ("2016/03/01"[PDAT] : "3000"[PDAT]) |
| 7 | (#6) NOT "The Cochrane database of systematic reviews"[Journal] |
| 8 | (#7) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Leitlinien in Medline (PubMed) am 18.03.2021**

| # | Suchfrage |
|---|---|
| 1 | asthma[majr] |
| 2 | asthma*[ti] |
| 3 | #1 OR #2 |
| 4 | (#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti]) |
| 5 | (#4) AND ("2016/03/01"[PDAT] : "3000"[PDAT]) |
| 6 | (#5) NOT (retracted publication [pt] OR retraction of publication [pt]) |

## Referenzen


1. **Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, et al.** Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. Allergy 2020;75(5):1023-1042.
2. **Agache I, Rocha C, Beltran J, Song Y, Posso M, Solà I, et al.** Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. Allergy 2020;75(5):1043-1057.
3. **Agache I, Song Y, Rocha C, Beltran J, Posso M, Steiner C, et al.** Efficacy and safety of treatment with dupilumab for severe asthma: A systematic review of the EAACI guidelines-Recommendations on the use of biologicals in severe asthma. Allergy 2020;75(5):1058-1068.
4. **Ando K, Tanaka A, Sagara H.** Comparative Efficacy and Safety of Dupilumab and Benralizumab in Patients with Inadequately Controlled Asthma: A Systematic Review. Int J Mol Sci 2020;21(3):889.
5. **Bourdin A, Husereau D, Molinari N, Golam S, Siddiqui MK, Lindner L, et al.** Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review. Eur Respir J 2018;52(5):1801393.
6. **Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).** Nationale VersorgungsLeitlinie Asthma; Langfassung, 4. Auflage [online]. AWMF-Registernummer nvl-002. 09.2020. Berlin (GER): Ärztliches Zentrum für Qualität in der Medizin (ÄZQ); 2020. [Zugriff: 23.03.2021]. URL: https://www.leitlinien.de/mdb/downloads/nvl/asthma/asthma-4aufl-vers1-lang.pdf.
7. **Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).** Nationale VersorgungsLeitlinie Asthma; Leitlinienreport, 4. Auflage [online]. AWMF-Registernummer nvl-002. 09.2020. Berlin (GER): Ärztliches Zentrum für Qualität in der Medizin (ÄZQ); 2020. [Zugriff: 23.03.2021]. URL: https://www.leitlinien.de/mdb/downloads/nvl/asthma/asthma-4aufl-vers1-llr.pdf.
8. **Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, et al.** Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. J Allergy Clin Immunol 2019;143(1):190-200.
9. **Casale TB, Pacou M, Mesana L, Farge G, Sun SX, Castro M.** Reslizumab Compared with Benralizumab in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis. J Allergy Clin Immunol Pract 2019;7(1):122-130.
10. **Farne HA, Wilson A, Powell C, Bax L, Milan SJ.** Anti-IL5 therapies for asthma. Cochrane Database of Systematic Reviews [online]. 2017(9):Cd010834. URL: http://dx.doi.org/10.1002/14651858.CD010834.pub3.
11. **Fu Z, Xu Y, Cai C.** Efficacy and safety of omalizumab in children with moderate-to-severe asthma: a meta-analysis. J Asthma 2020:1-9.

12. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) – Anlage IV: Therapiehinweis Omalizumab, vom 17. Dezember 2015 [online]. Berlin (GER): G-BA; 2015. [Zugriff: 23.03.2021]. URL: https://www.g-ba.de/downloads/39-261-2418/2015-12-17_AM-RL-IV_TH_Omalizumab_BAnz.pdf.

13. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL), zuletzt geändert am 17. Dezember 2020, in Kraft getreten am 01. Januar 2021 [online]. Berlin (GER): G-BA; 2021. [Zugriff: 23.03.2021]. URL: https://www.g-ba.de/downloads/62-492-2416/DMP-A-RL_2020-11-20_iK-2021-02-25.pdf.

14. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage IV zum Abschnitt H der Arzneimittel-Richtlinie: Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung; Therapiehinweise gemäß § 92 Abs. 2 Satz 7 SGB V i. V. m. § 17 AM-RL zur wirtschaftlichen Verordnungsweise von Arzneimitteln, letzte Änderung in Kraft getreten am: 27.06.2020 [online]. Berlin (GER): G-BA; 2020. [Zugriff: 23.03.2021]. URL: https://www.g-ba.de/downloads/91-1385-487/2020-02-20_Geltende-Fassung_Dupilumab_nAWG_D-482.pdf.

15. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 2. August 2018 - Benralizumab [online]. Berlin (GER): G-BA; 2018. [Zugriff: 23.03.2021]. URL: https://www.g-ba.de/downloads/91-1385-347/2018-08-02_Geltende-Fassung_Benralizumab_D-341.pdf.

16. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Juli 2017 / 6. Dezember 2018 - Reslizumab [online]. Berlin (GER): G-BA; 2018. [Zugriff: 23.03.2021]. URL: https://www.g-ba.de/downloads/91-1385-274/2018-12-06_Geltende-Fassung_Reslizumab_D-271.pdf.

17. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. Februar 2020 - Dupilumab (neues Anwendungsgebiet: Asthma bronchiale) [online]. Berlin (GER): G-BA; 2020. [Zugriff: 23.03.2021]. URL: https://www.g-ba.de/downloads/91-1385-487/2020-02-20_Geltende-Fassung_Dupilumab_nAWG_D-482.pdf.

18. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Juli 2016 / 06. Dezember 2018 - Mepolizumab [online]. Berlin (GER): G-BA; 2018. [Zugriff: 23.03.2021]. URL: https://www.g-ba.de/downloads/91-1385-216/2018-12-06_Geltende-Fassung_Mepolizumab_D-211.pdf.

19. **Global Initiative for Asthma (GINA).** Global strategy for asthma management and prevention (2020 update) [online]. Fontana (USA): GINA; 2020. [Zugriff: 23.03.2021]. URL: https://ginasthma.org/gina-reports/.

20. **Henriksen DP, Bodtger U, Sidenius K, Maltbaek N, Pedersen L, Madsen H, et al.** Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti-IL-5 treatments of severe asthma - a systematic review and meta-analysis. Eur Clin Respir J 2018;5(1):1536097.

21. **Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al.** Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2020;55(1):1900588.

22. **Li J, Wang F, Lin C, Du J, Xiao B, Du C, et al.** The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: A systematic review and meta-analysis. J Asthma 2017;54(3):300-307.

23. **Liu W, Ma X, Zhou W.** Adverse events of benralizumab in moderate to severe eosinophilic asthma: A meta-analysis. Medicine (Baltimore) 2019;98(22):e15868.

24. **Meng JF, Li H, Luo MJ, Li HB.** Efficacy of tiotropium in treating patients with moderate-to-severe asthma: A meta-analysis and systematic review based on 14 randomized controlled trials. Medicine (Baltimore) 2019;98(33):e16637.

25. **Murphy KR, Chipps BE.** Tiotropium in children and adolescents with asthma. Ann Allergy Asthma Immunol 2020;124(3):267-276.e263.

26. **National Institute for Health and Care Excellence (NICE).** Chronic asthma: management [online]. 03.2021. London (GBR): NICE; 2017. [Zugriff: 23.03.2021]. (NICE guideline; Band 80). URL: https://www.nice.org.uk/guidance/ng80/evidence/full-guidelines-november-2017-7079863933?tab=evidence.

27. **Ramonell RP, Iftikhar IH.** Effect of Anti-IL5, Anti-IL5R, Anti-IL13 Therapy on Asthma Exacerbations: A Network Meta-analysis. Lung 2020;198(1):95-103.

28. **Rodrigo GJ, Neffen H.** Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review. Pediatr Allergy Immunol 2017;28(6):573-578.

29. **Rogliani P, Ritondo BL, Calzetta L.** Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies. Eur Respir J 2021.

30. **Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society.** British guideline on the management of asthma. A national clinical guideline [online]. 07.2019. Edinburgh (GBR): SIGN; 2019. [Zugriff: 23.03.2021]. (SIGN publication; Band 158). URL: https://www.sign.ac.uk/media/1773/sign158-updated.pdf.

31. **Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, et al.** Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists With Asthma Control in Patients With Uncontrolled, Persistent Asthma: A Systematic Review and Meta-analysis. JAMA 2018;319(14):1473-1484.

32. **Sobieraj DM, Baker WL, Weeda ER, Nguyen E, Coleman CI, White CM, et al.** AHRQ Comparative Effectiveness Reviews [online]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018. [Zugriff: 23.03.2021]. (Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma). URL: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-194-final-corticosteroids-asthma.pdf.

33. **Tian BP, Zhang GS, Lou J, Zhou HB, Cui W.** Efficacy and safety of benralizumab for eosinophilic asthma: A systematic review and meta-analysis of randomized controlled trials. J Asthma 2018;55(9):956-965.

34. **Wang FP, Liu T, Lan Z, Li SY, Mao H.** Efficacy and Safety of Anti-Interleukin-5 Therapy in Patients with Asthma: A Systematic Review and Meta-Analysis. PLoS One 2016;11(11):e0166833.

35. **Wang FP, Xiong XF, Liu T, Li SY, Cheng DY, Mao H.** Anti-interleukin 5 Therapy for Eosinophilic Asthma: a Meta-analysis of Randomized Clinical Trials. Clin Rev Allergy Immunol 2018;54(2):318-330.

36. **Xiong XF, Zhu M, Wu HX, Fan LL, Cheng DY.** Efficacy and safety of dupilumab for the treatment of uncontrolled asthma: a meta-analysis of randomized clinical trials. Respir Res 2019;20(1):108.

37. **Yan K, Balijepalli C, Sharma R, Barakat S, Sun SX, Falcao S, et al.** Reslizumab and mepolizumab for moderate-to-severe poorly controlled asthma: an indirect comparison meta-analysis. Immunotherapy 2019;11(17):1491-1505.

38. **Zayed Y, Kheiri B, Banifadel M, Hicks M, Aburahma A, Hamid K, et al.** Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. J Asthma 2019;56(10):1110-1119.

# Anhang

*Agache I et al., 2020 [1].*

Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma

**TABLE 3** Summary of findings for Benralizumab compared to standard of care for eosinophilic asthma

| Outcomes | No. of participants (studies) Follow-up (range) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects: Risk with standard of care | Anticipated absolute effects: Risk difference with benralizumab |
|---|---|---|---|---|---|
| **Exacerbations** Assessed with annualized asthma exacerbation rate | 1373 (3 RCTs)[39-41] 28 to 56 weeks | ⨁⨁⨁⨁ HIGH[a,b] | **Incidence rate ratio 0.53** (0.39 to 0.72)[c,d] | 1500 exacerbations per 1000 patients per year | **705 fewer exacerbations per 1.000 patients per year** (915 fewer to 420 fewer) |
| **Asthma Control** Assessed with ACQ-6 score between-group difference at the end of the study | 1373 (3 RCTs)[39-41] 28 to 56 weeks | ⨁⨁⨁⨁ HIGH[b,d,e,f] | – | | mean difference−**0.26** (−0.46 to − 0.07 fewer)[f,g] |
| **Quality of life** Assessed with Asthma Quality of Life Questionnaire for 12 years and older | 1333 (3 RCTs)[39-41] 28 to 52 weeks | ⨁⨁⨁⨁ HIGH[b,d,h,j,k] | – | | mean difference + **0.23** (+0.11 to + 0.36)[c] |
| **Any drug-related adverse event (AE)** Assessed with number of events | 478 (1 RCT)[40] 56 wk | ⨁⨁⨁◯ MODERATE[b,h,l] | **Risk ratio 1.41** (0.87 to 2.27) | 105 per 1.000 | **43 more per 1.000** (14 fewer to 133 more) |
| **Any serious adverse event (SAE) unrelated to asthma exacerbation** Assessed with number of events | 148 (1 RCT)[41] 28 wk | ⨁⨁◯◯ LOW[b,h,l] | **Risk ratio 0.56** (0.22 to 1.44) | 147 per 1.000 | **65 fewer per 1.000** (114 fewer to 65 more) |
| **Decrease in OCS use** Assessed with reduction in daily OCS dose of ≥50% | 148 (1 RCT)[41] 28 wk | ⨁⨁⨁⨁ HIGH[b,h] | **Risk ratio 1.76** (1.26 to 2.47) | 373 per 1.000 | **284 more per 1.000** (97 more to 549 more) |
| **Lung function** Assessed with prebronchodilator FEV1 (mL) between-group difference at the end of the study | 1370 (3 RCTs)[39-41] 28 to 56 wk | ⨁⨁⨁◯ MODERATE[b,h,i,l] | – | | mean difference + **140 mL** (+90 to + 190)[c] |
| **Rescue medication use** Assessed with puffs/day | 0 studies | – | Not estimable | | |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**GRADE Working Group grades of evidence**
**High certainty:** High confidence that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

***Explanations***

a. Statistically significant ($I^2$ = 65%) but probably unimportant heterogeneity.
b. All included studies were funded by industry, and all showed positive results. No industry-independent observational or randomized studies were identified to contrast results. Therefore, the quality of the evidence was downgraded for potential publication bias.[70]
c. The pooled data were assessed at 28 wk [41] and at 48-52 wk.[71] Goldman 2017 included patients aged 12-17 y old.
d. In the current systematic review, 2 studies reporting the effect on exacerbation leading to emergency room visits or hospitalizations were also included. The pooled risk ratio was 0.24 (95% CI 0.03-1.72; see full-text report).
e. Statistically significant ($I^2$ = 61%) but probably unimportant heterogeneity.
f. The minimal important difference (MID) for ACQ-6 is 0.5 points.[35]
g. In the current systematic review 3, studies reporting the effect on total asthma control score change were also included. The pooled mean difference was −0.19 (95CI% −0.31 to −0.08), see full-text report.
h. Quality of the evidence was downgraded because FEV1 is considered a surrogate outcome for asthma control, with a variable correlation with asthma symptoms.[72]
i. The panel agreed that minimal important difference for FEV1 is 0.20 L.
j. Statistically significant ($I^2$ = 55%) but probably unimportant heterogeneity.
k. For AQLQ(S)+12 the MID is 0.5.[37]
l. The effect may both be harmful or beneficial. Small sample size and number of events.

**TABLE 4** Summary of findings of Dupilumab compared to standard of care for eosinophilic asthma

| Outcomes | No. of participants (studies) Follow-up (range) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with standard of care | Risk difference with dupilumab |
| **Exacerbations** Assessed with annualized asthma exacerbation rate | 1712 (3 RCTs)[42-44] 24 to 52 wk | ⨁⨁⨁⨁ HIGH[4,a,b] | **Incidence rate ratio 0.44** (0.32 to 0.59) | 1570 exacerbations per 1000 patients per year | **894 fewer exacerbations per 1000 patients per year** (1086 fewer to 655 fewer)[c] |
| **Asthma control** assessed with: Asthma Control Questionnaire −5 Scale from: 1 to 5 | 507 (1 RCT)[42] 24 wk | ⨁⨁⨁◯ MODERATE[4,d,a,b,g] | – | | mean difference—**0.48** (−0.88 lower to −0.09) |
| **Quality of life** Assessed with asthma Quality of Life Questionnaire Scale from: 1 to 7 | 958 (2 RCTs)[43,44] 24 to 52 wk | ⨁⨁⨁◯ MODERATE[4,9,a,b,h] | – | | mean difference + **0.42** (+0.25 to +0.59) |
| **Treatment-related adverse events (AE)** Assessed with number of events | 264 (1 RCT)[42] 24 wk | ⨁⨁⨁◯ MODERATE[4,a,b,m] | **Risk ratio 1.00** (0.88 to 1.13) | 794 per 1.000 | **0 fewer per 1.000** (95 fewer to 103 more) |
| **Treatment-related serious adverse events (SAE)** Assessed with number of events | 264 (1 RCT)[42] 24 wk | ⨁⨁◯◯ LOW[4,a,b,n] | **Risk ratio 1.46** (0.60 to 3.54) | 59 per 1.000 | **27 more per 1.000** (24 fewer to 149 more) |
| **Decrease in OCS dose** Assessed with percentage of reduction compared to baseline | 150 (1 RCT)[42] 24 wk | ⨁⨁⨁⨁ HIGH[4,a,b] | – | | mean difference—**29.4%** (−43.23 to −15.57) |
| **Lung function** Assessed with FEV1 in mL | 1030 (3 RCTs)[42-44] 24 to 52 wk | ⨁⨁◯◯ LOW[4,7,a,b,d,e,f] | – | | mean difference + **180 mL** (+110 to +250) |
| **Fraction of exhaled nitric oxide** Assessed with mean % change (ppb) from baseline | 150 (1 RCT)[42] 24 wk | ⨁⨁◯◯ LOW[4,10-12,a,b,i,j] | – | | mean difference—**40.11%** (−78.68 to −1.55) |
| **Rescue medication use** Assessed with puffs/day | 143 (1 RCT)[42] 24 to 52 wk | ⨁⨁⨁◯ MODERATE[4,7,a,b,k,l] | – | | mean difference—**0.56 puff/day** (−2.28 to +1.16) |

[c]**The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**GRADE Working Group grades of evidence**
**High certainty:** High confidence that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.
**Very low certainty:** Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

***Explanations***

a. All included studies had a high risk of selective reporting bias.[42-44] However, the evidence quality was not downgraded because most of the outcomes of interest for our analysis were reported.

b. All included studies were founded by industry and the same company (Sanofi and Regeneron Pharmaceuticals), and all showed positive results. No industry-independent observational or randomized trials were identified to contrast the results. Therefore, the quality of the evidence was downgraded for potential publication bias.[70]

c. Two studies (Rabe 2018, Wenzel 2016) assessed exacerbations at 24 wk and Castro 2018 at 52 wk.

d. The quality of the evidence was downgraded because FEV1 is considered a surrogate outcome of asthma control, with a variable correlation with asthma symptoms.[72]

e. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L and considered the effect as imprecise.

f. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L and thus the effect was considered as imprecise.

g. Downgraded because the effect of dupilumab is beneficial but the lower side of the CI is less than the MID(0.5 points).[37]

h. Downgraded because the effect of dupilumab is beneficial but the lower side of the CI is less than the MID(0.5 points).[37]

**TABLE 4** (Continued)

i. Downgraded because FeNO is not consistently considered a good surrogate of eosinophilic inflammation.[73,74]

j. From one visit to the next, a change greater than 20% for basal values over 50 ppb or more than 10 ppb for basal values lower than 50 ppb may indicate significant response.[38]

k. Downgraded because the effect may both be beneficial and harmful.

l. The MID for rescue medication use is a reduction by 0.81 puffs/d.[35]

m. The effect may both be harmful or beneficial. Small number of events.

**TABLE 5** Summary of findings of mepolizumab compared to standard of care for eosinophilic asthma

| Outcomes | No. of participants (studies) Follow-up (range) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects: Risk with standard of care | Anticipated absolute effects: Risk difference with mepolizumab |
|---|---|---|---|---|---|
| **Exacerbations** Exacerbation rate ratio Assessed with the annualized rates of asthma exacerbations | 1071 (3 RCTs)[45-47] 24 to 32 wk | ⨁⨁⨁⨁ HIGH[4,5,a,b,c] | **Incidence rate ratio 0.49** (0.38 to 0.66) | 1700 exacerbations per 1000 patients per year | **870 fewer exacerbations per 1000 patients per year** (592 fewer to 1079 fewer) |
| **Exacerbations leading to hospitalization** Assessed with the annualized rate of asthma exacerbations leading to hospitalization | (2 RCTs)[45,47] 24 to 32 wk | ⨁⨁⨁⨁ HIGH[4,5] | **Incidence rate ratio 0.30** (0.13 to 0.71) | 100 exacerbations per 1000 patients per year | **70 fewer exacerbations per 1000 patients per year** (29 fewer to 87 fewer) |
| **Asthma control** Assessed with: ACQ-5 score between-group difference at the end of the study Scale from: 0 to 6[9,i] | 912 (3 RCTs)[45,47] | ⨁⨁⨁◯ MODERATE[4,5,a,c,i] | – | | mean difference−**0.43** (−0.56 to −0.31) |
| **Quality of life** Assessed with St. George's Respiratory Questionnaire between-group difference at the end of the study | 1045 (3 RCTs)[45-47] 24 to 32 wk[10,k] | ⨁⨁⨁◯ MODERATE[4,5,a,c,l] | – | | mean difference−**7.14** (−9.07 to −5.21) |
| **Treatment-related adverse events (AE)** Assessed with number of events | 1071 (3 RCTs)[45-47] | ⨁⨁⨁⨁ HIGH[4,5,z] | **Risk ratio 1.35** (1.01 to 1.80) | 796 per 1.000 | **279 more per 1.000** (8 more to 637 more) |
| **Treatment-related serious adverse events (SAE)** Assessed with number of events | 385 (1 RCT)[47] | ⨁◯◯◯ VERY LOW[4,5,c,m,n] | **Risk ratio 0.98** (0.06 to 15.63) | 5 per 1.000 | **0 fewer per 1.000** (−5 fewer to 77 more) |
| **Lung function** assessed with prebronchodilator FEV1 (mL) between-group difference at the end of the study | 1043 (3 RCTs)[45-47] 24 to 32 wk[6,o] | ⨁⨁⨁◯ MODERATE[4,5,7,a,c,f] | – | | mean difference + **110.9 mL** (+58.91 to +162.89) |
| **Lung function** assessed with AM peak expiratory flow (PEF) | 936 (2 RCTs)[77] 24 wk[6,h,g] | ⨁⨁◯◯ LOW[4,5,c,h,j] | – | | mean difference + **22.46** (+13.98 to +30.94) |
| **Rescue medication use** assessed with puffs/day | (1 RCT)[45] 21 to 24 wks[o] | ⨁⨁⨁⨁ HIGH[4,5,z] | – | | mean difference **−0.1 puff/d** (−0.35 to +0.15) |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**GRADE Working Group grades of evidence**
**High certainty:** High confidence that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.
**Very low certainty:** Little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

(Continues)

**TABLE 5** (Continued)

***Explanations***

a. Two of three studies had a high risk of attrition bias.[45,47] Modified intention-to-treat analysis was conducted (ie patients were analysed as treated, not as randomized).

b. Probable unimportant heterogeneity

c. Included studies were all funded by industry, and all showed positive results. We identified two industry-independent observational trials that showed similar effects with our meta-analysis.[76,77]

d. Mean rates of exacerbation requiring hospitalization across studies were very low (ie from 0.02 to 0.10 exacerbations requiring hospitalization per person-year), both in the placebo and intervention arms

e. The panel agreed that minimal important difference (MID) for FEV1 is 0.20 L.

f. Downgraded because FEV1 is considered a surrogate outcome of asthma control of symptoms, with a variable correlation with asthma symptoms.[72]

g. The MID of PEF is 18.8 L/min.[35]

h. Potential attrition bias because PEF baseline values reported in the primary publication[47] differed from values reported in post hoc analysis publication.[77]

i. Downgraded because the lower CI boundary crosses the MID threshold

j. 0.5 points is the minimal important difference for the Asthma Control Questionnaire (ACQ-5 score).[37]

k.>−4.0 was considered the threshold for the MID for quality of life measured with the St. George's Respiratory Questionnaire.[36]

l. The St. George's Respiratory Questionnaire SGRQ is not a disease-specific questionnaire for asthma.

m. Findings from only 1 RCT available. Downgraded due to publication bias

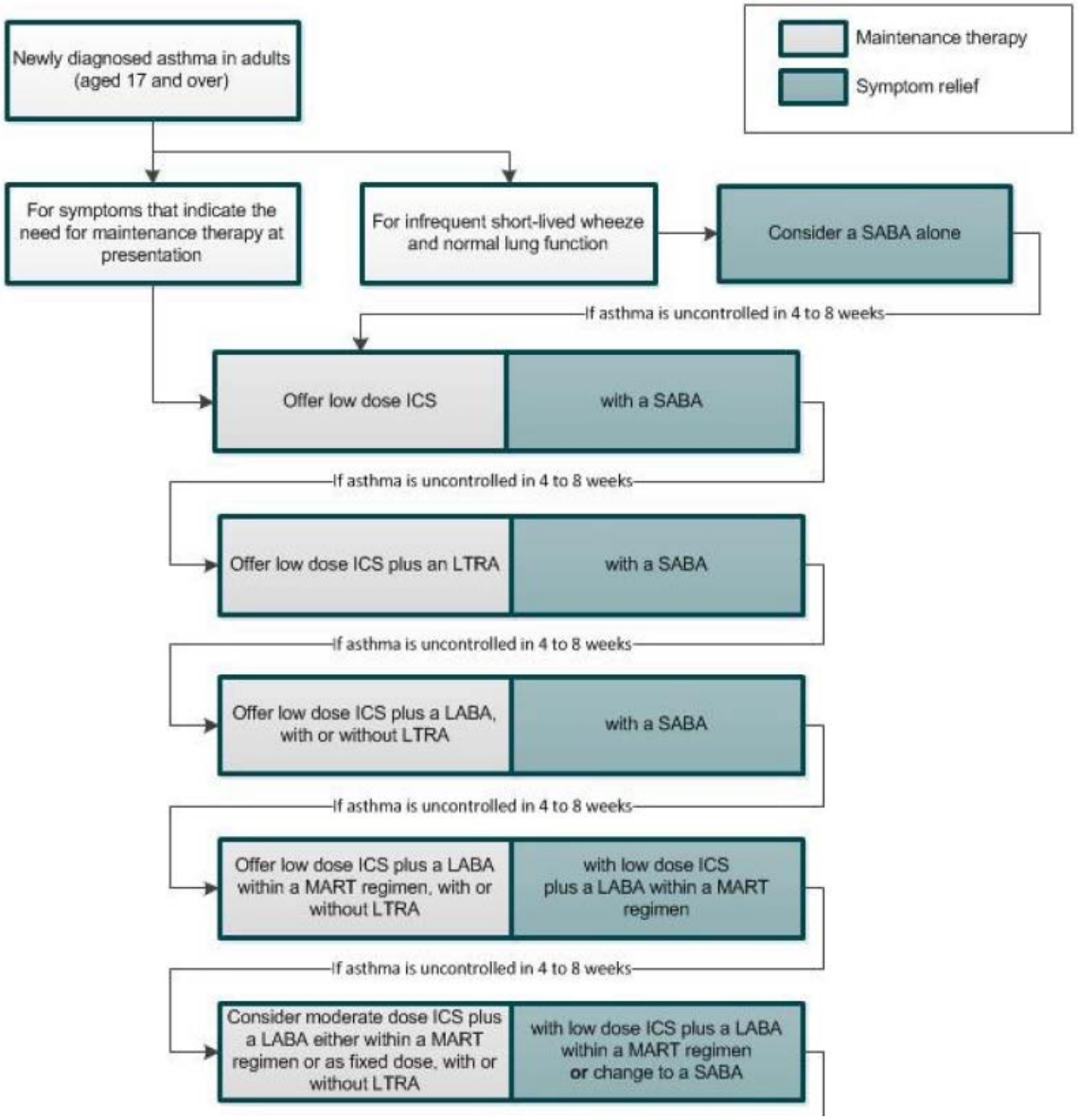
n. Very few numbers of events per arm

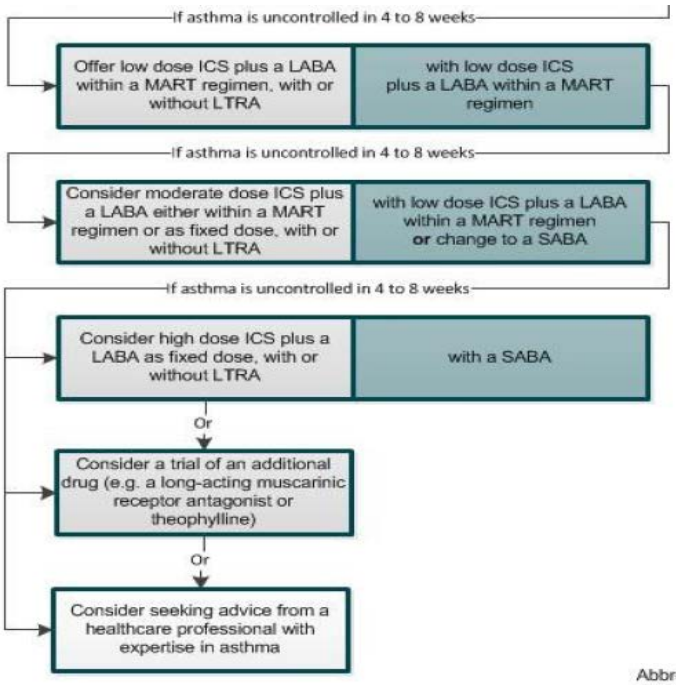
o. The minimal important difference for rescue medication use is −0.81 puffs/d.[35]

*National Institute for Health and Care Excellence (NICE), 2017 [26].*

Asthma: diagnosis, monitoring and chronic asthma management.

**Algorithm C: Pharmacological treatment of chronic asthma in adults aged 17 and over**






Abbreviations:
ICS, inhaled corticosteriod
LABA, long-acting beta agonist
LTRA, leukotriene receptor antagonist
MART, maintenance and reliever therapy
SABA, short-acting beta agonist

**Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6**

**2021-B-064**

**Kontaktdaten**
Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 13.04.2021

Indikation gemäß Beratungsantrag
Patienten zwischen 6 und 11 Jahren mit schwerem Asthma mit Typ-2-Inflammation, gekennzeichnet durch eine erhöhte Anzahl der Eosinophilen im Blut und/oder eine erhöhte exhalierte Stickstoffmonoxid-Fraktion (FeNO), das trotz mittel- bis hochdosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist.

**Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?**

In der oben geschilderten Situation stehen in der Altersgruppe 6–11 Jahre neben den mittel- bis hochdosierten ICS vier weitere Optionen zur Verfügung, die in Kombination oder einzeln zum Erreichen der Asthmakontrolle eingesetzte werden: a) Langwirksame Betamimetika (LABA) b) Langwirksame Anticholinergika (LAMA); c) Leukotrien-Rezeptor-Antagonisten; d) Monotherapie mit einer hochdosierten ICS-Gabe. Es gibt einige wenige Studien, die in dieser Indikation das Therapieansprechen auf Option a – c und d verglichen haben. Da die Zulassung von LAMA noch nicht lange besteht, fehlen hier vergleichende Daten, entsprechende klinische Studien sind aber in Vorbereitung. Zusammenfassend zeigen die Studien, dass das Therapieansprechen auf die unterschiedlichen Optionen individuell unterschiedlich ist. Numerisch ist das Therapieansprechen auf Option a am besten. Offenbar ist das Therapieansprechen auch vom ethnischen Hintergrund der Patienten abhängig.

In der derzeitigen Versorgungspraxis in Deutschland ist nach den Vorgaben der Nationalen Versorgungsleitlinie folgendes praktisches Vorgehen vorgesehen:

1) Ausschöpfen aller in Therapiestufe IV und V vorgesehenen Möglichkeiten, einschließlich einer Kombination dieser Wirkstoffe.
2) Überprüfen der Asthmadiagnose und der Therapieadhärenz (ggf. Vorstellung an einem kinderpneumologischen Zentrum; ggf. Überprüfen von Rehabilitationsmaßnahmen).
3) Sollten die unter 1 und 2 aufgeführten Maßnahmen keinen Erfolg zeigen, so ist der Einsatz eines Biologikums zu erwägen.
4) Die meiste Erfahrung in dieser Altersgruppe besteht mit dem monoklonalen Anti-IgE-Antikörper Omalizumab. Der Einsatz in dieser Altersgruppe ist auf Kinder beschränkt, die eine perenniale Sensibilisierung aufweisen (z. B. gegen Hausstaubmilbe oder Katze etc.), die trotz der unter Punkt 1 und 2 geschilderten Maßnahmen und Therapie weiterhin ein unkontrolliertes Asthma haben und die mit ihren gesamt-IgE-Konzentrationen im Serum im angegebenen Dosisbereich für Omalizumab liegen.
5) Mit Mepolizumab ist ein Anti-IL-5 Antikörper verfügbar. Die Datengrundlage im Kindes-

und Jugendalter ist bislang noch beschränkt.

6) Mit Dupilumab ist ein Anti-IL4/IL13-Rezeptor-Antikörper für Asthma bronchiale ab 12 Jahren und für die schwere atopische Dermatitis (AD) ab 6 Jahren zugelassen. Da Effekte auf die Lungenfunktion für Dupilumab in der Altersgruppe ab 12 Jahre vielversprechend sind und Effekte auf die AD ab 6 Jahren in klinischen Studien gut belegt sind, erscheint diese Therapieoption insbesondere für Patienten mit Asthma und der AD als atopischer Komorbidität vielversprechend.

**Literatur I**

1. Agache I, Beltran J, Akdis C et al.: Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. Allergy 2020; 75: 1023-1042.

2. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): Nationale VersorgungsLeitlinie Asthma – Langfassung: https://www.leitlinien.de/nvl/asthma (letzter Zugriff: 6. April 2021). AWMF-Register Nr. nvl-002, 4. Auflage, Version 1, 2020.

3. Cork MJ, Thaci D, Eichenfield LF et al.: Dupilumab provides favourable long-term safety and efficacy in children aged >/= 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. Br J Dermatol 2020: Epub ahead of print.

4. De Keyser HH, Ramsey R, Federico MJ: They just don't take their medicines: Reframing medication adherence in asthma from frustration to opportunity. Pediatr Pulmonol 2020; 55: 818-825.

5. Gupta A, Ikeda M, Geng B et al.: Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. J Allergy Clin Immunol 2019; 144: 1336-1342.

6. Gupta A, Pouliquen I, Austin D et al.: Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. Pediatr Pulmonol 2019; 54: 1957-1967.

7. Liu NM, Carlsen KCL, Cunningham S et al.: First analysis of the Severe Paediatric Asthma Collaborative in Europe registry. ERJ Open Res 2020; 6: 00566-2020.

8. McGregor MC, Krings JG, Nair P, Castro M: Role of biologics in asthma. Am J Respir Crit Care Med 2019; 199: 433-445.

9. Simpson EL, Paller AS, Siegfried EC et al.: Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. JAMA Dermatol 2020; 156: 44-56.

10. Tan DJ, Bui DS, Dai X et al.: Does the use of inhaled corticosteroids in asthma benefit lung function in the long-term? A systematic review and meta-analysis. Eur Respir Rev 2021; 30: 200185.

11. Vogelberg C, Goldstein S, Graham L et al.: A comparison of tiotropium, long-acting beta2-agonists and leukotriene receptor antagonists on lung function and exacerbations in paediatric patients with asthma. Respir Res 2020; 21: 19.

**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „**Patienten zwischen 6 und 11 Jahren mit schwerem Asthma mit Typ-2-Inflammation, gekennzeichnet durch eine erhöhte Anzahl der Eosinophilen im Blut und/oder eine erhöhte exhalierte Stickstoffmonoxid-Fraktion (FeNO), das trotz mittel- bis hochdosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist**“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Bislang gibt es außer den genannten Eosinophilenzahlen und dem exhalierten Stickstoffmonoxid folgende Kriterien, die bei der Therapieentscheidung regelmäßig berücksichtigt werden:

- Gesamt-IgE-Konzentration (für die Entscheidung z. B. für oder gegen Omalizumab)
- Spezifisches IgE gegen ein perenniales, inhalatives Allergen (für die Entscheidung z. B. für oder gegen Omalizumab)
- Atopische Komorbiditäten wie z. B. das atopische Ekzem (für die Entscheidung z. B. für oder gegen Dupilumab)

**Literatur II**

2. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): Nationale VersorgungsLeitlinie Asthma – Langfassung: https://www.leitlinien.de/nvl/asthma (letzter Zugriff: 6. April 2021). AWMF-Register Nr. nvl-002, 4. Auflage, Version 1, 2020.