Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-199z (Mepolizumab)

Stand: Dezember 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Mepolizumab Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei Kindern und Jugendlichen im Alter von ≥ 6 bis < 18 Jahren	
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): - Mepolizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 21. Juli 2016) - Reslizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 6. Juli 2017) - Benralizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 2. August 2018) *Hinweis:alle drei Beschlüsse nur für Erwachsene* Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL) - Anlage IV: Therapiehinweis zu Omalizumab (Beschluss vom 17. Dezember 2015) 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 **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Mepolizumab R03DX09 Nucala®	<u>*Zugelassenes AWG:*</u> *Nucala ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei Erwachsenen, Jugendlichen und Kindern ab* ***≥ 6 Jahren.*** <u>Zu beratendes AWG:</u> *Nucala ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma* ***bei Kindern und Jugendlichen im Alter von*** ***≥ 6 bis < 18 Jahren****.*
Beta-2-Sympathomimetika (inhalativ; kurzwirkend) (SABA)	
Salbutamol R03AC02 Salbutamol CT	Zur Verhütung und Behandlung von Atemwegserkrankungen mit reversibler Obstruktion, wie z. B. Asthma bronchiale oder chronische Bronchitis. Salbutamol-CT Dosieraerosol wird angewendet bei Erwachsenen, Jugendlichen und Kindern im Alter von 5 bis 12 Jahren (für die Anwendung bei Kleinkindern und Kindern unter 5 Jahren siehe Abschnitte 4.2 und 5.1). Hinweis: Eine längerfristige Behandlung soll symptomorientiert und nur in Verbindung mit einer entzündungshemmenden Dauertherapie erfolgen. (FI Salbutamol CT, Stand 04/2015)
Fenoterol R03AC04 Berotec N®	- Symptomatische Behandlung von akuten Asthmaanfällen. - Prophylaxe von belastungsinduziertem Asthma bronchiale. - 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. Hinweis:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	- Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen. 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: (FI Berotec, Stand 09/2015)
Beta-2-Sympathomimetika (systemisch; kurzwirkend) (SABA)	
Reproterol R03CC14 Bronchospasmin	Zur kurzfristigen Behandlung des schweren bronchospastischen Anfalls und des Status asthmaticus. Aus Dosierung: Kinder (Säuglinge ab 3. Monat, Klein- und Schulkinder) […] (FI Bronchospasmin, Stand 02/2016)
Beta-2-Sympathomimetika (inhalativ; langwirkend) (LABA)	
Salmeterol R03AC12 Serevent® Dosier-Aerosol Serevent® Diskus	Zur Langzeitbehandlung von Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z. B. Asthma bronchiale (anfallsweise auftretende Atemnot durch Atemwegsverkrampfung, insbesondere nächtliches Asthma), chronische Bronchitis und Blählunge (Lungenemphysem). 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. Warnhinweis: Serevent Dosier-Aerosol und Serevent Diskus sollen nicht für die Akutbehandlung eines Asthmaanfalls eingesetzt werden. *Aus Dosierung: Für Erwachsene und Kinder ab 4 Jahren gelten folgende Empfehlungen:* *Serevent Dosier-Aerosol: Erwachsene: 2-mal täglich 2 Sprühstöße inhalieren. Bei stärkeren Beschwerden kann die Dosis auf Anweisung des Arztes auf 2-mal täglich 4 Sprühstöße erhöht werden. Kinder ab 4 Jahren: 2-mal täglich 2 Sprühstöße inhalieren.* *Serevent Diskus Erwachsene: 2-mal täglich 1 Einzeldosis inhalieren. Bei stärkeren Beschwerden kann die Dosis auf Anweisung des Arztes auf 2-mal täglich 2 Einzeldosen erhöht werden. Kinder ab 4 Jahren: 2-mal täglich 1 Einzeldosis inhalieren.* (FI Serevent ® Dosier-Aerosol, Stand 02/2015)
Formoterol R03AC13 Formoterol CT®	- Symptomatische Langzeitbehandlung des chronischen mäßigen bis schweren Asthma bronchiale in Kombination mit einer entzündungshemmenden Dauertherapie (z. B. Kortikosteroide). - […]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Hinweis: 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. *Aus Dosierung: Kinder ab 6 Jahren, Jugendliche und Erwachsene (auch Ältere) gilt: Die übliche Erhaltungsdosis ist 1 Kapsel mit Pulver zur Inhalation (12 Mikrogramm) zweimal täglich.* (FI Formoterol-CT, Stand 06/2015)
Beta-2-Sympathomimetika (oral; kurz-, langwirkend)	
Terbutalin R03AC03 Aerodur Turbohaler®	Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z.B. Asthma bronchiale, chronische Bronchitis und Blählunge (Lungenemphysem). *Aus Dosierung: Für Erwachsene und Kinder ab 5 Jahren gelten folgende Empfehlungen: […]* (FI Aerodur Turbohaler, Stand 05/2017)
Salbutamol R03CC02 Salbubronch®	Verhütung und Behandlung von Atemwegserkrankungen bei Erwachsenen und Kindern ab 2 Monaten, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen), wie z. B. bei Asthma bronchiale, chronischer Bronchitis und Blählunge (Lungenemphysem). Hinweis SALBUBRONCH Elixier ist nur für Patienten, die nicht symptomorientiert mit inhalativen β2-Sympathomimetika behandelt werden können, geeignet. Eine Behandlung mit SALBUBRONCH Elixier sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie mit Glukokortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen. (FI SALBUBRONCH® Elixier, Stand 02/2014)
Bambuterol R03CC12 Bambec®	Verhütung und Behandlung von Atemwegserkrankungen, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen). Hinweis: 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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Aus Dosierung: Kinder von 6 - 12 Jahren: […] (FI Bambec®, Stand 05/2016)
Clenbuterol R03CC13 Spiropent®	Symptomatische Behandlung chronisch obstruktiver Atemwegserkrankungen mit reversibler Atemwegsverengung, wie z. B. Asthma bronchiale oder chronisch obstruktive Bronchitis mit und ohne Emphysem. Hinweis Spiropent Tabletten sind nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Eine Behandlung mit Spiropent Tabletten sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie mit Kortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen. *Aus Dosierung: Bei Kindern bis zu 12 Jahren ist im Allgemeinen wie in der nachfolgenden Tabelle angegeben zu dosieren: […]* (FI Spiropent® Tropfen, Stand 03/2014)
Clenbuterol/ Ambroxol R03CC63 Spasmo-Mucosolvan Saft®	Akute und chronische Atemwegserkrankungen, die mit spastischen Verengungen, veränderter Sekretbildung und gestörtem Sekrettransport einhergehen, insbesondere spastische Bronchitiden, Emphysembronchitiden und Asthma bronchiale. Hinweis 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. *Soweit nicht anders verordnet wird, ist bei Kindern bis zu 12 Jahren im Allgemeinen wie in der folgenden Tabelle angegeben zu dosieren:[…]* (FI Spasmo-Mucosolvan® Saft, Stand 03/2016)
Anticholinergika (inhalativ)	
Tiotropium-bromid R03BB04 Spiriva® Respimat®	[…] <u>Asthma</u> Spiriva Respimat ist indiziert als zusätzlicher dauerhaft einzusetzender Bronchodilatator bei Patienten ab 6 Jahren mit schwerem Asthma, die im Vorjahr mindestens eine schwere Exazerbation erfahren haben (siehe Abschnitte 4.2 und 5.1). (FI Spiriva® Respimat®, Stand 05/2018) <u>Kinder und Jugendliche</u> *Asthma* Die empfohlene Tagesdosis für Patienten im Alter von 6 bis 17 Jahren beträgt 5 Mikrogramm Tiotropium entsprechend der Inhalation von 2 Hüben aus dem Respimat Inhalator einmal täglich zur gleichen Tageszeit.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Bei Jugendlichen (12 - 17 Jahre) mit schwerem Asthma sollte Tiotropium zusätzlich zu inhalativen Kortikosteroiden (> 800 - 1600 µg Budesonid/Tag oder Äquivalent) und einem Controller, oder zusätzlich zu inhalativen Kortikosteroiden (400 - 800 µg Budesonid/Tag oder Äquivalent) und zwei Controllern angewendet werden. Bei Kindern (6 - 11 Jahre) mit schwerem Asthma sollte Tiotropium zusätzlich zu inhalativen Kortikosteroiden (> 400 µg Budesonid/Tag oder Äquivalent) und einem Controller, oder zusätzlich zu inhalativen Kortikosteroiden (200 - 400 µg Budesonid/Tag oder Äquivalent) und zwei Controllern angewendet werden. Die Sicherheit und Wirksamkeit von Spiriva Respimat ist bei Kindern und Jugendlichen im Alter von 6 bis 17 Jahren mit mittelgradigem Asthma sowie bei Kindern unter 6 Jahren nicht erwiesen. Die derzeit verfügbaren Daten sind in den Abschnitten 5.1 und 5.2 beschrieben, jedoch kann keine Dosierungsempfehlung gegeben werden.
Inhalative Corticosteroide (ICS)	
Beclometason R03BA01 Junik® junior	Antientzündliche Therapie von Asthma bronchiale. *Aus Dosierung:* *Erwachsen: 2-mal täglich 4 – 6 Sprühstöße (entsprechend 0,4 – 0,6 mg Beclometasondipropio nat/Tag).* *Jugendliche ab 12 Jahre : 2-mal täglich 4 – 6 Sprühstöße (entspre chend 0,4 – 0,6 mg Beclometasondipro pionat/Tag).* *Kinder von 5 bis 11 Jahre : 2-mal täglich 2 – 4 Sprühstöße (entsprechend 0,2 – 0,4 mg Beclometasondipropionat/Tag).* (FI Junik® junior, Stand 05/2017)
Budesonid R03BA02 Budenid Easyhaler ®	Zur Behandlung persistierender Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei: - Asthma bronchiale […] *Aus Dosierung: Erwachsene (einschließlich ältere Personen und Jugendliche von 12 bis 17 Jahren) mit leichtem, mittelschwerem und schwerem Asthma: Die übliche Erhaltungsdosis beträgt 100 – 400 µg zweimal täglich. Bei schwerem Asthma kann die Tagesdosis zeitweise bis auf 1600 µ g, aufgeteilt auf mehrere (zwei) Dosen, erhöht, und sobald sich das Asthma stabilisiert hat, wieder reduziert werden. Kinder von 6 bis 11 Jahren: Die übliche Erhaltungsdosis beträgt 100 – 200 µg zweimal täglich. Wenn nötig, kann die Tagesdosis bis auf 800 µg, aufgeteilt auf mehrere (zwei) Dosen, erhöht, und sobald sich das Asthma stabilisiert hat, wieder reduziert werden* (FI budenid Easyhaler ®, Stand 03/2017)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ciclesonid R03BA08 ALVESCO®	Zur Behandlung von persistierendem Asthma bei Erwachsenen und Jugendlichen (ab 12 Jahren). (FI Alvesco®, Stand 04/2016)
Fluticason R03BA05 FLUTIDE® Junior 50 Diskus®	Dauerbehandlung eines persistierenden Asthma bronchiale aller Schweregrade. Hinweis: Flutide Diskus ist nicht zur Akutbehandlung eines Asthmaanfalles geeignet. *Aus Dosierung: Kinder über 4 Jahre: […]* (FI Flutide®, Stand 02/2017)
Mometason R03BA07 ASMANEX®	Bei Erwachsenen und Jugendlichen ab 12 Jahren zur regelmäßigen Behandlung, um anhaltendes Asthma bronchiale zu kontrollieren. (FI ASMANEX® Twisthaler®, Stand 10/2014)
Corticosteroide (systemisch, oral)	
Prednisolon, Prednisolon ratiopharm®	[…] Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren. *Aus Dosierung: 2. Kinder:* *Hochdosiert: 2 – 3 mg/kg KG/Tag* *Mittlere Dosierung: 1 – 2 mg/kg KG/Tag* *Erhaltungsdosis: 0,25 mg/kg KG/Tag* (FI Prednisolon-ratiopharm®, Stand 08/2010)
Prednison, Prednison ratiopharm®	[…] Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren. *Aus Dosierung: 2. Kinder* *Hochdosiert: 2 – 3 mg/kg KG/Tag* *Mittlere Dosierung: 1 – 2 mg/kg KG/Tag* *Erhaltungsdosis: 0,25 mg/kg KG/Tag* (FI Prednison-ratiopharm®, Stand 05/2017)
Weitere	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Theophyllin (systemisch) R03DA04 z.B. Theophyllin retard-ratiopharm	Bronchospasmolytikum/Antiasthmatikum 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). *Hinweis:* *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.* *Dosierung: Kinder ab 6 Monaten […]* (FI Theophyllin retard-ratiopharm, Stand 04/2014)
Montelukast (Kautabletten 4 mg) R03DC03 Montelukast AbZ	Montelukast ist indiziert als Zusatzbehandlung bei Patienten im Alter von 6 bis 14 Jahren, die unter einem leichten bis mittelgradigen persistierenden Asthma leiden, das mit einem inhalativen Kortikoid nicht ausreichend behandelt und das durch die bedarfsweise Anwendung von kurz wirksamen β-Agonisten nicht ausreichend unter Kontrolle gebracht werden kann. Montelukast kann auch eine Behandlungsalternative zu niedrig dosierten inhalativen Kortikosteroiden bei Patienten mit leichtem persistierenden Asthma sein, die in letzter Zeit keine schwerwiegenden, mit oralen Kortikosteroiden zu behandelnden Asthmaanfälle hatten und zeigten, dass sie nicht imstande sind, inhalative Kortikosteroide anzuwenden (siehe Abschnitt 4.2). Darüber hinaus kann Montelukast bei Patienten von 6 bis 14 Jahren zur Vorbeugung von Belastungsasthma eingesetzt werden, dessen überwiegende Komponente die durch körperliche Belastung ausgelöste Bronchokonstriktion darstellt. (FI Montelukast AbZ 5 mg Kautabletten, Stand 11/2016)
Omalizumab R03DX05 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). Erwachsene und Jugendliche (ab 12 Jahren) – Erwachsene und Jugendliche (ab 12 Jahren): 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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	dokumentierte, schwere Asthma-Exazerbationen hatten. – Kinder (6 bis < 12 Jahre): 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. (FI Xolair®, Stand 05/2018)
Kombinationspräparate (ICS/LABA)	
Salmeterol/ Fluticason R03AK06 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: – bei Patienten, die mit inhalativen Kortikoiden und kurzwirksamen Beta2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind oder – bei Patienten, die mit inhalativen Kortikoiden und langwirksamen Beta2-Agonisten ausreichend eingestellt sind. Hinweis: Die Stärke Viani 50 µg/100 µg ist nicht angezeigt bei Erwachsenen und Kindern mit schwerem Asthma bronchiale. *Aus Dosierung: Kinder ab 4 Jahren: […] Die für Kinder maximal zugelassene Dosis Fluticasonpropionat, abgegeben aus einem Viani Dosier-Aerosol, ist 100 Mikrogramm 2-mal täglich.* (FI Viani®, Stand 04/2015)
Vilanterol/ Fluticason R03AK10 Relvar® Ellipta®	Relvar Ellipta ist angezeigt für die regelmäßige Behandlung von Asthma bei Erwachsenen und Jugendlichen ab 12 Jahren, bei denen ein Kombinationspräparat (langwirksamer Beta2-Agonist und inhalatives Kortikosteroid) angezeigt ist: • Patienten, die mit inhalativen Kortikosteroiden und einer Bedarfsmedikation mit inhalativen kurzwirksamen Beta2-Agonisten nicht ausreichend eingestellt sind. (FI Relvar® Ellipta®, Stand 10/2016)
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. Hinweis: Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen. *Aus Dosierung: Für Erwachsene und Kinder ab 6 Jahren gelten folgende Empfehlungen:[…]* (FI Berodual®, Stand 10/2014)

Quellen: AMIS-Datenbank, Fachinformationen, Lauer-Fischer-Taxe

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-199z (Mepolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. November 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACQ	Asthma Control Questionnaire
AE	adverse events
AQLQ	Asthma Quality of Life Questionnaire
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BUD	budesonide
F	formoterol
FEV1	forciertes exspiratorisches Volumen (engl. Forced Expiratory Volume in 1 second)
FP	fluticasone
FVC	Forced vital capacity
G-BA	Gemeinsamer Bundesausschuss
GINA	Global Initiative for Asthma
GIN	Guidelines International Network
ICS	inhaled corticosteroids
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LABA	long-acting beta2-agonists
LAMA	long-acting muscarinic antagonist
LTRA	Leukotrienantagonist
NICE	National Institute for Health and Care Excellence
OCS	orales Glucocorticosteroid
PAS	patient access scheme
PEF	Peak expiratory flow
SABA	short-acting beta-agonist
SAE	Serious adverse events
SAL	salmeterol
SIGN	Scottish Intercollegiate Guidelines Network
SoC	standard of care
SiT	'single inhaler therapy'
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei Kindern und Jugendlichen im Alter von ≥ 6 bis < 18 Jahren

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 27.09.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, 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.

Die Recherche ergab 1318 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 24 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2015 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) - Anlage IV: Therapiehinweis Omalizumab vom 17. Dezember 2015

G-BA, 2018 [10].

Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach §137f Abs. 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL): in der Fassung vom 20. März 2014; veröffentlicht im Bundesanzeiger (BAnz AT 26. Juni 2014 B3 AT 26. August 2014 B2) in Kraft getreten am 1. Juli 2014; zuletzt geändert am 19. April 2018 veröffentlicht im Bundesanzeiger (BAnz AT 23. August 2018 B2) Inkrafttreten 24. August 2018

Anlage 9: Anforderungen an das strukturierte Behandlungsprogramm für Patientinnen und Patienten mit Asthma bronchiale (ab dem vollendeten 1. Lebensjahr)

Anwendungsgebiet

Asthma bronchiale (ab dem vollendeten 1. Lebensjahr)

Vergleichstherapie

Keine Angabe

Normative Vorgaben

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)

3. 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.

1.5.8.3 Bedarfstherapie/Therapie der Exazerbation

Eine Bedarfsmedikation soll bei akuten asthmatypischen Beschwerden eingesetzt werden. Vorrangig sollten bei der Bedarfstherapie/Therapie der Exazerbation folgende Wirkstoffgruppen Anwendung finden:

- kurz wirksame Beta-2-Sympathomimetika (bevorzugt inhalativ)

Bei unzureichendem Ansprechen kommen in Betracht:

- der kurzfristige Einsatz systemischer Glukokortikosteroide (maximal bis zu zwei Wochen). In der Regel ist bei Kindern ein Einsatz für drei bis fünf Tage, bei Erwachsenen für fünf bis sieben Tage ausreichend.
- kurz wirksame Anticholinergika
- Theophyllin (Darreichungsform mit rascher Wirkstofffreisetzung)

Siehe auch [9].

G-BA, 2016 [11].

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 – Mepolizumab

(gültig bis: 01.08.2019)

Anwendungsgebiet

Zugelassenes Anwendungsgebiet (laut Zulassung vom 2. Dezember 2015):

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

Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Mepolizumab als Zusatztherapie bei erwachsenen Patienten mit schwerem refraktärem eosinophilem Asthma ist:

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

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

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.

G-BA, 2017 [8].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Reslizumab vom 06.07.2017
(gültig bis: 31. Juli 2020)

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

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 langwirksamen Bronchodilatatoren (LABA) mit oralen Corticosteroiden*

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

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.

G-BA, 2018 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Benralizumab vom 2. August 2018

Anwendungsgebiet

Anwendungsgebiet (laut Zulassung vom8. Januar 2018): 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

Zweckmäßige 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 OCSa,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

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

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.

3.2 Cochrane Reviews

Chauhan BF et al., 2015 [4].

Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children

Fragestellung

To assess the safety and efficacy of adding a LABA to an ICS in children and adolescents with asthma. To determine whether the benefit of LABA was influenced by baseline severity of airway obstruction, the dose of ICS to which it was added or with which it was compared, the type of LABA used, the number of devices used to deliver combination therapy and trial duration.

Methodik

Population:

Children and adolescents two to 18 years of age with persistent asthma who had received daily ICS therapy for at least four weeks before study entry. (alle Schweregrade eingeschlossen, mehrheitlich aber mild – moderate)

Intervention/ Komparator:

LABA (salmeterol or formoterol) versus placebo administered daily for at least four weeks. LABA added to ICS was compared: with the same ICS dose; or with an increased dose of ICS.

Endpunkte:

Primär: Number of asthma exacerbations of moderate intensity, that is, requiring a short course of systemic corticosteroids,

Sekundär: Admissions to hospital, urgent care visits, pulmonary function tests, symptoms, quality of life scores, use of rescue SABA, night-time awakening, changes in measures of inflammation, rates of clinical and biochemical adverse effects, any adverse effects

Recherche/Suchzeitraum:

zwischen 2008 und Januar 2015 in Cochrane Airways Group Specialised Register of asthma trials, which is derived from systematic searchesof bibliographicdatabases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and theCumulative Index toNursing and Allied Health Literature (CINAHL), and we handsearched respiratory journals and meeting abstracts

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

33 trials representing 39 control-intervention comparisons and included 6381 children

Qualität der Studien:

Risiko für Bias der meisten Studien niedrig bzw. unklar

Studienergebnisse:

LABA and ICS versus increased dose of ICS (step 3 vs step 3)

LABA + ICS compared with same dose of ICS for children with chronic asthma

Patient or population: children with chronic asthma
Settings: outpatients
Intervention: LABA + ICS
Comparison: same dose of ICS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Increased dose of ICS	LABA + ICS				
Number of participants with exacerbations requiring systemic steroids	86 per 1000	94 per 1000	RR 0.95 (0.70 to 1.28)	1669 (12 studies)	⊕⊕⊕○ Moderate[a]	
Number of participants with exacerbations requiring hospitalisation	19 per 1000	33 per 1000	RR 1.74 (0.90 to 3.36)	1292 (6 studies)	⊕⊕⊕○ Moderate[a]	
Serious adverse events	16 per 1000	18 per 1000	RR 1.17 (0.75 to 1.85)	4022 (16 studies)	⊕⊕⊕○ Moderate[a]	
Total number of withdrawals	127 per 1000	94 per 1000	RR 0.80 (0.67 to 0.94)	4374 (23 studies)	⊕⊕○○ Low[a,b]	
Change in FEV_1 (L) at endpoint	Baseline mean FEV_1 ranged from 1.65 L to 1.9 L (baseline data reported in 4 studies only)	Mean FEV_1 change from baseline with LABA + ICS was 0.08 L higher (0.06 to 0.1 higher)		1942 (9 studies)	⊕⊕○○ Low[a,b]	
Change in morning PEF (L/min) at endpoint	Illustrative post-treatment PEFs range from 235 to 290 L/min (data from 3 recent studies)	Mean PEF change from baseline with LABA + ICS was 10.20 L/min higher (8.14 to 12.26 higher)		3934 (16 studies)	⊕⊕⊕○ Moderate[a]	
Total number of adverse events	547 per 1000	568 per 1000	RR 1.04 (0.98 to 1.10)	3284 (15 studies)	⊕⊕⊕○ Moderate[b]	

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **FEV_1:** Forced expiratory volume in 1 second; **ICS:** Inhaled corticosteroids; **LABA:** Long-acting $beta_2$-agonists; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

[a] Larger sample size may change the outcome.
[b] Open-label study contributed data.

Anmerkung/Fazit der Autoren

In children with persistent asthma, the addition of LABA to ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic steroids, but it was superior for improving lung function compared with the same or higher doses of ICS. No differences in adverse effects were apparent, with the exception of greater growth with the use of ICS and LABA compared with a higher ICS dose. The trend towards increased risk of hospital admission with LABA, irrespective of the dose of ICS, is a matter of concern and requires further monitoring.

Overall the quality of evidence was moderate. Most outcomes showed wide confidence intervals, which led to downgrading of evidence quality to moderate. In a few outcomes for which open-label studies contributed data, evidence quality was further downgraded to low.

Kew KM et al., 2013 [13].

Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children

Fragestellung

To assess the efficacy and safety of budesonide/formoterol in a single inhaler (SiT) to be used for both maintenance and reliever therapy in asthma in comparison with maintenance treatment provided through combination inhalers with a higher maintenance steroid dose (either fluticasone/salmeterol or budesonide/ formoterol), along with additional fast-acting beta2-agonists for relief of symptoms.

Methodik

Population:

- Adults and children with a diagnosis of chronic asthma

Intervention:

- Any dose of combined budesonide and formoterol delivered through a single inhaler for maintenance and reliever therapy (SiT)

Komparator:

- Combination ICS/LABA inhalers (fluticasone/salmeterol or budesonide/formoterol) at a higher maintenance steroid dose than the maintenance dose in the SiT group, with additional fast-acting beta2-agonist inhaler for symptom relief.

Endpunkte:

(1) primäre Endpunkte: Exacerbations requiring hospitalization; Exacerbations requiring oral corticosteroids; Serious adverse events (including mortality and life threatening events).

(2) sekundäre Endpunkte: Severe exacerbations (composite outcome of hospitalisation/ER visit); Diary card morning and evening peak expiratory flow (PEF, L/min); Clinic spirometry (FEV1, mL); Number of rescue medication puffs required per day; Days with symptoms/symptom-free days (%); Nocturnal awakenings (%); Quality of life.

Recherche/Suchzeitraum:

- bis November 2013

Qualitätsbewertung der Studien:

- Cochrane Collaboration's 'Risk of bias' tool; Sensitivity analysis has been conducted on the basis of risk of bias in studies and baseline severity (based on baseline use of ICS and baseline percentage predicted FEV1).

Ergebnisse

Anzahl eingeschlossener Studien:

4

Charakteristika der Population:

All 4 trials included outpatients at least 12 years of age and thus were treated as adult and adolescent studies (N=9130).

Qualität der Studien:

All studies were funded by only one pharmaceutical company (AstraZeneca) and were mostly free from methodological biases, although two studies were rated at high risk for blinding because the inhalers were delivered in an open-label design. Evidence of selective outcome reporting was found in two of the trials, and this is reflected in the grade ratings of the affected outcomes.

Studienergebnisse:

Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children (Review)

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

SIT for maintenance/relief compared with ICS/LABA combination at a higher fixed dose + SABA for chronic asthma in adults and children

Patient or population: Studies recruited adults and adolescents aged 12 and older with chronic asthma
Intervention: SiT for maintenance and relief
Comparison: higher-dose ICS/LABA as maintenance + SABA as relief
Setting: community

Outcomes Follow-up calculated as weighted means, with range	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Overall heterogeneity and subgroup differences (ICS/LABA combination in control group)
	Assumed risk	Corresponding risk				
	Higher-dose ICS/LABA+ SABA	SIT for maintenance/relief				
People with exacerbations requiring hospitalisation	No data	No data	-	-	-	AstraZeneca could not provide data for hospitalisations separate to ER visits
Patients with exacerbations requiring oral steroids Follow-up: eight months (six to 12)	10 per 100	Eight per 100 (seven to nine)	OR 0.75 (0.65 to 0.87)	9096 (four studies)	⊕⊕⊕⊕ high	I^2 = 0%; P value 0.82 Subgroup differences (P value 0.45)
Patients with serious adverse events Follow-up: eight months (six to 12)	Four per 100	Four per 100 (three to five)	OR 0.92 (0.74 to 1.13)	9130 (four studies)	⊕⊕⊕◯ moderate[1]	I^2 = 0%; P value 0.98 Subgroup differences (P value 0.88)
Patients with severe exacerbations (requiring hospitalisation *or* ER visit) Follow-up: eight months (six to 12)	Five per 100	Four per 100 (three to five)	OR 0.72 (0.57 to 0.90)	7768 (three studies)	⊕⊕⊕⊕ high	I^2 = 0%; P value 0.66 Subgroup differences (P value 0.21)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **OR:** Odds ratio; **ICS/LABA:** inhaled corticosteroid/long-acting $beta_2$-agonist combination inhaler; **SABA:** short-acting $beta_2$-agonist; **SIT:** single-inhaler therapy with budesonide/formoterol inhaler.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

1. Wide confidence intervals, downgraded once for imprecision.
Although issues with blinding were noted in two of the studies, and one study recruited a less severe population, sensitivity analyses did not change the main results, so outcomes were not downgraded.

- Separate data for exacerbations leading to hospitalisations, to emergency room (ER) visits or to a course of oral steroids could not be obtained. Compared with higher fixed-dose combination inhalers, fewer people using SiT had exacerbations requiring hospitalization or a visit to the ER (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.57 to 0.90; I2 = 0%, P = 0.66), and fewer had exacerbations requiring a course of oral corticosteroids (OR 0.75, 95%CI 0.65 to 0.87; I2 = 0%, P = 0.82). This translates to one less person admitted to hospital or visiting the ER (95% CI 0 to 2 fewer) and two fewer people needing oral steroids (95% CI 1 to 3 fewer) compared with fixed-dose combination treatment with a short-acting beta-agonist (SABA) reliever (per 100 treated over eight months).

- No statistical heterogeneity was observed in either outcome, and the evidence was rated of high quality. Although issues with blinding were evident in two of the studies, and one study recruited a less severe population, sensitivity analyses did not change the main results, so quality was not downgraded.

We could not rule out the possibility that SiT increased rates of serious adverse events (OR 0.92, 95% CI 0.74 to 1.13; I2 = 0%, P = 0.98; moderate-quality evidence, downgraded owing to imprecision). We were unable to say whether SiT improved results for several secondary outcomes (morning and evening peak expiratory flow (PEF), rescue medication use, symptoms scales), and in cases where results were significant, the effect sizes were not considered clinically meaningful (predose FEV1, nocturnal awakenings and quality of life).

Anmerkung/Fazit der Autoren

SiT reduces the number of people having asthma exacerbations requiring oral steroids and the number requiring hospitalisation or an ER visit compared with fixed-dose combination inhalers. Evidence for serious adverse events was unclear. The mean daily dose of inhaled corticosteroids (ICS) in SiT, including the total dose administered with reliever use, was always lower than that of the other combination groups. This suggests that the flexibility in steroid administration that is possible with SiT might be more effective than a standard fixed-dose combination by increasing the dose only when needed and keeping it low during stable stages of the disease. Data for hospitalisations alone could not be obtained, and no studies have yet addressed this question in children younger than age 12.

Farne HA et al., 2017 [5].

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

- Provided sufficient studies were included, we planned to carry out subgroup analyses according to:

  1. eosinophilic individuals versus non-eosinophilic individuals(as eosinophilia may be a prescribing requirement e.g. NICE 2017); and

  2. age (0 to 5 years, 6 to 16 years, 17 years and older).

  Using the outcomes:

  - 'clinically significant' asthma exacerbations;
  - HRQoL (as measured by a validated questionnaire); and
  - 3. measures of lung function (e.g. FEV1).

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),

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 ormore 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

Charakteristika der Population:

Study (Number of Participants)	Design, follow-up (weeks)	Baseline asthma severity	Baseline treatment	Intervention (route)	Primary and secondary outcomes
Chupp 2017 (551)	RCT, double-blind, placebo-controlled (24)	Blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in previous 12 months; and ≥ 2 exacerbations in previous 12 months; and FEV_1 < 80%	High-dose ICS for ≥ 12 months; + additional controller for ≥ 3 months; ± maintenance OCS	Mepolizumab 100 mg (SC) or placebo every 4 weeks for 24 weeks (last dose at 20 weeks)	- SGRQ - Mean change from baseline pre-bronchodilator FEV_1 - Proportion of SGRQ total score responders at week 24 - Mean change from baseline in ACQ-5
Haldar 2009 (61)	RCT, double-blind, placebo-controlled, parallel-group (50)	≥ 3% sputum eosinophils; and ≥ 2 exacerbations in previous 12 months	High-dose ICS	Mepolizumab 75 (IV) or matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 y	- Severe exacerbations per person - Change in AQLQ - post-bronchodilator FEV_1 - Airway hyperresponsiveness - Blood/sputum eosinophil counts
Ortega 2014 (576)	RCT, double-blind, double-dummy, phase 3 (32)	Blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in previous 12 months; and ≥ 2 exacerbations in previous 12 months; and FEV_1 < 80%	High-dose ICS for ≥ 12 months; + additional controller for ≥ 3 months; ± maintenance OCS	Mepolizumab 75 mg (IV) or 100 mg (SC) or placebo every 4 weeks for 32 weeks	- Exacerbations per y - Mean change from baseline pre-bronchodilator FEV_1 - Mean change from baseline SGRQ total score
Pavord 2012a (621)	Multicentre, double-blind, placebo-controlled (52)	≥ 3% sputum eosinophils or blood eosinophil ≥ 300 cells/μL; and ≥ 2 exacerbations in previous 12 months	High-dose ICS (i.e. ≥ 880 μg/d FP or equivalent daily); + additional controller; ± maintenance OCS	Mepolizumab 75 mg, 250 mg or 750 mg (IV) or placebo every 4 weeks for 13 doses	- Time to first clinically significant exacerbation - Frequency of exacerbations requiring hospitalisation - Time to first exacerbation requiring hospitalisation or ED visit - Mean change from baseline pre-bron-

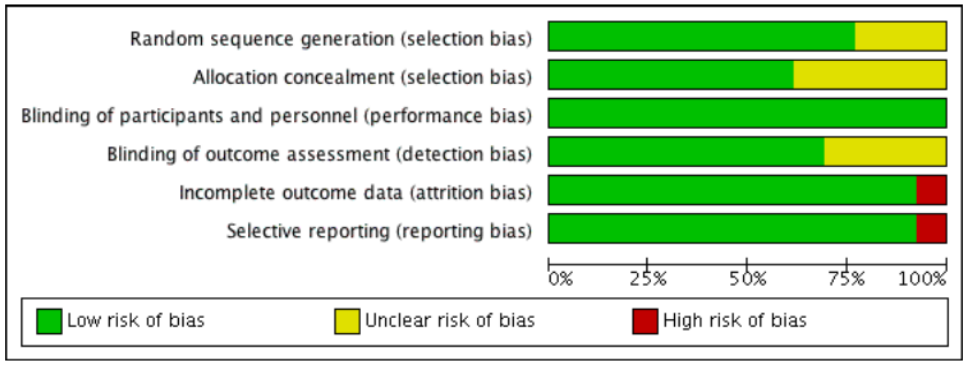
					chodilator FEV_1 - Mean change from baseline post-bronchodilator FEV_1 - Mean change from baseline ACQ
Bjermer 2016 (315)	RCT, double-blind, placebo-controlled, parallel-group, fixed-dosage, multicentre phase 3 (16)	Blood eosinophils ≥ 400 cells/μL during 2-4 weeks screening period; and ACQ-7 score ≥ 1.5	Medium-dose ICS; maintenance OCS not allowed	Reslizumab 0.3 mg/kg or 3 mg/kg (IV) or placebo every 4 weeks for 4 doses	- Pre-bronchodilator FEV_1, FVC, FEF_{25-75} - ACQ, ACQ-6, ACQ-5 - ASUI - AQLQ - Rescue inhaler use - Blood eosinophil levels
Castro 2015a (489) and Castro 2015b (464)	2 x duplicate RCT double-blind, placebo-controlled, parallel-group, multicentre, phase 3 (52)	Blood eosinophils ≥ 400 cells/μL during 2-4 week screening period; and ACQ-7 score ≥ 1.5	Medium-dose ICS (i.e. ≥ 440 μg/day FP or equivalent daily); ± additional controller or maintenance OCS	Reslizumab 3 mg/kg (IV) or matching placebo every 4 weeks for 13 doses (last dose week 48)	- Annual frequency of exacerbations - Change in FEV_1 from baseline over 16 weeks - ACQ-7 score - ASUI score - Rescue use of SABA - Blood eosinophil count - AQLQ total score at weeks 16, 32 and 52
Corren 2016 (496)	RCT double-blind, placebo-controlled, multicentre phase 3 (16)	ACQ-7 score ≥ 1.5 (no selection based on blood eosinophils)	Medium-dose ICS; maintenance OCS not allowed	Reslizumab 3 mg/kg (IV) or matching placebo every 4 weeks for 4 doses	- Change in FEV_1 from baseline - ACQ-7 score - Rescue (SABA) use within previous 3 days - FVC - Blood eosinophils
Bleecker 2016 (1204)	RCT double-blind, parallel-group, placebo-controlled multicentre (52)	≥ 2 exacerbations in the previous 12 months; and ACQ-6 score ≥ 1.5 at enrolment; and FEV_1 < 80% (if 12-17 years old, < 90%)	Adults (> 18 y) high-dose (≥ 500 μg/d FP or equivalent) ICS/LABA for ≥ 12 months Children (12-17 y) at least medium-	Benralizumab 30 mg (SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses then every 8 weeks or placebo for	- Annual exacerbation rate - Pre-bronchodilator FEV_1 - Total asthma symptom score - Time to first exac-

			dose (≥ 250 μg/day FP or equivalent) ICS/LABA	48 weeks	erbation - Annual rate of exacerbations requiring ED visit or hospital admission - Post-bronchodilator FEV_1 - ACQ-6 - AQLQ(S)+12 score
Castro 2014a (606)	RCT double-blind, placebo-controlled, multicentre dose-ranging (52)	2-6 exacerbations in the previous 12 months; and ACQ-6 score ≥ 1.5 at least twice during screening; and morning pre-bronchodilator FEV_1 40%-90%	Medium- to high-dose ICS in combination with LABA for ≥ 12 months	Benralizumab 2 mg, 20 mg or 100 mg (SC) or placebo every 4 weeks for the first 3 doses, then every 8 weeks (total 7 doses)	- Annual exacerbation rate - Change from baseline in FEV_1 - Mean ACQ-6 score - Overall symptom score - Mean AQLQ score
FitzGerald 2016 (1306)	RCT, double-blind, parallel-group, placebo-controlled multicentre (56)	≥ 2 exacerbations in the previous 12 months; and ACQ-6 score ≥ 1.5 at enrolment; and FEV_1 < 80%	Medium- (≥ 250 μg/d FP or equivalent) to high-dose (≥ 500 μg/d FP or equivalent) ICS/LABA for ≥ 12 months; high-dose ICS/LABA for ≥ 3 months	Benralizumab 30 mg (SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses then every 8 weeks or placebo	- Annual exacerbation rate for participants with blood eosinophils ≥ 300 cells/μL - Pre-bronchodilator FEV_1 - Total asthma symptom score - Time to first exacerbation - Annual rate of exacerbations requiring ED visit or hospital admission - Post-bronchodilator FEV_1 - ACQ-6 - AQLQ(S)+12 score
NCT01947946 2013 (13)	RCT double-blind, parallel-group, placebo-controlled multicentre (48)	Uncontrolled asthma taking medium-dose ICS plus LABA	Medium-dose ICS (>250ug and ≤500ug fluticasone dry powder formulation equivalents total daily dose) and LABA for at least 3 month prior to first visit	Benralizumab 30 mg (SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses then every 8 weeks or placebo	Asthma exacerbations over 48-week treatment period
Park 2016 (103)	RCT double-blind, placebo-controlled, dose-ranging multicentre (52)	2-6 exacerbations in the previous 12 months; and ACQ-6 score ≥ 1.5 at least twice during screening; and morning pre-bronchodilator FEV_1 40%-90%	Medium- to high-dose ICS in combination with LABA for ≥ 12 months	Benralizumab 2 mg, 20 mg or 100 mg (SC) or placebo every 4 weeks for the first 3 doses, then every 8 weeks (total 7 doses)	- Annual exacerbation rate - Lung function - ACQ-6 - FeNO - Blood eosinophil counts

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **ASUI**: Asthma Symptom Utility Index; **BDP**: beclomethasone dipropionate; **b**: day; **ECP**: eosinophil cationic protein; **ED**: emergency department; **FEF_{25-75}** : forced expiratory flow at 25% to 75% of FVC; **FeNO**: exhaled fraction of nitric oxide; **FEV_1** : Forced expiratory volume in 1 second; **FVC**: forced vital capacity; **FP**; fluticasone propionate; **ICS**; inhaled corticosteroid; **IV**: intravenous; **LABA**: long-acting beta$_2$ agonist**OCS**; oral corticosteroid; **PC_{20}** : histamine provocative concentration causing a 20% drop in FEV_1; **PEFR**: peak expiratory flow rate; **RCT**: randomised controlled trial; **SABA**: short-acting beta$_2$-agonists; **SC**: subcutaneous; **SGRQ**: St George's Respiratory Questionnaire; **y**: year

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



- four included studies comparing mepolizumab versus placebo
- four included studies comparing reslizumab versus placebo

Studienergebnisse:

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 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 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) Scale from: 0 to 6 (lower is better) 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) Scale from: 0 to 100 (lower is better) 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 (2 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 4 is considered the minimum clinically significant difference
Pre-bronchodilator FEV_1 (L) 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 (2 RCTs)	⊕⊕⊕⊕ High	
Adverse events leading to discontinuation Follow-up: range 24 to 32 weeks	15 per 1000	7 per 1000 (2 to 27)	Risk ratio 0.45 (0.11 to 1.80)	936 (2 RCTs)	⊕⊕⊕◯ 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.

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

[d] 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).

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 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 (0.33 to 0.55)	953 (2 RCTs)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission 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 (0.39 to 1.17)	953 (2 RCTs)	⊕⊕⊕⊕ High	
Health-related quality of life (AQLQ) Scale from: 1 to 7 (higher is better) 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 (0.17 higher to 0.39 higher)[d]	-	1164 (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 16	The mean change in the placebo group ranged from −0.368 to −0.80 units	MD -0.25 lower (-0.33 lower to -0.17 lower)[b]	-	1652 (4 RCTs)	⊕⊕⊕⊕ 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)

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.

Results in adolescents were not reported separately and thus we could not perform a subgroup analysis on this population.

Normansell R et al., 2014 [18].

Omalizumab for asthma in adults and children

Fragestellung

To assess the effects of omalizumab versus placebo or conventional therapy for asthma in adults and children.

Methodik

Population:

- Adults and children with chronic asthma from all referral sources.

Intervention:

- Anti-IgE therapy at any dose or route

Komparator:

- placebo

Endpunkte:

- primary: 1. Asthma exacerbations as defined by “events”, i.e. hospital admissions, emergency room visits, days lost from work/school, unscheduled doctor visits, increase in

medication. 2. Reduction or termination of steroid (inhaled, oral, both) use from baseline or run-in period;

- secondary: 1. Asthma symptoms, 2. Health-related quality of life, 3. Rescue medication use, 4. Measures of lung function: forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), 5. Adverse events

Recherche/Suchzeitraum:

- until 06/2013

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

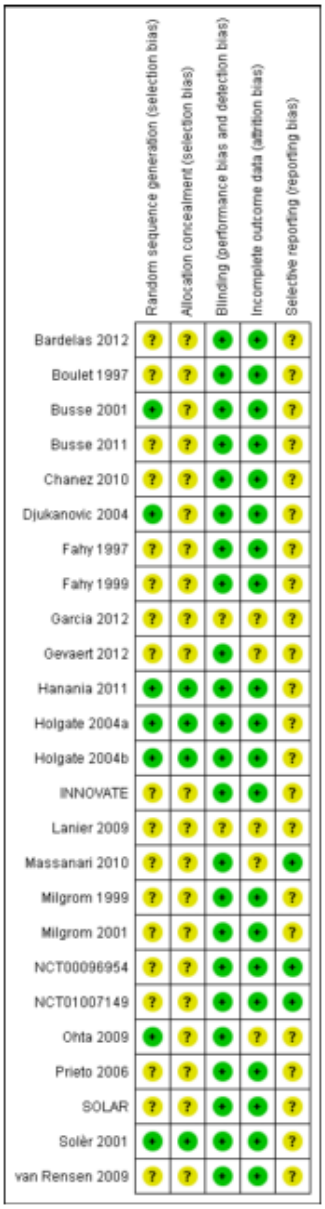
- 25 studies

Charakteristika der Population:

- 6382 patients

Qualität der Studien:

- The evidence presented in this review is generally of moderate quality. Most of the studies did not clearly explain how investigators decided which people would receive omalizumab and which would receive placebo, and this decision is an important part of well-conducted studies.



Studienergebnisse:

Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid) for asthma in adults and children

Patient or population: adults and children with asthma
Settings:
Intervention: subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Subcutaneous omalizumab+ steroid versus placebo + steroid (stable steroid)				
Number of participants with at least one exacerbation All asthmatic participants (16 to 60 weeks)	262 per 1000	163 per 1000 (130 to 176)	OR 0.55 (0.46 to 0.65)	3261 (10 studies)	⊕⊕⊕○ moderate[1]	
Number of participants with at least one exacerbation Moderate to severe asthma (16 to 60 weeks)	274 per 1000	159 per 1000 (137 to 185)	OR 0.5 (0.42 to 0.6)	2889 (7 studies)	⊕⊕⊕○ moderate[1]	
Number of participants with at least one exacerbation Severe asthma (16 to 32 weeks)	145 per 1000	145 per 1000 (78 to 252)	OR 1 (0.5 to 1.99)	277 (2 studies)	⊕⊕○○ low[2]	

Mortality 16 to 60 weeks	**2 per 1000**	**0 per 1000** (0 to 3)	**OR 0.19** (0.02 to 1.67)	4245 (9 studies)	⊕⊕◯◯ **low**[3,4]
Hospitalisations 28 to 60 weeks	**31 per 1000**	**5 per 1000** (2 to 13)	**OR 0.16** (0.06 to 0.42)	1824 (4 studies)	⊕⊕⊕◯ **moderate**[5]
Adverse event-serious 16 to 60 weeks	**64 per 1000**	**47 per 1000** (37 to 58)	**OR 0.72** (0.57 to 0.91)	5713 (15 studies)	⊕⊕⊕◯ **moderate**[6]

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (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).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

[1]A point was deducted for risk of bias to reflect the fact that most studies scored UNCLEAR on both sequence generation and allocation concealment.
[2]A point was deducted for risk of bias to reflect the fact that only one of the two trials scored LOW on both sequence generation and allocation concealment. The remaining trial scored UNCLEAR on both sequence generation and allocation concealment. An additional point was deducted because of the imprecision of the results.
[3]A point was deducted for risk of bias to reflect the fact that only two of the nine trials scored LOW on both sequence generation and allocation concealment. Most (five) scored UNCLEAR on both sequence generation and allocation concealment.
[4]An additional point was deducted to reflect that a death occurred in only two of the nine trials; therefore, the contribution of most of the trials (seven) was non-estimable.
[5]A point was deducted for risk of bias to reflect the fact that only one of the four trials scored LOW on both sequence generation and allocation concealment.
[6]A point was deducted for risk of bias to reflect the fact that only two of the 15 trials scored LOW on both sequence generation and allocation concealment. Most (10) scored UNCLEAR on both sequence generation and allocation concealment.

- Primary outcomes:

  1. Asthma exacerbations

  Treatment with omalizumab resulted in fewer exacerbations overall. This effect was maintained during the steroid stable and steroid reduction phases of the included trials but with much greater uncertainty when only participants with severe disease were considered.

  2. Steroid withdrawal/reduction

  Participants treated with omalizumab were significantly more likely to be able to reduce and completely withdraw their inhaled corticosteroids. For the subset of participants receiving oral corticosteroids, we remain uncertain whether benefit is derived fromomalizumab over placebo for those withdrawing or reducing their steroid treatment

  Secondary outcomes:

  1. Asthma symptoms

  Treatmentwithomalizumabgenerally improvedasthma symptomscores in both steroid stable and steroid reduction phases.

  2. Health-related quality of life

  In most trials reporting quality of life, a significant benefit of omalizumab over placebo was reported during both steroid stable and steroid reduction phases.

  3. Rescue medication use

  Participants were more likely to be able to reduce their rescue medication when using omalizumab.

  4. Measures of lung function

  Improvements in lung function were inconsistent across the trials analysed, and the range of different measures presented in the trials prevented meaningful meta-analysis.

  5. Adverse events including withdrawals and mortality

  Participants receiving subcutaneous omalizumab experienced significantly fewer serious adverse events compared with those given placebo. However, they also experienced significantly more injection site reactions.No significant difference inmortality was detected

Anmerkung/Fazit der Autoren

Omalizumab was effective in reducing asthma exacerbations and hospitalisations as an adjunctive therapy to inhaled steroids and during steroid tapering phases of clinical trials. Omalizumab was significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their inhaled steroids. Omalizumab was generally well tolerated, although more injection site reactions were seenwith omalizumab. Further assessment in paediatric populations is necessary, as is direct double-dummy comparison with ICS. Although subgroup analyses suggest that participants receiving prednisolone had better asthma control when they received omalizumab, it remains to be tested prospectively whether the addition of omalizumab has a prednisolone-sparing effect. It is also not clear whether there is a threshold level of baseline serum IgE for optimum efficacy of omalizumab. Given the high cost of the drug, identification of biomarkers predictive of response is of major importance for future research.

Pruteanu Al et al., 2014 [19].

Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth

Fragestellung

To assess whether increasing the dose of ICS is associated with slower linear growth, weight gain and skeletal maturation in children with asthma.

Methodik

Population:

- Children one to 17 years of age with the diagnosis of persistent asthma.

Intervention:

- lower-dose ICS

Komparator:

- higher-dose ICS

Endpunkte:

- primär: Linear growth velocity, obtained by measuring height at a number of time points during the study and performing linear regression of height against time.
- Sekundär: Change in height standard deviation score (SDS) over time, defined as the difference between an individual's growth velocity and predicted normal growth velocity divided by the predicted normal growth velocity standard deviation (SD) for individuals of the same age, sex and ethnicity, if available; Change from baseline in height (cm) over time; Change in height z-score over time, Change in weight (kg or z-score) over time, Change in body mass index (added post hoc), Change in skeletal maturation (added post hoc).

Recherche/Suchzeitraum:

- We identified trials fromthe Cochrane Airways Group Specialised Register of Trials (CAGR), which were derived through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMEDand PsycINFO, and through handsearching of respiratory journals, meeting abstracts & ClinicalTrials.gov website.
- until March 2014

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

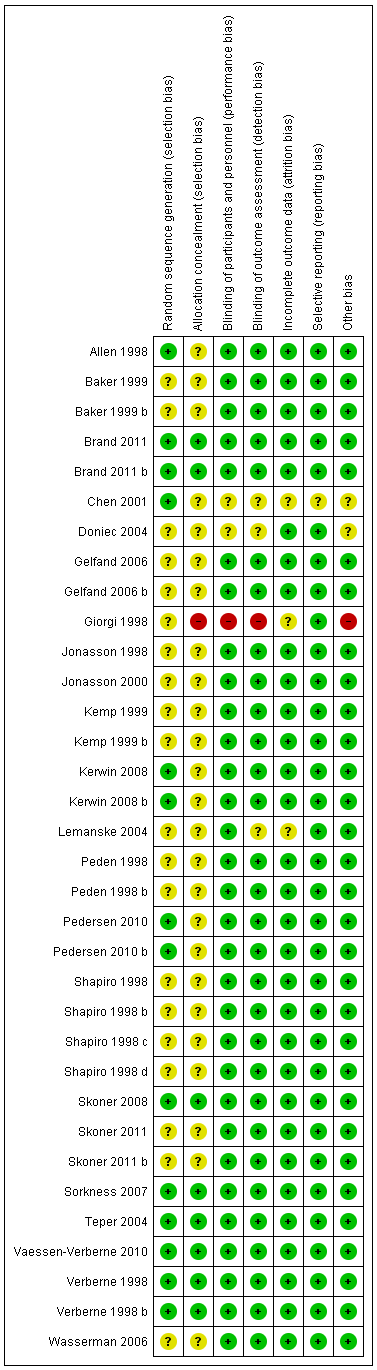
Anzahl eingeschlossener Studien:

- 10

Charakteristika der Population:

- N=3394; mild-to-moderate asthma

Qualität der Studien:



Studienergebnisse:

- **Linear growth velocity (cm/y):** statistically significant higher growth over 12 months in intervention (lower ICS dose) than in control (higher ICS dose) group (four comparisons; N = 728; MD 0.20 cm/y, 95% CI 0.02 to 0.39; I^2=0%); no difference between molecules used (mometasone, ciclesonide and fluticasone)
  ICS dose difference: varying between 100 and 150 µg/d (although most vary by 100 µg/d) of HFA-propelled beclomethasone or equivalent
  Quality of Evidence (GRADE): high
- **Change in growth velocity (cm/y) (0-12 month):**1 comparison; N = 181; MD 0.06 cm/y, 95% CI -0.43 to 0.55
- **Change in height (cm) (0-12 month):** 4 comparisons; N = 548; MD 0.25, 95% CI -0.04 to 0.54; I^2 =64%
  Quality of Evidence (GRADE): moderate
- **Change in standard deviation score (SDS) (height) (0-12 month):** 3 comparisons; N= 328; MD 0.08, 95%CI -0.03 to 0.20, I^2 =82%
  Quality of Evidence (GRADE): moderate
- **Change in BMI (kg/m2) (0-12 month):** 1 comparison; N = 408; MD -0.20 kg/m2, 95% CI -0.49 to 0.09
  Quality of Evidence (GRADE): low

Change in skeletal maturation (0-12 month): statistically significant group difference from zero to 12 months in favour of a lower ICS dose (1 comparison; N = 181; MD 0.18, 95% CI 0.02 to 0.34)
Quality of Evidence (GRADE): low

Anmerkung/Fazit der Autoren

In prepubescent school-aged children with mild to moderate persistent asthma, a very small but statistically significant difference in linear growth over 12 months was observed between groups using ICS, with a dose difference ≤150 µg HFA-beclomethasone equivalent over 52 weeks. Findings support use of the minimal effective ICS dose in children with asthma.

Kommentare zum Review

Es wurden nur Studien identifiziert, die Kinder mit ‚mild to moderate persistent asthma' einschlossen, dementsprechend wurden auch nur niedrige bis mittlere Dosen an ICS betrachtet.

Zhang L et al., 2014 [24].

Inhaled corticosteroids in children with persistent asthma: effects on growth

Fragestellung

To assess the impact of ICS on the linear growth of children with persistent asthma and to explore potential effect modifiers such as characteristics of available treatments (molecule, dose, length of exposure, inhalation device) and of treated children (age, disease severity, compliance with treatment)

Methodik

Population:

- children up to 18 years with the diagnosis of persistent asthma

Intervention:

- daily use of ICS

Komparator:

- placebo or non-steroidal drugs

Endpunkte:

- primär: Linear growth velocity, obtained by measuring height at a number of time points during the study and performing linear regression of height against time.
- Sekundär: Change in height standard deviation score (SDS) over time, defined as the difference between an individual's growth velocity and predicted normal growth velocity divided by the predicted normal growth velocity standard deviation (SD) for individuals of the same age, sex and ethnicity, if available; Change from baseline in height (cm) over time; Change in height z-score over time

Recherche/Suchzeitraum:

- bis 01/2014

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

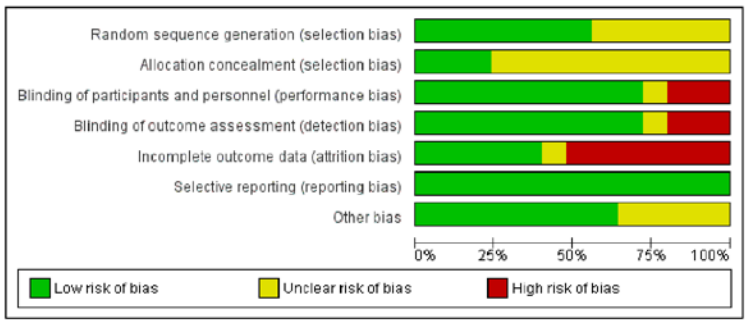
- 25 RCT

Charakteristika der Population:

- 8471 children with mild to moderate persistent asthma

Qualität der Studien:

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

	1 year treatment	2 year treatment	3 year treatment
Linear	MD = -0.47 cm/y	MD=-0.19 cm/y, 95%	No meta-analysis: 2

growth velocity (cm/y)	(95%CI -0.66 to -0.27, P< 0.00001, I^2=60%,13 trials, n=5659) Signifikante Unterschiede zwischen verschiedenen ICS Molekülen (siehe Anhang)	CI -0.48 to 0.11, P = 0.22, I^2 = 75%, 5 trials, n=3174)	trials Pauwels 2003 (n=1974): (MD = -0.33 cm/y, 95%CI -0.52 to -0.14, P = 0.0005)
Change from baseline in height (cm)	MD =-0.61 cm (95% CI -0.83 to -0.38, P< 0.00001, I^2=63%, 15 trials, n=3217	MD=-0.30 cm, 95%CI -2.09 to 1.49, P= 0.74, I^2 = 88%, 2 trials, n=437	-
Change in height SDS	MD =-0.13 (95% CI -0.24 to -0.01, P = 0.03, I^2=68%, 4 trials, n=258)	-	-

Adult height (1 trial, n=658): participants treated with budesonide 400µg/d for a mean duration of 4.3 years at a prepubertal age had a mean reduction of 1.20 cm (95% CI -1.90 to -0.50, P = 0.001) in adult height compared with those treated with placebo

Anmerkung/Fazit der Autoren

Regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm/y in linear growth velocity and a 0.61 cm change from baseline in height during a one-year treatment period in children with mild to moderate persistent asthma. The effect size of ICS on linear growth velocity appears to be associated more strongly with the ICS molecule than with the device or dose (low to medium dose range). ICS-induced growth suppression seems to be maximal during the first year of therapy and less pronounced in subsequent years of treatment

Kommentare zum Review

Es wurden nur Studien identifiziert, die Kinder mit ‚mild to moderate persistent asthma' einschlossen, dementsprechend wurden auch nur niedrige bis mittlere Dosen an ICS betrachtet.

3.3 Systematische Reviews

Castro-Rodriguez JA et al., 2015 [3].

Principal findings of systematic reviews for chronic treatment in childhood asthma

Fragestellung

To summarize the principal findings pertaining to most effective long-term pharmacologic treatment of childhood asthma.

Methodik

Population:

children (1–18 years) with persistent asthma

Intervention:

any pharmacological treatment of chronic asthma

Komparator:

Keine Angabe

Endpunkte:

Keine Angabe

Recherche/Suchzeitraum:

We identified published studies from MEDLINE, EMBASE, CINAHL, SCOPUS, and the Cochrane Database of Systematic Reviews (CDSR) (up to January 2014) database, using the terms: Asthma AND Meta-Analysis OR Systematic Review AND Child OR Children.

Qualitätsbewertung der Studien:

AMSTAR (Assess Systematic Reviews) tool

Ergebnisse

Anzahl eingeschlossener Studien:

39 systematische Reviews (9 related to steps 3 and 4, and 4 to step 5)

Charakteristika der Population:

Keine Angaben (z.B. in Tabellenform)

Qualität der Studien:

Qualität der Studien: The methodological qualification, using the AMSTAR tool (total score 11 points), showed that 30 SRCTs had ≥10 points, five had nine points, and three had ≤ 6 points.

Studienergebnisse:

Table 2. Principal findings of the 39 SRCTs included according to the international asthma guideline's steps [2,3].

Outcomes	Step 1	Step 2	Step 3	Steps 4 and 5
Reduction of severe exacerbations	SABA = IB SABA = SABA + IB	ICS > LTRA ICS > cromones ICS > xanthines FP = HFA-DBP or ciclosenide Daily = intermittent ICS Moderate = low ICS doses	ICS + LTRA = ICS ICS + LABA = ICS ICS + LABA = 2ICS	ICS + OMA > ICS
Improvement of clinical outcomes	SABA = IB SABA = SABA + IB	ICS > LTRA ICS > cromones ICS > xanthines FP = HFA-DBP or ciclosenide Daily > intermittent ICS Moderate = low ICS doses	ICS + LTRA = ICS ICS + LABA = ICS ICS + LABA = 2ICS	
Improvement of lung function parameters	SABA = IB SABA = SABA + IB	ICS > LTRA ICS > cromones Daily > intermittent ICS Moderate > low ICS doses FP > BDP or BUD FP = HFA-BDP or ciclosenide	ICS + LTRA > ICS ICS + LABA > ICS ICS + LABA > 2ICS	

> (better than); = (equal to); + (plus), 2 (double doses). BDP, beclomethasone dipropionate; BUD, budesonide; FP, fluticasone propionate; ICS, inhaled corticosteroids; HFA, hydrofluoroalkane; IB, ipratropium bromuro; LABA, long acting beta2-agonits; OMA, omalizumab; SABA, short-acting beta2-agonists; SRCTs, systematic reviews of randomized clinical trials.

For steps 3 and 4: adding LTRA to ICS confers a small benefit; adding LABA improves lung function but does not reduce exacerbations more than double or higher ICS doses.

Adding LABA or LTRA to ICS

Two RCTs, n=332, recruited children (6–17 years of age). In one RCT, no difference was reported in exacerbation requiring OCS (primary outcome) between LABA+ICS and LTRA+ICS; however, LTRA+ICS improved significantly the 5% fall in FEV1 post-exercise compared with LABA+ICS (MD=3.07, 95% CI [0.68–5.47], p=0.012).

Castro-Rodriguez and Rodrigo [26] reported that there was no significant difference in the incidence of asthma exacerbation requiring OCS between ICS+montelukast and ICS in children (two RCTs, n=610, RR 0.53, 95% CI [0.10–2.74], p=0.05, I2=86%).

One trial compared montelukast+ICS with a higher dose of ICS (step 3 vs. step 3). No significant group difference was observed in this trial for exacerbations requiring rescue OCS over 16 weeks, or differences in exacerbations requiring hospitalization or in withdrawals.

- LABA+ICS vs. similar or higher ICS doses
- Ni Chroinin et al. [34] compared the safety and the benefit of adding LABA to ICS with the same or an increased dose of ICS in persistent asthmatic children (mean age 10 years). A total of 25 RCTs (n=5572 children inadequately controlled on the current ICS dose) were included. Compared with ICS alone, the addition of LABA to ICS was not associated with a significant reduction in exacerbations requiring OCS. On the contrary, the addition of LABA showed a significantly greater improvement in the change in FEV1 (nine RCTs, n=1235, WMD=0.08 L, 95% CI [0.06–0.11], p<0.00001, I2=33%)and morning PEF (14 RCTs, n=2934, WMD=10.38 L/min, 95% CI [8.23–12.52], p<0.00001, I2=3%); but no statistically significant differences were seen in symptom-free days, hospital admission, quality of life, use of reliever medication, AE, and SAE. The use of LABA+ICS compared with increased dose of ICS (seven RCTs, n=1021 children) did not exhibit significant differences in the risk of an exacerbation requiring OCS or hospital admissions. Compared with double-dose ICS, the use of LABA was associated with a significantly greater improvement in morning and evening PEF (four RCTs, n=1002, MD 7.55 L/min, 95% CI [3.57–11.53], p<0.0001, I2=0%; and three RCTs, n=888, MD=5.5 L/min, 95% CI [1.21–9.79], p=0.012, I2=0%, respectively), but there were insufficient data to aggregate data on FEV1, symptoms, rescue reliever use, and quality of life.

- Short-term growth was significantly greater in children treated with combination therapy and double dose ICS (two RCTs, MD 1.2 cm/year, 95% CI [0.72–1.7], p<0.0001, I2=31%). There was no group difference in the risk of AEs.
- Ducharme et al. [35] assessed the safety and the efficacy of the addition of LABAs to ICS vs. same dose ICS in children and adult patients insufficiently controlled with ICS alone (28 out of the 77 RCTs were done on children aged 8–14 years, n=4625). The difference of the effect on asthma exacerbations requiring OCS in pediatric trials was not statistically significant between groups. The change in FEV1 at the endpoint was higher in LABA+ICS vs. same dose ICS (nine RCTs, WMD 0.08, 95% CI [0.05–0.11], p<0.00001, I2=36%).
- Also, Ducharme et al. [36] evaluated the addition of LABA to ICS vs. higher dose ICS in adults and children with persistent asthma (six out of the 48 RCTs were done in children aged 6–19 years, n=1155). In contrast to adults, the use of LABA is not beneficial for reducing OCS use in children. One study assessed growth over 12 months in children, with a significantly better short-term rate of growth in the LABA+ICS vs. higher ICS dose (0.9 cm, 95% CI [0.20–1.60]).
- Castro-Rodriguez and Rodrigo [37] evaluated the efficacy of ICS+LABA vs. higher doses of ICS in children/adolescents (4–17 years of age) with uncontrolled persistent asthma (nine RCTs, n=1641). There was no statistically significant difference in asthma exacerbations requiring systemic corticosteroids between children receiving LABA+ICS and higher doses of ICS. However, patients on

  LABA+ICS had significantly higher morning and evening PEF (five RCTs, n=1312, WMD=-8.74, 95% CI [-12.27 to -5.21 L/min], p<0.0001, I2=0; and three RCTs, n=992, WMD=-4.41, 95% CI [-7.05 to -1.77 L/min], p=0.001, I2=0, respectively), less use of rescue SABA medication (five RCTs, n=697, WMD=-0.11 [-0.20 to -0.01], p=0.02, I2=0), and higher short-term growth (three RCTs, n=430, I2=0, WMD=0.66 cm/year, 95% CI [0.08–1.25], p=0.02, I2=0) than those on higher doses of ICS. In two RCTs where LABA+ICS were compared with higher than a double dose of ICS, the combination therapy significantly reduced exacerbations (n=346, OR=0.48, 95% CI [0.28–0.82], p=0.007, I2=0, NNT=8, 95% CI [5–29]).

  Comparing different combination therapies (LABA+ICS)

  Cates and Lasserson [39] assessed the comparison of formoterol+ budesonide used for relief of asthma symptoms with the same maintenance treatment with terbutaline for symptom relief (three RCTs, 5905 patients). In the only RCT done in children aged 4–11 years (n=341), the use of formoterol+budesonide for relief of symptoms showed a trend of reduction in asthma hospitalizations (OR: 0.06, 95% CI [0.00–1.10]) and less SAEs for any cause (OR 0.11, 95% CI [0.02–0.48], NNT=8, 95% CI [5–22]) than a combination therapy plus terbutaline.

For step 5: adding omalizumab decreases exacerbations

Rodrigo et al. [41] evaluated the efficacy and the safety of subcutaneous omalizumab vs. placebo as an add-on therapy to ICS in adults and children (two out of the eight RCTs were done in pediatric population, n=910 children aged 5–12 years). Omalizumab patients showed a decreased risk of asthma exacerbations at the end of the stable (RR=0.57, 95% CI [0.48–0.66], p=0.0001, NNT=10, 95% CI [7–13]) and adjustable-steroid phases (RR=0.55, 95% CI [0.47–0.64], p=0.0001, NNT=8, 95% CI [6–10]). Post-hoc analysis suggests this effect was independent of age, duration of treatment, severity of asthma, and risk of bias. There was no increased risk of SAE among those patients on omalizumab.

Anmerkung/Fazit der Autoren

This review of 39 SRCTs gives us the possibility of quickly choosing the best method for chronic childhood asthma management (Table 2), and it accords with the principal international guidelines.

Loke YK et al., 2015 [16].

Bone mineral density and fracture risk with long-term use of inhaled corticosteroids in patients with asthma: systematic review and meta-analysis

Fragestellung

analyse the effects of long-term (≥12 months) ICS use in patients with asthma alone, concentrating on fracture and bone mineral density (BMD) outcomes

Methodik

Population:

- participants with asthma of any severity

Intervention/Komparator:

- ICS as the intervention versus a control treatment, where the comparison groups consisted of ICS versus other asthma therapy (or placebo), or ICS in combination with long-acting β-agonist (LABA) versus a LABA alone

Endpunkte:

- Frakturen oder Knochendichte (BMD)

Recherche/Suchzeitraum:

- We initially searched MEDLINE and EMBASE in June 2013 using a broad strategy for a wide range of adverse effects potentially associated with ICS use, and we subsequently updated this through a more focused PubMed search in December 2014

Qualitätsbewertung der Studien:

- RCTs: reporting of blinding of participants and personnel, randomisation sequence, allocation concealment, withdrawals and the loss to follow-up;
- Beobachtungsstudien: participant selection, ascertainment of exposure and outcomes, and methods of addressing confounding

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 Studien mit Kindern (4 RCTs, und 5 Beobachtungsstudien)

Charakteristika der Population:

Four of the RCTs focused solely on children,14 15 19 20 while the remaining three were in adults.16–18 Treatment duration was up to 4 years in one study,15 while the remaining six trials had ICS therapy for between 52 and 104 weeks. Intervention arms of the trials included fluticasone (5 trials), budesonide (3 trials) and mometasone (one trial). Fluticasone and mometasone were the ICS used in the intervention arms of one trial, and in this trial, we evaluated the results of all ICS users combined against montelukast.18 Five of the observational studies focused solely on children, 21–23 25 29 while the remainder looked at

adults or a mixture of age groups. The observational studies looked at wider range of ICS than the RCTs, with the inclusion of beclometasone, flunisolide and triamcinolone users.

Qualität der Studien:

- RCTs: major limitation discontinuations and substantial losses to follow-up;
- Beobachtungsstudien: Mehrheit der Studien mittleres bis hohes Risiko von Bias aufgrund von Confounding, fehlender Erhebung der Therapieadhärenz und Querschnittsdesign; Eine der Studien etwas besser.

Studienergebnisse:

Frakturen

- one large long-term RCT in children that reported adjusted fracture rate of 5.7 per 100 patient years with budesonide as compared to 5.1 per 100 patient years with placebo (p=0.53)
- no significant increase in likelihood of fracture in a meta-analysis of two observational studies in children (OR 1.02, 95% CI 0.94 to 1.10, I2=0%)
- nicht sign. erhöhtes Risiko für Frakturen bei höheren Dosen, eine Studie mit OR von 1.15 (0.89 to 1.48) mit ≥20 Verschreibungen und einer weiteren Studie mit OR of 1.17 (0.93 to 1.45) bei tägl Dosis von >400 µg beclomethasone dipropionate equivalents gegenüber niedrigerer Dosis (unter Grenzwert)

Ergebnisse zur Knochendichte:

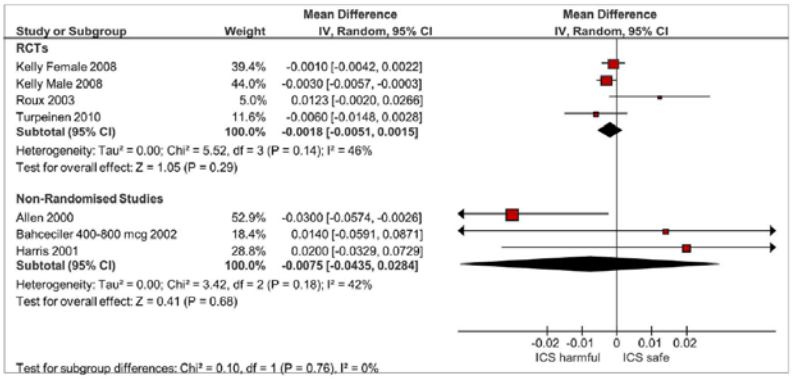


Figure 3 BMD in lumbar spine children, ICS use versus non-use. BMD, bone mineral density; ICS, inhaled corticosteroids.

- no clear signal of dose responsiveness in one observational study that separated participants into different dose levels
- one RCT suggested that longer term users of budesonide with greater cumulative doses had lower BMD compared to those who received lower cumulative doses

Anmerkung/Fazit der Autoren

Our systematic review demonstrates that there is no consistent evidence of serious skeletal harm from use of ICS. Although there are intrinsic limitations to the evidence, we believe that our systematic review provides some reassurance to patients and prescribers of ICS.

Kommentare zum Review

Es wurden nur die Daten für Kinder extrahiert.

Rodrigo GJ et al., 2015 [20].

Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents

Fragestellung

To explore the efficacy and safety of subcutaneous omalizumab as an add-on therapy to corticosteroids in children with moderate-to-severe persistent allergic asthma

Methodik

Population:

- subcutaneous omalizumab therapy at any dose vs. placebo as an add-on therapy to corticosteroids (oral or parenteral)

Intervention /Komparator:

- subcutaneous omalizumab therapy at any dose vs. placebo as an add-on therapy to corticosteroids (oral or parenteral)

Endpunkte:

- primär: asthma exacerbations (defined as hospital admissions, emergency department visits, increase in rescue medication, or use of corticosteroids).
- sekundär: measures were as follows: downtapering in steroids (inhaled, oral, or both), lung function (forced volume in the first second [FEV1] or peak expiratory flow [PEF], use of rescue medication, asthma symptoms, health-related quality of life, and adverse events (AEs)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, CINAHL, SCOPUS, the Cochrane Controlled Trials Register (CENTRAL) (January 2015) and ClinicalTrials.gov databases; Additionally, we performed a search of relevant files from the drug manufacturer's clinical trials register (http://www.novartisclinicaltrials.com)

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 Studien (n=1381)

Charakteristika der Population:

Table 1 Characteristics of included studies*

Study	Design	No. of patients (% of males)	Age, mean (range), years	Asthma severity@baseline % predicted FEV1 mean)	Mean baseline IgE serum IU/ml	Mean BDP mc/d O/P	Intervention
Milgrom (14)	R, DB, PG, PC	334 (69)	9.4 (–12)	M (84)	335	284/267	O S/C (0.016 mg/kg/IgE (IU/ml) every 2–4 weeks depending on participant's body weight. Run-in phase lasted 4–6 weeks with stabilization on ICS; there then followed a stable-steroid phase (16 weeks) and a steroid reduction phase (12 weeks).
Lanier (15)	MC, R, DB, PG, PC	576 (68)	8.6 (6–12)	M-S (86)	470	1036/1018	O S/C (75–350 mg) every 2–4 weeks over a period of 52 weeks (24 weeks fixed-steroid phase followed by a 28 weeks adjustable-steroid phase).
Busse (16)	MC, R, DB, PG, PC	419 (58)	10.8 (6–20)	M-S (92)	NA	772/775	O S/C (0.016 mg/kg/IgE (IU/ml) every 2 or weeks over a period of 60 weeks. The first 12 weeks served as a wash-in period and were not included in the analysis. The analysis included data from weeks 12 through 60

*BDP, beclomethasone dipropionate; DB, double blind; FEV_1, forced expiratory volume in the first second M, moderate; MC, multicenter; NA, not available; O, omalizumab; P, placebo; PC, placebo controlled; PG, parallel group; R, randomized; S, severe; S/C, subcutaneous.

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
Milgrom (14)	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Lanier (15)	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Busse (16)	Low risk	Unclear risk	Low risk	Low risk	Low risk

Studienergebnisse:

Signifikante Reduktion von

- Anzahl an Patienten mit mindestens 1 Exazerbation: RR=0,69 (95% KI: 0.59; 0.80), I2=0%, n=1329; 26.7% vs. 40.6%, NNTB = 7, 95% CI, 5, 11)
- Anzahl an Patienten mit schwerwiegenden Exazerbationen mit Hospitalisierung: RR=0.35 (95% KI: 0.20; 0.64), I2=29%, n=1381; 2.0% vs. 4.7%, NNTB = 36, 95% CI, 21,215
- Durchschnittliche Anzahl an Exazerbationen pro Patient Mittelwertdifferenz -0,30 (95% KI: -0,41; -0,19), I2=95%, n=1312

In Steroid Reduktionsphase signifikante Reduktion von (2 Studien):

- Anzahl an Patienten mit mindestens 1 Exazerbation: RR=0,48 (95% KI: 0,38; 0,61), I2=0%, NNTB = 6, 95% CI, 4, 8)
- Durchschnittliche Anzahl an Exazerbationen pro Patient Mittelwertdifferenz -0,44 (95% KI: -0,78; -0,17), I2=58%

Sekundäre Endpunkte:

Table 4 Analysis of secondary outcomes (omalizumab vs. placebo)

Outcome	References	N	Omalizumab vs. placebo	Measure (95% CI)	p	I^2%
Asthma symptom score (stable phase)	(15, 16)	1,047	−0.57 vs. −0.45*	MD = 0.12 (0.04–0.20)	0.005	0
Final pulmonary function (FEV_1 or PEF) (stable phase)	(14, 16)	680	7.95 vs. 7.80*†	SMD = 0.07 (0.08, 0.23)	0.36	0
Mean in morning PEF (L/m) (stable phase)	(14, 16)	859	304.1 vs. 302.3*	MD = 2.2 (8.4, 13.0)	0.67	0
Prematurely discontinued patients	(14–16)	1381	10.6% vs. 11.3%	RR = 0.84 (0.56, 1.25)	0.38	24
Withdrawals due to adverse events	(14–16)	1381	0.7% vs. 1.8%	RR = 0.52 (0.10, 2.64)	0.43	37
Any adverse event	(14–16)	1381	76.3% vs. 74.2%	RR = 1.02 (0.96, 1.09)	0.50	9
Serious adverse events	(14–16)	1381	5.2% vs. 5.6%	RR = 0.91 (0.58, 1.42)	0.57	0
Hypersensitivity reactions	(14–16)	1381	4.6% vs. 4.0%	RR = 1.23 (0.74, 2.06)	0.43	0
Urticaria	(14–16)	1381	2.4% vs. 1.9%	RR = 1.40 (0.32, 6.21)	0.66	48
Skin rush	(14–16)	1394	6.7% vs. 8.4%	RR = 0.81 (0.56, 1.19)	0.28	0
Injection site reactions	(14, 16)	753	20.7% vs. 15.0%	RR = 1.02 (0.76, 1.36)	0.92	0
Anaphylactic reactions	(12–14)	1381	0.58% vs. 1.04%	RR = 0.51 (0.09, 2.82)	0.44	24

FEV1, forced expiratory volume in the first second; MD, mean difference; N, number of patients; PEF, peak expiratory flow; RR, relative risk; SMD, standard mean difference.
*Mean value.
†Expressed in standard deviation units.

Anmerkung/Fazit der Autoren

Data indicate that the efficacy of an add-on omalizumab in patients with moderate-to-severe allergic asthma uncontrolled with recommended inhaled steroid treatment is accompanied by an acceptable safety profile.

Rodrigo GJ et al., 2016 [21].

Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma

Fragestellung

The objective of this systematic review was to assess the efficacy and safety of fluticasone furoate-vilanterol compared with ICS monotherapy or twice daily ICS-LABA formulations.

Methodik

Population:

patients with asthma (12 years or older) with documented use of an ICS with or without a LABA

Intervention/Komparator:

- comparison of Fluticasone furoate evilanterol with ICS monotherapy or ICS-LABA twice-daily combinations

Endpunkte:

pulmonary function (forced expiratory volume in 1 second [FEV1] or peak expiratory flow rate [PEF]) as a primary outcome, rescue medication use, health status (Asthma Quality of Life Questionnaire [AQLQ] total score16), asthma control, number of patients with at least 1 severe asthma exacerbation (defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥3 days or a hospitalization or emergency department visit due to asthma), withdrawals, and safety of treatment (adverse events [AEs], serious adverse events [SAEs], cardiac events, and pneumonia). A SAE was defined as any untoward medical occurrence that sometimes results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability or incapacity

Recherche/Suchzeitraum:

- bis Januar 2016

Qualitätsbewertung der Studien:

risk of bias assessment according to recommendations outlined in the Cochrane Handbook

Ergebnisse

Anzahl eingeschlossener Studien:

7 RCTs (n=5668)

Charakteristika der Population:

Characteristics of the Included Studies

Study	Duration, ek	Patients, No. (% female)	Mean age (range), y	Racial characteristics	Mean baseline FEV_1, % predicted	Primary outcome	Selected comparisons
Bateman et al[24]	24–78	2019 (67)	42 (≥12)	W, 74%; A, 11%; AA, 5%	68	Asthma exacerbations	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate, 100 μg once daily
Bernstein et al[25]	12	1039 (61)	46 (≥12)	W, 88%; A, <1%; AA, <1%	68	Weighted mean FEV_1	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate –vilanterol, 200/25 μg once daily, vs fluticasone furoate, 100 μg once daily
Bleecker et al[26]	12	609 (58)	40 (≥12)	W, 84%; A, 8%; AA, <1%	68	Trough FEV_1 and @weighted mean FEV_1	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate, 100 μg once daily
Busse et al[27]	52	503 (63)	38 (≥12)	W, 67%; A, 25%; AA, 7%	74	AEs, SAEs Asthma exacerbations	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate –vilanterol, 200/25 μg once daily, vs fluticasone propionate, 500 μg twice daily
Lin et al[28]	12	309 (59)	48 (≥12)		63	PM PEF	Fluticasone furoate–vilanterol, 200/25 μg once daily, vs fluticasone propionate, 500 μg twice daily
O'Byrne et al[29]	24	586 (59)	46 (≥12)	W, 84%; A, 9%; AA, 7%	67	Trough FEV_1 and weighted mean FEV_1	Fluticasone furoate–vilanterol, 200/25 μg once daily, vs fluticasone furoate, 200 μg once daily, vs fluticasone propionate, 500 μg twice daily
Woodcock et al[30]	24	806 (61)	43 (≥12)	W, 59%; A, 31%; AA, 10%	64	Weighted mean FEV_1	Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone propionate –salmeterol, 250/50 μg twice daily

Abbreviations: A, Asian; AA, African American; AE, adverse event; ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; SAE, serious adverse event; W, white.

Qualität der Studien:

the studies had a high methodologic quality

Studienergebnisse:

Fluticasone FuroateeVilanterol Group vs Fluticasone Furoate, 100 mg (3 Studien)

- • fluticasone furoate-vilanterol significantly increased the percentage of patients symptom free and reduced the use of rescue medication. Fluticasone furoate-vilanterol also reduced significantly the number of patients with at least 1 severe asthma exacerbation (9.1% vs 13.2%, NNTB ¼ 24).
- no statistical significant differences in the rate of AEs, SAEs, pneumonia, or cardiac events (1.4% vs 1.3%) among both groups

- Fluticasone Furoate-Vilanterol Group vs Fluticasone Propionate, 500 mg (3 Studien27-29)
- mean change from baseline in weighted FEV1 significantly increased by 140 mL at the end of treatment (fluticasone furoate-vilanterol)
- fluticasone furoate-vilanterol group presented significantly increases in morning and evening PEF (32.6 and 25.7 L/min, respectively)

- fluticasone furoate-vilanterol significantly increased the percentage of patients symptom free and reduced the number of patients with at least 1 severe asthma exacerbation (1.3% vs 2.4%, NNTB ¼ 88).
- No statistical difference in health status. Safety outcomes revealed no significant differences in AEs (1.4% vs 2.4%) or in the occurrence of pneumonia (0.4% vs 0.2%)
- fluticasone furoate-vilanterol group had a nonsignificant small increase in the frequency of cardiac events (6.4% vs 1.8%) compared with fluticasone propionate (Ergebnis von einer Studie27)

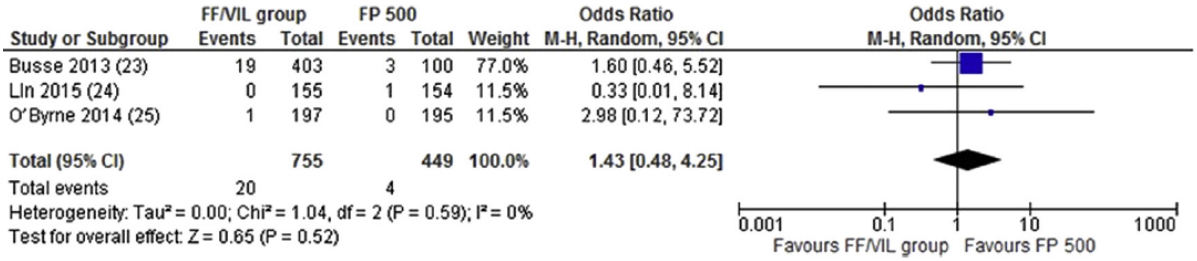
Fluticasone FuroateeVilanterol, 100/25 mg, vs Fluticasone FuroateeVilanterol, 200/25 mg (2 Studien25,27)

- overall incidence of withdrawals, severe asthma exacerbations, AEs, SAEs, or pneumonia was similar across both fluticasone furoate-vilanterol doses.
- On the basis of data available in 1 study25 there were nonsignificant differences in terms of pulmonary function (FEV1, and PEF) and symptoms. Finally, also according to data from 1 study27 the increase of the fluticasone furoate dose was associated with a rise of cardiac events (2.0% to 7.4%).

Fluticasone FuroateeVilanterol, 100/25 mg, vs Fluticasone PropionateeSalmeterol, 250/50 mg (1 Studie30)

- At 24 weeks, there were no differences in trough FEV1, asthma control, health status, and safety across both treatment groups.

Figure 3. Pooled odds ratios for the rate of cardiac events on treatment with 95% confidence intervals of eligible studies comparing fluticasone furoateevilanterol group and fluticasone propionate, 500 mg.



Anmerkung/Fazit der Autoren

In conclusion, according to the data from this systematic review, the use of once-daily fixed fluticasone furoate-vilanterol combination revealed a slight increase in terms of lung function compared with ICS monotherapy (fluticasone furoate and fluticasone propionate). However, the significance of advantages in other outcomes was unclear. The lack of therapeutic advantage and a trend toward an increased risk of cardiac events do not support the use of fluticasone furoateevilanterol, 200/25 mg, and require close and careful monitoring. Future studies should focus on comparison of fluticasone furoateevilanterol and other combination therapies for safety and efficacy in larger and racially diverse cohorts and studies conducted for a longer duration

Kommentare zum Review

- Patientenpopulation: Erwachsene und Jugendliche (ab 12 Jahre)

Sobieraj DM et al., 2018 [23].

Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma. AHRQ Comparative Effectiveness Review

Fragestellung

To assess efficacy of intermittent inhaled corticosteroid (ICS) therapy in different populations (0 to 4 years old with recurrent wheezing, 5 years and older with persistent asthma, with or without long-acting beta agonist [LABA]), and to assess efficacy of added long-acting muscarinic antagonist (LAMA) in patients 12 years and older with uncontrolled, persistent asthma.

Methodik

Population:

To assess efficacy of intermittent inhaled corticosteroid (ICS) therapy in different populations:

- Patients 0 to 4 years old with recurrent wheezing
- Patients 5 years and older with persistent asthma (with or without long-acting beta agonist (LABA)

• To assess efficacy of adding long-acting muscarinic antagonist (LAMA) to ICS with or without LABA in:

- Patients 12 years and older with uncontrolled, persistent asthma.

Intervention:

Table A. Drugs included in the review

Class	Drugs
ICS	Beclomethasone,[a] budesonide,[a] ciclesonide,[a] Flunisolide,[a] fluticasone,[a] mometasone,[a] triamcinolone[b]
LABA	Arformoterol, formoterol,[a] olodaterol, salmeterol,[a] vilanterol,[a,c]
LAMA	Aclidinium, glycopyrrolate, tiotropium,[a] umeclidinium

FDA = Food and Drug Administration; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist

Komparator:

Comparators: We are interested in direct comparisons of therapies as described per KQ. Table 2 demonstrates the intervention and comparator for each KQ in a tabular format. The definition of “controller therapy” is provided in the Glossary.

• KQ1a: No treatment (placebo or control) OR pharmacologic therapy which includes controller therapy or as-needed short-acting β2-agonist (SABA) OR nonpharmacologic therapy. Controller therapies include ICS, inhaled LABA, leukotriene modifiers, cromolyn, methylxanthines, immunomodulators, and systemic corticosteroids. Nonpharmacologic treatment is as per EPR-3 (e.g., avoiding environmental triggers).

• KQ1b: ICS controller therapy

• KQ1c: ICS controller therapy OR ICS and LABA controller therapy

• KQ2a: ICS controller therapy, with or without placebo, where the ICS dose is the same or increased relative to the intervention arm dose

• KQ2b: ICS and another controller therapy, including LABA, leukotriene modifiers, cromolyn, methylxanthines, immunomodulators and systemic corticosteroids

• KQ2c: ICS and LABA controller therapy

Table 2. Intervention and comparator per Key Question

	Comparator: No treatment, pharmacologic or nonpharmacologic therapy[a]	Comparator: ICS controller therapy	Comparator: ICS and LABA controller therapy	Comparator: ICS and other controller therapy[b]
Intervention: Intermittent ICS	KQ 1a	KQ 1a, 1b	---	---
Intervention: ICS and LABA used as controller and quick relief therapy	---	KQ 1c	KQ 1c	---
Intervention: ICS and LAMA controller therapy	---	KQ 2a[c]	KQ 2b	KQ 2b
Intervention: ICS and LAMA and LABA controller therapy	---	---	KQ 2c	---

Note: The first column represents interventions and the first row represents comparators of interest in this review. The key questions for each intervention are listed below the relevant comparator(s).

ICS = inhaled corticosteroid; KQ = Key Question; LAMA = long-acting muscarinic antagonist; --- = not applicable

Endpunkte:

- Asthma exacerbations
- Requiring systemic (oral and/or parenteral) corticosteroids, requiring hospitalization, requiring emergency room (ER) visit, requiring intensive care unit or intubation, or as defined by the study
- Asthma-related hospitalizations, ER visits, urgent care and outpatient visits
- Death
- All-cause, asthma-specific
- Asthma control: Composite Measures: Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), various versions; Spirometry: forced expiratory volume in 1 second (FEV1) forced vital capacity (FVC), FEV1/FVC
- • Asthma-specific quality of life:
- Asthma Quality of Life Questionnaire (AQLQ), Pediatric Asthma Quality of Life Questionnaire (PAQLQ), Pediatric Asthma Caregiver's Asthma Quality of Life Questionnaire (PACQLQ)
- • Health care utilization:
- Additional asthma-medication use/need
- Additional resource use related to intervention (e.g. personnel time, equipment)

Recherche/Suchzeitraum:

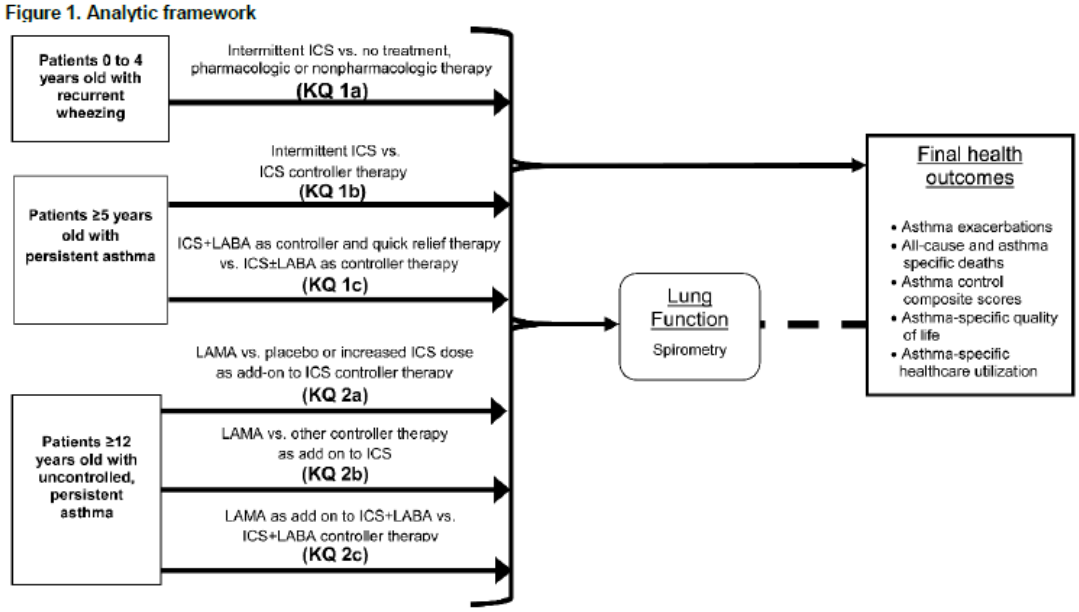
bis 23.03.2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias Tool18 for randomized controlled trials (RCTs) and Newcastle Ottawa Scale19 for observational studies

Ergebnisse

Figure 1. Analytic framework



ICS = inhaled corticosteroid; KQ = Key Question; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; vs = versus

Anzahl eingeschlossener Studien/ Charakteristika der Population / Qualität der Studien:

Table 5. Number of studies included per KQ, study design, and age group

	Characteristic	KQ1a	KQ1b	KQ1c (RCT/NonRCT)	KQ2a	KQ2b	KQ2c
Study Design	RCTs	6	11	22	8	8	4
	Non RCTs	0	0	2	0	0	0
Age Group	≥12y	NA	9	22 (20/2)	8	8	4
	5-11y	NA	0	0	NA	NA	NA
	0-4y	5	0	0	NA	NA	NA
	Mixed	1	2	2 (2/0)	0	0	0
TOTAL		6	11	24	8	8	4

KQ = Key Question; NA = not applicable; RCT = randomized controlled trial; y = years

Qualität und Studiencharakteristika – siehe unten

Studienergebnisse:

KQ1b: What is the comparative effectiveness of intermittent ICS compared to ICS controller therapy in patients 5 years of age and older with persistent asthma?

- In patients 12y of age or older, intermittent ICS and ICS controller versus ICS controller does not significantly differ in effect on the risk of exacerbations (low SOE) with exception of asthma-related outpatient visits (low SOE) which favors intermittent ICS with ICS controller versus ICS controller. Evidence is insufficient to draw conclusions in patients 5 to 11y old.
- In patients 12y of age or older, intermittent ICS versus ICS controller therapy does not significantly differ in the risk of exacerbations (low SOE), Asthma Control Questionnaire (ACQ)-7 or ACQ-5 score (low SOE), spirometry (low to high SOE), Asthma Quality of Life Questionnaire (AQLQ)-(S) score (moderate SOE), albuterol rescue use (moderate SOE). Evidence is insufficient to draw conclusions in patients 5 to 11y old aside from Pediatric Asthma Quality of Life Questionnaire (PAQLQ) score and rescue inhaler use which was no different between groups (low SOE).

KQ1c: What is the comparative effectiveness of ICS with long-acting beta agonist (LABA) used as both controller and quick relief therapy compared to ICS with or without LABA used as controller therapy in patients 5 years of age and older with persistent asthma?

Key Points—ICS and LABA Controller and Quick Relief Versus ICS Controller

- In patients 12 years of age and older, ICS and LABA controller and quick relief versus ICS controller at the same comparative ICS dose reduces the risk of exacerbations as composite outcomes (all moderate SOE), improves FEV1 (moderate SOE) and reduces rescue medication inhalations per day (low SOE).
- In patients 12 years of age and older and in patients 4 to 11y old, ICS and LABA controller and quick relief versus ICS controller at a higher comparative ICS dose reduces the risk of exacerbations as composite outcomes (all low SOE).

Key Points—ICS and LABA Controller and Quick Relief Versus ICS and LABA Controller

- In patients 12 years of age and older, ICS and LABA controller and quick relief versus ICS and LABA controller at the same comparative ICS dose reduces the risk of composite exacerbations including systemic corticosteroid, hospitalization, or ER visits (high SOE) as well as each of the individual components of the composite outcome (moderate to high SOE). The chance of being an ACQ-5 responder (moderate SOE) and the mean inhalations per week of rescue inhaler (low SOE) also favored controller and quick relief therapy. Results of a subgroup of patients 4-11y old favor ICS and LABA controller and quick relief on composite exacerbation outcomes and on mild exacerbation risk (all low SOE).
- In patients 12 years of age and older, ICS and LABA controller and quick relief versus ICS and LABA controller at a higher comparative ICS dose reduces the risk of composite exacerbations including systemic corticosteroid, hospitalization, or ER visits (high SOE) but not individual components of the composite outcome (moderate SOE).
- There is insufficient evidence to determine the impact of ICS and LABA controller and quick relief versus ICS and LABA controller at a lower comparative ICS dose.

Key Points—ICS and LABA Controller and Quick Relief Versus CBP

- In patients 12 years of age and older, ICS and LABA as controller and quick relief versus CBP reduces the risk of composite exacerbations (requiring systemic corticosteroids, hospitalization, ER visit, moderate SOE) but not of the individual components of the composite outcome (low SOE). ACQ-5 scores were improved with ICS and LABA controller and quick relief (moderate SOE) and rescue medication use also favored ICS and LABA controller and quick relief (moderate SOE).

KQ2a: What is the comparative effectiveness of long-acting muscarinic antagonist (LAMA) as add-on to ICS controller therapy compared to placebo or increased ICS dose in patients 12 years of age and older with uncontrolled, persistent asthma?

- Key Points—LAMA Versus Placebo as Add-on to ICS
  - LAMA versus placebo as add-on to ICS reduces the risk of exacerbations requiring systemic corticosteroids (high SOE) and the risk of asthma worsening (high SOE), and leads to improved mean differences in peak, trough and area under the curve (AUC) for FEV1 and FVC (all high SOE).
  - LAMA versus placebo as add-on to ICS does not significantly differ in effect on asthma control composite scores (moderate SOE), asthma-specific quality of life (low to high SOE) or rescue medication use (moderate SOE).
- Key Points—LAMA Add-on to ICS Versus Increasing ICS Dose

- LAMA added on to ICS versus doubling the ICS dose does not significantly differ in effect on the risk of exacerbations requiring systemic corticosteroids or the mean difference in ACQ-6 score, FEV1 trough or AQLQ score (all low SOE).

KQ2b: What is the comparative effectiveness of LAMA compared to other controller therapy as add-on to ICS in patients 12 years of age and older with uncontrolled, persistent asthma?

- o LAMA versus LABA as add-on to ICS does not significantly differ in their effect on the risk of exacerbations requiring systemic corticosteroids (low SOE) or risk of asthma worsening (moderate SOE), death (low SOE), asthma control composite scores (low to high SOE), spirometry measures (low to high SOE), asthma-specific quality of life (low to high SOE) or rescue medication use (low SOE).
- Few studies, limited to outcomes of FEV1 percent predicted and rescue medication use, compared LAMA to controllers other than LABA as add-on to ICS.

KQ2c: What is the comparative effectiveness of LAMA as add-on to ICS plus LABA compared to ICS plus LABA as controller therapy in patients 12 years of age and older with uncontrolled, persistent asthma?

- o LAMA added to ICS plus LABA versus ICS plus LABA does not significantly differ in effect on the risk of asthma exacerbations (low to moderate SOE) but does decrease the risk of asthma worsening (high SOE).
- o • LAMA added to ICS plus LABA versus ICS plus LABA improved the mean difference in FEV1 AUC and of peak, trough and AUC for FVC (all high SOE), the chance of being an ACQ responder (low to moderate SOE) and the chance of being an AQLQ responder (moderate SOE). There was no difference in asthma control composite scores (low to moderate SOE) or in rescue medication use (moderate SOE).
- In the single trial that compared LAMA added to ICS plus LABA versus increasing the ICS dose and continuing LABA found no significant difference in effect on the mean difference in ACT score.

Anmerkung/Fazit der Autoren

In patients 12 years and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected, although few studies provided evidence, leading to primarily low strength of evidence ratings. Using ICS and LABA as both a controller and quick relief therapy reduced the risk of exacerbations and improved symptom control in patients 12 years and older compared to ICS controller (with or without LABA). Data in patients 4 to 11 years old suggest lower risk of exacerbations with ICS and LABA controller and quick relief use, but with a lower strength of evidence than in the older population. In patients 12 years and older with uncontrolled, persistent asthma, LAMA versus placebo as add-on to ICS reduces the risk of exacerbations requiring systemic corticosteroids and improves lung function measure through spirometry. Current evidence does not suggest that a difference exists in the efficacy of LAMA versus LABA as add-on to ICS. Triple therapy of ICS, LAMA, and LABA improves lung function measured through spirometry, although the risk of exacerbation was not different versus ICS and LABA.

Kommentare zum Review

- Aufgrund der umfangreichen Ergebnisdarstellung im SR wird der hier extrahierte Text auf die Key Points beschränkt.

- Seitens der Autoren fand grundsätzlich keine Auswertung/ Ergebnisdarstellung nach verschiedenen Asthma-Typen (z.B. eosinophilem Asthma) statt.

Lai T et al., 2015 [15].

Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis.

Fragestellung

Currently, limited information is available to clinicians regarding the long-term efficacy of omalizumab treatment for allergic asthma. In this report, we aimed to (i) systematically review the evidence regarding the long-term efficacy of omalizumab in patients with persistent uncontrolled allergic asthma, and to (ii) discuss the cost-effectiveness evidence published for omalizumab in this patient population.

Methodik

Population:

- patients with persistent, uncontrolled, moderate-to severe allergic asthma in spite of high-dose ICS or ICS plus LABA

Intervention:

- Omalizumab, mindestens 52 Wochen

Komparator:

- Keine Angabe

Endpunkte:

- Keine Angabe

Recherche/Suchzeitraum:

- until March 2014

Qualitätsbewertung der Studien:

- Cochrane five risk of bias domains tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6

Charakteristika der Population:

- N= 2749

Qualität der Studien:

Table 2 | Risk of bias of the included studies

Study	Sequence generation	Allocation concealment	Data collection blinded	Complete outcome data	Selective outcome reporting
Finn et al[44]	No	Yes	Yes	Yes	Yes
Lanier et al[45]	No	Yes	Yes	Yes	Yes
Niven et al[46]	Yes	No	Yes	Yes	Yes
Buhl et al[47]	No	Yes	Yes	Yes	Yes
Lanier et al[48]	Yes	Yes	Yes	Yes	Yes
Busse et al[49]	No	Yes	Yes	Yes	Yes

Studienergebnisse:

- The overall designs of these studies were as follows: after a run-in phase (4–8 weeks), omalizumab was administrated as an adjunctive therapy to inhaled or oral corticosteroids for 16 to 28 weeks (stable steroid phase), followed by a steroid-reduction phase of 12 to 28 additional weeks, during which doses were decreased only if patients met strict criteria for steroid reduction.

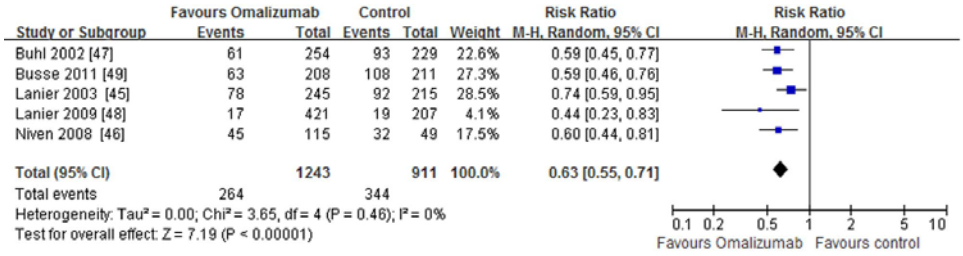
  We double-counted two end points (stable steroid phase and steroid-reduction phase), and using these single primary efficacy endpoints (end of the steroid-reduction phase), included the rates of clinically significant asthma exacerbations, reductions in ICS doses, Global Evaluation of Treatment Effectiveness (GETE), Asthma Quality of Life Questionnaire (AQLQ), asthma symptom scores, lung function, and adverse events (AEs), over a period of 52 weeks.

Table 1 | Characteristic of randomized controlled trials included

Source	Study design	Female/Patients (No.)	Age (y)‡	IgE (IU/ml)‡	Severity/FEV_1 (%pred)‡	Study duration (weeks)	Exacerbation definition
Finn 2003[44]	**DB**				**S**	**52**	
Omalizumab		164/268	39.3	172.5	68.2		A worsening of asthma symptoms and was severe enough to require treatment with oral or intravenous corticosteroids or a doubling of the subject's baseline inhaled BDP dose.
Control		146/257	39.0	186.3	67.7		
Lanier 2003[45]	**DB**				**S**	**52**	
Omalizumab		150/245	68.8	173.4	68.8		Worsening of asthma requiring treatment with oral or intravenous corticosteroids or doubling of the patient's most recent BDP maintenance dose.
Control		119/215	68.2	186.2	68.2		
Niven 2008[46]	**OL**				**S**	**52**	
Omalizumab		86/115	38.7	NA	65.6		Asthma worsening requiring treatment with systemic corticosteroids and the ADRIs, unscheduled physician visit, or hospitalization/emergency room visit.
Control		34/49	39.3	NA	64.1		
Buhl 2002[47]	**DB**				**M-S**	**52**	
Omalizumab		124/254	41	220.2	70.0		Worsening of asthma requiring treatment with oral or parenteral corticosteroids or doubling of the patient's most recent BDP maintenance dose.
Control		120/299	40	204.1	70.4		
Lanier 2009[48]	**DB**				**M-S**	**52**	
Omalizumab		134/421	8.7	476.0	86.0		Worsening of asthma symptoms requiring doubling of baseline ICS dose and/or treatment with rescue systemic corticosteroids for 3 days.
Control		69/207	8.4	456.9	87.2		
Busse 2011[49]	**DB**				**M-S**	**60**	
Omalizumab		86/208	10.9	NA	92.9		A need for systemic glucocorticoids, hospitalization, or both, in accordance with a recent report by the American Thoracic Society/European Respiratory Society[5].
Control		91/211	10.8	NA	92.2		

‡The data are shown as mean.
FEV_1, forced expiratory volume in one second; DB, Double-blind; OL, Open-label; M, moderate; S, severe; BDP, beclomethasone dipropionate; ADRIs, annual rate of asthma deterioration-related incidents; NA, not available.
[5]Reddel HK, *et al.* An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* **180**, 59–99 (2009).

Exazerbationen



During the steroid-reduction phase, ICS doses were significantly decreased in omalizumab-treated patients compared with the placebo group (RR 1.86, 95% CI [1.51, 2.29]; p <, 0.0001).

Heterogeneity was not observed (I2 5 0%, p = 0.47).

At 52 weeks, both GETE (an excellent or good response) and AQLQ scores (≥1.5 points from baseline) favored omalizumab (RR1.54, 95%CI [1.38, 1.72]; p < 0.00001 and RR 2.08, 95% CI [1.03, 4.20]; p = 0.04 respectively) (table 3).

Symptoms and FEV/ PEF

With regard to asthma symptoms and lung function, descriptive analysis methods were utilized, as most of these data were unavailable or unsuitable for analysis. Two RCTs demonstrated greater reductions in asthma symptom scores than placebo46,48. However, the effects of omalizumab on lung function were discrepant.

Only one RCT demonstrated that pulmonary function (FEV1) was significantly better in the omalizumab group than in the control group.

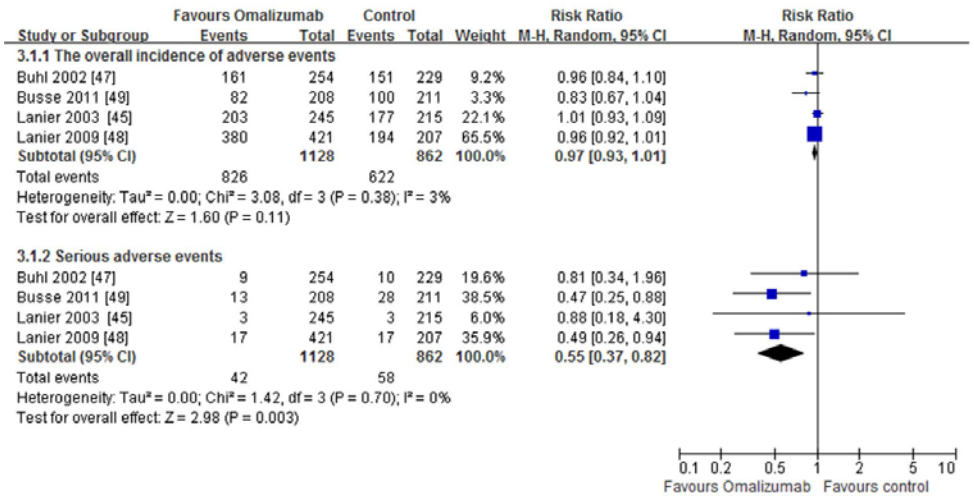
Supplemental table 2. Analysis of other outcomes (Omalizumab vs control)

Outcome measure	Omalizumab effect	No. (O/C)	O (Δ)	C (Δ)	Difference between groups: *P* value	Comments
Asthma symptom score						
	Niven 2008 [46] ↑↑	115/49	NA	NA	$p < 0.05$	At 1 year, asthma score was significantly improved in the omalizumab group compared with control.
	Liner 2009 [48] ↑↑	421/207	NA	NA	$p < 0.01$	Nocturnal asthma symptom score, -0.63 [0.72] vs -0.50 [0.71].
Pulmonary function						
Lanier 2003 [45]		245/215				
	FEV_1, L ↔		NA	NA	$P = 0.16$	The corresponding between-group differences in FEV_1 at weeks 52 were 52 ml.
Niven 2008 [46]		115/49				
	FEV_1, L ↑↑		Δ = + 0.19	NA	$P < 0.05$	Throughout the 1-year treatment period representing a between-group difference of 320 ml.
Buhl 2002 [47]						
	FEV_1, %predicted ↔	254/299	NA	NA	NA	No statistically significant differences in FEV_1 were seen between the treatment groups at any time point during the extension.
Busse 2011 [49]						
	FEV_1, %predicted ↔	208/211	NA	NA	$p = 0.30$	No statistically significant differences in FEV_1 were seen between two groups during follow-up.

↑↑ Omalizumab better than (with statistical significance); ↑ Omalizumab better than control (without statistical significance); ↔ Omalizumab comparable with control. O, Omalizumab; C, Control; Δ, The mean change from baseline; NA, not available; FEV_1, forced expiratory volume in 1 second.

Adverse events

Four studies assessed adverse events (AEs), and omalizumab was well tolerated. Common adverse events included the following: lower respiratory tract infection, nasopharyngitis, headache, injection site pain, injection site reaction and arthralgia. Based on the results of the meta-analysis, the numbers of patients reporting AEs was similar in both treatment groups (RR 0.97, 95% CI [0.93, 1.01]; p = 0.11). Statistical heterogeneity was not observed (I2 5 3%, p = 0.38). Serious adverse events, such as death, asthma exacerbation, pruritus, acute appendicitis, sphenoid sinusitis, intestinal obstruction, and mild chest pain were reported. However, none of these was considered drug-related. The incidence and profile of serious adverse events were slightly lower in the omalizumab group (RR 0.55, 95% CI [0.37, 0.82]; p= 0.003). Statistical heterogeneity was not observed (I2=0%, p=0.70). No clinically relevant abnormalities in laboratory tests (including platelet count) were observed.



Gesamtauswertungen und Subgruppen

Table 3 | Results of subgroup and sensitivity analyses from a meta-analyses of randomized controlled trials

Trials	Asthma exacerbation[44–49]	Withdrew ICS completely[45,47]	Change in GFTE score[44,48,49]	AQLQ ≥ 1.5[44,46]	Adverse events[45,47–49]
	← RR (95%CI), P value →				
All trials[44–49]	0.63 [0.55, 0.71] <0.0001	1.86 [1.51, 2.29] <0.0001	1.54 [1.38, 1.72] <0.00001	2.08 [1.03, 4.20] =0.04	0.97 [0.93, 1.01] =0.11
Subgroup analyses					
Risk of bias					
Low[46,48]	0.57 [0.43, 0.74] <0.0001	–	1.42 [1.24, 1.62] <0.00001	3.23 [1.58, 6.59] =0.001	0.96 [0.92, 1.01] =0.12
High[44,45,47,49]	0.64 [0.55, 0.75] <0.00001	1.86 [1.51, 2.29] <0.0001	1.65 [1.45, 1.87] <0.00001	1.57 [1.23, 2.01] =0.0003	0.96 [0.88, 1.06] =0.44
Age of patients					
Adolescents and adults[44–47]	0.65 [0.56, 0.76] <0.00001	1.86 [1.51, 2.29] <0.0001	1.60 [1.30, 1.97] <0.00001	2.08 [1.03, 4.20] =0.04	0.99 [0.93, 1.07] =0.54
Children[48,49]	0.41 [0.29, 0.58] <0.00001	–	1.53 [1.30, 1.80] <0.00001	–	0.91 [0.75, 1.12] =0.06
Asthma severity					
Moderate-sever[44–46]	0.68 [0.55, 0.84] =0.0004	2.37 [1.17, 4.78] =0.02	1.60 [1.30, 1.97] <0.00001	2.08 [1.03, 4.20] =0.04	1.01 [0.93, 1.09] =0.88
Severe[47–49]	0.58 [0.49, 0.69] <0.00001	1.82 [1.46, 2.26] <0.0001	1.53 [1.30, 1.80] <0.00001	–	0.95 [0.89, 1.02] =0.28
Intervention					
Omalizumab/ ICS[44,45,47,48]	0.63 [0.50, 0.80] =0.0002	1.86 [1.51, 2.29] <0.0001	1.49 [1.33, 1.66] <0.00001	1.57 [1.23, 2.01] =0.0003	0.98 [0.93, 1.02] =0.32
Omalizumab/ICS + LABA[46,49]	0.59 [0.49, 0.72] <0.00001	–	1.68 [1.43, 1.97] <0.00001	3.23 [1.58, 6.59] =0.001	0.83 [0.67, 1.04] =0.10
Sensitivity analyses					
Open label[46]	0.60 [0.44, 0.81] =0.001	–	–	3.23 [1.58, 6.59] =0.001	–
Double-blinded[44,45,47–49]	0.63 [0.54, 0.73] <0.0001	1.86 [1.51, 2.29] <0.0001	1.54 [1.38, 1.72] <0.00001	1.57 [1.23, 2.01] =0.0003	0.97 [0.93, 1.01] =0.11
Fixed-effects model[44–49]	0.62 [0.55, 0.71] <0.00001	1.88 [1.52, 2.33] <0.0001	1.52 [1.37, 1.68] <0.00001	1.77 [1.40, 2.24] <0.00001	0.96 [0.91, 1.01] =0.08

RR, relative risk; CI, confidence interval; ICS, included inhaled corticosteroid; GETE, Global Evaluation of Treatment Effectiveness; AQLQ, Asthma Quality of Life Questionnaire; LABA, long-acting beta2-agonists.

Anmerkung/Fazit der Autoren

Omalizumab was associated with significant improvements in quality of life and the Global Evaluation of Treatment Effectiveness. Omalizumab also allowed patients to completely withdraw from inhaled corticosteroid therapy and did not increase the overall incidence of adverse events.

However, there was insufficient evidence that omalizumab reduced the incidence of exacerbations, and the cost-effectiveness of omalizumab varied across studies. Our data indicated that omalizumab use for at least 52 weeks in patients with persistent uncontrolled allergic asthma was accompanied by an acceptable safety profile, but it lacked effect on the asthma exacerbations.

Therefore, it seems reasonable to explore this issue further. In contrast to previous systematic reviews that included studies of short duration (less than 1 year), we included only long-term trials involving patients with persistent uncontrolled allergic asthma to assess the efficacy of and risk associated with omalizumab. Based on the pooled analyses, we found that omalizumab significantly reduced the incidence of asthma exacerbations and ICS use and improved scores on the GETE and AQLQ. and is likely to be associated with improvements in asthma-related quality of life and reductions in the burdens imposed on patients and health care systems. Our meta-analysis demonstrated that compared with the control group, a significant reduction was observed in the rate of exacerbation for patients receiving omalizumab add-on treatment.

However, there was some degree of heterogeneity in the definition of exacerbations within trials (Table 1), which may influence the efficacy of omalizumab on asthma exacerbations. Moreover, in placebo controlled study if you reduce treatment you will see more exacerbations allied to treatment dose reduction (e.g., steroid, LABA or a third controller). Therefore, the results should be interpreted cautiously due to these limitations. In other words, a lack of robust evidence existed that omalizumab reduced exacerbations in allergic asthma patients who were uncontrolled by the best available therapy.

Kommentare zum Review

Siehe auch Corrigendum: Lai T et al., 2015 [14].

3.4 Leitlinien

Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), 2018 [2].

Nationale VersorgungsLeitlinie Asthma: Langfassung; 3. Auflage

Leitlinienorganisation/Fragestellung

Das NVL-Programm zielt auf die Entwicklung und Implementierung versorgungsbereichsübergreifender Leitlinien zu ausgesuchten Erkrankungen hoher Prävalenz unter Berücksichtigung der Methoden der Evidenzbasierten Medizin (EbM). Insbesondere sind NVL inhaltliche Grundlage für die Ausgestaltung von Konzepten der strukturierten und Integrierten Versorgung

Methodik

Grundlage der Leitlinie

Die 3. Auflage der NVL Asthma wurde auf Basis einer systematischen Recherche nach aggregierter Evidenz aktualisiert. Im Falle fehlender systematischer Übersichtsarbeiten wurde punktuell ergänzend und systematisch nach Primärliteratur recherchiert. Die systematischen Übersichtsarbeiten wurden methodisch mit dem AMSTAR-Tool bewertet, wobei nur systematische Übersichtsarbeiten mit einem AMSTAR-Score von mindestens 6 in die Synthese einbezogen wurden. In Bezug auf die einzelne Empfehlung wurden die Quellen nach ihrer inhaltlichen Aussagekraft (Datenqualität) in Anlehnung an GRADE (Grading of Recommendations, Assessment, Development and Evaluation) bewertet. Genauere Informationen zu der Recherchestrategie, dem Screening und der methodischen Bewertung der Quellen sind im Leitlinienreport detailliert aufgeführt.

Zur Ergänzung der Evidenz wurden Auswertungen von Routinedaten herangezogen. Das Zentralinstitut für die kassenärztliche Versorgung in Deutschland (Zi) führte eine Auswertung von Arzneiverordnungs- und vertragsärztlichen Abrechnungsdaten der Jahre 2014 und 2015 durch. Eingeschlossen wurden Patienten, die innerhalb eines Kalenderjahres mindestens zweimal die gesicherte Diagnose Asthma erhielten.

Die Suche nach Aktualisierungen der einstigen Quell- und Referenzleitlinien bei fachübergreifenden und fachspezifischen Leitliniendatenbanken und -anbietern ergab, dass zwei der Quell- und zwei der Referenzleitlinien der 2. Auflage der NVL Asthma aktualisiert wurden. Die anschließende strukturierte Suche nach Leitlinien zum Thema Asthma erbrachte 27 Treffer, von denen 17 wegen verschiedener Ausschlussgründe nicht für eine Leitliniensynopse infrage kamen. Die verbliebenen zehn Leitlinien waren potentiell als Grundlage für eine Leitliniensynopse geeignet. Bei näherer Betrachtung ergab sich jedoch, dass die Suchzeiträume der Quell- und Referenzleitlinien zumeist weit in der Vergangenheit lagen, sodass sich eine zeitliche Lücke zwischen der Veröffentlichung der Evidenz und der der 3. Auflage der NVL Asthma ergeben hätte. Aufgrund dieser Überlegungen wurde auf eine Leitlinienadaptation verzichtet und stattdessen für die gesamte NVL eine systematische Recherche nach aggregierter Evidenz durchgeführt. Für einzelne Fragestellungen wurde auf

Referenzleitlinien Bezug genommen

Recherche/Suchzeitraum:

In der systematischen Recherche des ÄZQ (durchgeführt am 26.02.2016) wurden systematische Übersichtsarbeiten und HTA-Berichte zur Anwendung von FeNO in Diagnostik und Management identifiziert. Diese wiesen jedoch weit zurückliegende Suchzeiträume auf.

Dies war der Anlass eine Update-Recherche nach systematischen Übersichtsarbeiten durchzuführen, in denen aktuellere Primärstudien betrachtet werden. (08.06.2017)

LoE

GRADE; Die Bewertung von Primärstudien erfolgte entsprechend der Empfehlungen zur „Bewe rtung 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) [8]

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	⇓⇓

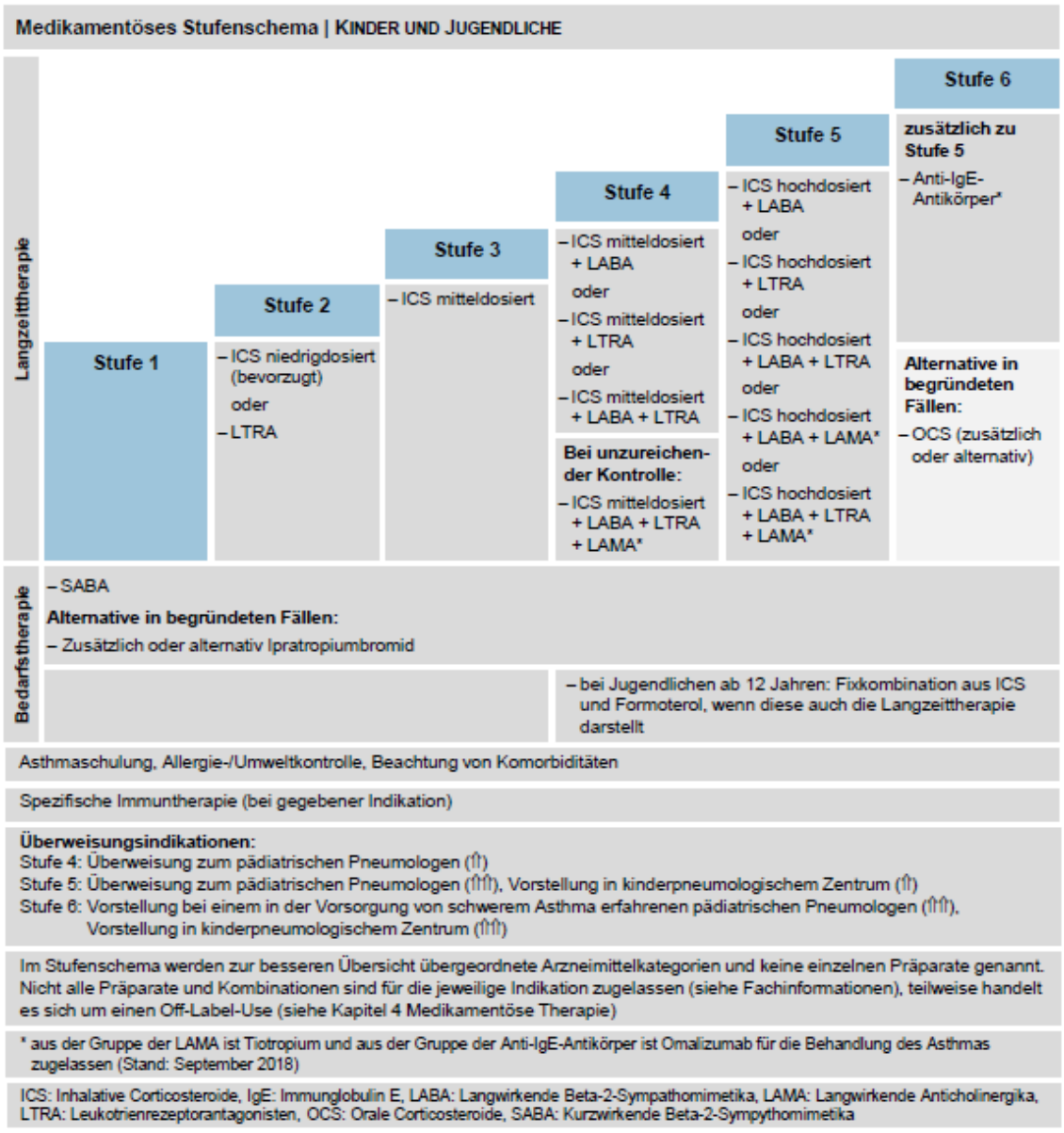
Sonstige methodische Hinweise

Bei der 3. Auflage der NVL Asthma handelt es sich um eine Teilpublikation. Die Themen Asthmaanfall, Asthma in der Schwangerschaft, Rehabilitation, Komplementäre Therapiemodalitäten und Berufsbedingtes Asthma werden zeitnah bearbeitet und ergänzt.

Diese Leitlinie wurde am 21.09.2018 durch die Träger des NVL-Programms verabschiedet und ist bis zur nächsten Überarbeitung bzw. spätestens bis Ende September 2023 gültig.

Empfehlungen

Abbildung 5: Medikamentöses Stufenschema | KINDER UND JUGENDLICHE



4.6 Langzeittherapie

Stufe 5 | KINDER UND JUGENDLICHE

Empfehlungen/Statements	Empfehlungs-grad
4-40 | KINDER UND JUGENDLICHE 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.	⇑⇑
4-41 | KINDER UND JUGENDLICHE Kinder und Jugendliche, deren Asthma eine Behandlung in Stufe 5 erfordert, sollen zu einem pädiatrischen Pneumologen überwiesen werden.	⇑⇑
4-42 | KINDER UND JUGENDLICHE Kinder und Jugendliche sollten vor dem Übergang in Stufe 5 zur erweiterten Diagnostik in einem kinderpneumologischen Zentrum vorgestellt werden.	⇑
4-43 | KINDER UND JUGENDLICHE Bei Kindern und Jugendlichen sollte vor der Behandlung in Stufe 5 die Indikation zu einer stationären Rehabilitation geprüft werden.	⇑
4-44 | KINDER UND JUGENDLICHE Bei Kindern und Jugendlichen soll in Stufe 5 eine Kombinationstherapie aus einem hochdosierten ICS mit einem LABA oder/und einem LTRA empfohlen werden.	⇑⇑

In der systematischen Recherche wurden zwei systematische Übersichtsarbeiten identifiziert, die den Übergang von Stufe 4 zu 5 untersuchen [75,93].

75. Chauhan BF, Ben SR, Ducharme FM. Addition of anti-leukotriene agents to inhaled corticosteroids in children with persis-tent asthma. Cochrane Database Syst Rev 2013; 10:CD009585. DOI: 10.1002/14651858.CD009585.pub2. http://www.ncbi.nlm.nih.gov/pubmed/24089325.

93. Ducharme FM, Ni CM, Greenstone I, et al. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose in-haled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010(4):CD005533. DOI: 10.1002/14651858.CD005533.pub2. http://www.ncbi.nlm.nih.gov/pubmed/20393943.

Indirekt kann die Subgruppenanalyse von Ducharme et al. [93] herangezogen werden. Ohne für die Altersgruppe zu differenzieren, wurde die Kombination aus einem mitteldosierten ICS plus LABA mit einer höher dosierten ICS-Monotherapie verglichen. Es ergab sich kein signifikanten Unterschied für das Risiko für Exazerbationen, die eine Behandlung mit OCS erforderten (RR 1,21 (95% KI 0,69; 2,12), n = 445, 3 RCTs). [93]

Die Kombinationstherapie aus ICS plus LTRA verglichen mit einer ICS-Monotherapie in höherer Dosis, zeigte keinen signifikanten Unterschied bezüglich der Exazerbationen, die OCS erfordern (RR 0,82 (95% KI 0,54; 1,25) 1 RCT, n = 182, Datenqualität niedrig) [75].

Die Therapieoptionen innerhalb der Stufe 5 wurden in zwei systematischen Übersichtsarbeiten verglichen, die in-direkt herangezogen werden können:

Für den geplanten Vergleich zwischen der Kombinationstherapie aus ICS hochdosiert plus LABA mit einer hoch-dosierten ICS-Monotherapie bei Kindern und Jugendlichen konnten Chauhan et al. keine Primärstudien identifizieren [74].

74. Chauhan BF, Chartrand C, Ni CM, et al. Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2015; 11:CD007949. DOI: 10.1002/14651858.CD007949.pub2. http://www.ncbi.nlm.nih.gov/pubmed/26594816.

Die Höhe der ICS-Dosis wurde im nächsten Vergleich dieses systematischen Reviews [74] nicht differenziert: Zwischen der Gruppe, die ICS plus LABA und der Gruppe, die nur ICS in der gleichen Dosis erhielten, unter-schied sich weder die Anzahl der Patienten, die eine Exazerbation mit der Notwendigkeit der Gabe von systemi-schen Corticosteroiden hatte (RR 0,95 (95% KI 0,70; 1,28) 12 RCTs n = 1 669; I^2 = 0) noch die Anzahl der Patien-ten mit Exazerbationen, die eine Hospitalisierung erforderte, signifikant (RR 1,74 (95% KI 0,90; 3,36) 6 RCTs, n = 1 292; I^2 = 0%). [74] Die Datenqualität wird jeweils aufgrund der Indirektheit auf niedrig abgewertet.

Zudem steht eine Subgruppenanalyse [53] zur Verfügung, die aufgrund der fehlenden Differenzierung des Alters indirekt genutzt werden kann. Der Vergleich der hochdosierten ICS-Monotherapie zu ICS hochdosiert plus LABA ergab keinen signifikanten Unterschied für den Endpunkt Exazerbationen, die eine Behandlung mit OCS erfordern (POR 0,94 (95% KI 0,58; 1,54); n = 1 366, 7 RCTs) [53].

53. Ducharme FM, Ni CM, Greenstone I, et al. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database Syst Rev 2010(5):CD005535. DOI: 10.1002/14651858.CD005535.pub2. http://www.ncbi.nlm.nih.gov/pubmed/20464739.

Zwei in der systematischen Recherche identifizierte Phase-III-Studien untersuchten die Wirksamkeit und Sicherheit von Tiotropium bei Patienten, die trotz einer Kombinationstherapie aus hochdosierten ICS plus mindestens einem weiteren Langzeittherapeutikum oder aus einem mitteldosierten ICS plus mindestens zwei weiteren Langzeittherapeutika ein symptomatisches Asthma aufwiesen [143,144].

143. Szefler SJ, Murphy K, Harper TI, et al. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma. J Allergy Clin Immunol. 2017; 140(5):1277–87. DOI: 10.1016/j.jaci.2017.01.014. http://www.ncbi.nlm.nih.gov/pubmed/28189771.

144. 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. DOI: 10.1183/13993003.01100-2016. http://www.ncbi.nlm.nih.gov/pubmed/27811070.

Ein RCT [144] untersuchte die Anwendung von Tiotropium bei 392 Jugendlichem im Verglichen zu Placebo bei einer Studiendauer von 12 Wochen. Die Asthmakontrolle unterschied sich nicht signifikant im Gruppenvergleich. Schwere Asthmaexazerbationen waren in der Gruppe, der mit 5 µg behandelten Patienten am häufigsten (2,5 µg: 0,79%; Placebo: 0,74%; 5 µg: 1,54%). Mindestens eine Episode einer Asthmaverschlechterung trat in der mit Placebo behandelten Gruppe am häufigsten auf (5 µg: 11,5%; 2,5 µg: 14,2%; Placebo: 18,5%). Asthmaexazerba-tionen und die Verschlechterung des Asthmas wurden als sekundärer Endpunkt und als unerwünschte Wirkung erfasst. [144] Das Risiko für Reporting Bias wird als hoch eingeschätzt.

Eine weitere Studie [143] untersuchte 635 Kinder im Alter zwischen sechs und elf Jahren, die zusätzlich über ei-nen Zeitraum von 12 Wochen mit Tiotropium in der Dosis von 2,5 µg oder 5 µg oder mit Placebo behandelt wur-den. Für die Endpunkte Veränderungen im ACQ-1A-Score, symptomfreie Tage und Notfallmedikation ergab sich jeweils kein signifikanter Unterschied zwischen der Placebogruppe und der jeweiligen Intervention in den unterschiedlichen Dosierungen. Die Häufigkeit von unerwünschten Wirkungen war in den Interventionsgruppen gerin-ger als in der Placebogruppe (5 µg: 43,1%; 2,5 µg: 43,4%, Placebo: 49,3%). Schwere unerwünschte Wirkungen traten in der Dosierung von 5 µg mit 3,1% am häufigsten auf und lagen in der Dosierung von 2,5 µg und unter Placebo jeweils bei 1,5%. [143] Limitierend ist das unklare Verzerrungspotentials bezüglich der Verblindung der Ergebnisevaluation.

Basierend auf diesen Ergebnissen und der eigenen klinischen Erfahrung erscheint es der Leitliniengruppe wichtig, darauf hinzuweisen, dass zunächst die individuell anwendbaren Therapiealternativen der Stufe 4 evaluiert werden, bevor eine Eskalation zur Stufe 5 erfolgt. Sicherheitsbedenken bezüglich einer höheren ICS-Dosierung stehen dabei im Vordergrund (siehe Empfehlung 4-25). Kinderpneumologische Zentren ermöglichen eine erwei-terte Diagnostik für den Fall, dass die Diagnose verifiziert werden müsste. In einer stationären Rehabilitations-maßnahme kann die Therapieadhärenz der Kinder im Sinne einer kontrollierten Therapie beobachtet und das Verhalten geschult werden. In diesen Maßnahmen sehen die Leitlinienautoren die Chance, eine unnötige Thera-pieeskalation zu vermeiden.

Empfehlungen/Statements	Empfehlungs-grad
4-45 | KINDER UND JUGENDLICHE Bevor bei Kindern und Jugendlichen die Eskalation der Therapie zur Stufe 6 er-folgt, soll die Wirksamkeit der verschiedenen möglichen Therapieoptionen der Stufe 5 evaluiert werden.	⇑⇑
4-46 | KINDER UND JUGENDLICHE Kinder und Jugendliche sollen vor dem Übergang in Stufe 6 zur Durchführung der Differentialdiagnostik und Untersuchung auf Komorbiditäten in einem kinder-pneumologischen Zentrum mit der Möglichkeit zur invasiven Diagnostik vorgestellt werden.	⇑⇑
4-47 | KINDER UND JUGENDLICHE Bei Kindern und Jugendlichen soll vor der Behandlung in Stufe 6 die Indikation zu einer stationären Rehabilitation geprüft werden.	⇑⇑

Vor dem Übergang zu der Behandlung in Stufe 6 empfiehlt die Leitliniengruppe die bereits in Stufe 5 genannten Maßnahmen, jedoch mit einem stärkeren Empfehlungsgrad. Vor der Behandlung mit monoklonalen Antikörpern oder OCS kommt dem Ausschluss von Differentialdiagnosen und relevanten Komorbiditäten eine höhere Bedeutung zu. Gleiches gilt für die Überprüfung der Therapieadhärenz im Rahmen einer stationären Rehabilitation.

Empfehlungen/Statements	Empfehlungs-grad
4-48 | KINDER UND JUGENDLICHE 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: • schweres IgE-vermitteltes allergisches Asthma und • positiver Hauttest oder in-vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen und • IgE-Serumkonzentration unter Berücksichtigung des Körpergewichts im therapierbaren Bereich und • erfolgte Eliminierung vermeidbarer Allergenexpositionen.	⇑⇑
4-49 | KINDER UND JUGENDLICHE Die Indikationsstellung und Initiierung einer Behandlung mit monoklonalen Antikörpern soll bei Kindern und Jugendlichen durch in der Versorgung mit schwerem Asthma erfahrene pädiatrische Pneumologen erfolgen.	⇑⇑

Die Evidenzgrundlage für die Empfehlung bilden die in der systematischen Recherche identifizierten systematischen Übersichtsarbeiten und HTA-Berichte [115,116,118–121]. Deren Inhalte sind im Hintergrundtext der Empfehlung 4-33 im Kapitel 4.6.6 Stufe 5 | Erwachsene dargestellt. Dort sind auch die Sicherheitsaspekte aufgeführt.

115. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014; 1:CD003559. DOI: 10.1002/14651858.CD003559.pub4. http://www.ncbi.nlm.nih.gov/pubmed/24414989.

116. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: A systematic review and economic evaluation. Health Technol Assess 2013; 17(52):1–342. DOI: 10.3310/hta17520. http://www.ncbi.nlm.nih.gov/pubmed/24267198.

117. Rodrigo GJ, Neffen H. Systematic review on the use of omalizumab for the treatment of asthmatic children and adolescents. Pediatr Allergy Immunol. 2015; 26(6):551–6. DOI: 10.1111/pai.12405. http://www.ncbi.nlm.nih.gov/pubmed/25963882.

118. Lai T, Wang S, Xu Z, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: A systematic review and meta-analysis. Sci Rep 2015; 5:8191. DOI: 10.1038/srep08191. http://www.ncbi.nlm.nih.gov/pubmed/25645133.

119. European Medicines Agency (EMA). Xolair Omalizumab. Product information. 2016 [cited: 2017-07-13]. http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf.

120.Warnung vor Anaphylaxie durch Asthmamittel Omalizumab (Xolair). Arznei-Telegramm 2007; 38(7):71.

121. Kardiovaskuläre Nebenwirkungen unter Omalizumab (Xolair). Arznei-Telegramm 2009; 40(8):76.

Zusätzlich zu der systematischen Übersichtsarbeit von Normansell et al., die Kinder und Erwachsene gemeinsam betrachtet [115], werden die Ergebnisse der systematischen Übersichtsarbeit von Rodrigo et al. zitiert, die Kinder und Jugendliche mit moderatem bis schwerem persistierendem allergischem Asthma untersucht [117].

Im Vergleich zu Placebo war unter Omalizumab sowohl die Anzahl der Patienten mit mindestens einer Exazerbation (26,7% vs. 40,6%, RR 0,69 (95% KI 0,59; 0,80); I^2 = 0%, 3 RCTs, n = 1 329) als auch die Anzahl der Patien-ten mit Exazerbationen, die eine Hospitalisierung erforderlich machten (2,0% vs. 4,7%; RR 0,35 (95% KI 0,2; 0,64); I^2 = 29%, 3 RCTs, n = 1 381), geringer [117]. Während schwere unerwünschte Wirkungen bei Patienten seltener waren, die mit Omalizumab behandelt wurden (5,2% vs. 5,6%), traten jegliche unerwünschte Wirkungen in der Placebogruppe etwas seltener auf (76,3% vs. 74,2%). Beide Ergebnisse waren statistisch nicht signifikant. [117] Als limitierend wird bei diesen Ergebnissen angesehen, dass aus dem systematischen Review nicht hervorgeht, ob Exazerbationen als Effektivitätsendpunkt zusätzlich mit in die unerwünschten Wirkungen (als Sicherheitsendpunkt) einfließen und damit eine doppelte Darstellung erfolgt.

In Zusammenschau der identifizierten Evidenz und der wenigen Therapiealternativen empfiehlt die Leitliniengruppe einen Therapieversuch mit Omalizumab bei Kindern ab einem Alter von sechs Jahren, wenn die in Empfehlung 4-48 genannten eng umschriebenen Kriterien erfüllt sind. Entscheidend ist, vor Initiierung der Therapie alle vermeidbaren Allergene zu eliminieren (siehe Kapitel 6.7 Verminderung der Allergenexposition) und – wenn bei Jugendlichen notwendig – die Möglichkeiten der Tabakentwöhnung vor Therapiebeginn auszuschöpfen (siehe Kapitel 6.4 Tabakentwöhnung).

Die Details der Anwendung monoklonaler Antikörper sind in den Empfehlungen 4-36 und 4-37 und dem dazugehörigen Hintergrundtext für Erwachsens beschrieben und gelten analog auch für Kinder und Jugendliche (siehe Kapitel 4.6.6 Stufe 5 | ERWACHSENE).

In Anbetracht der Schwere der Erkrankung, die eine Behandlung mit monoklonalen Anktikörpern notwendig macht, erachtet es die Leitliniengruppe als wichtig, dass Patienten einem pädiatrischen Pneumologen vorgestellt werden. Ziel der Beurteilung durch den pädiatrischen Pneumologen sind die Indikationsstellung, die Feststellung der Zeitpunkte einer Therapieintensivierung und -reduktion sowie das Erkennen von Risikosignalen, die sich während der Behandlung ergeben können. Da die Evidenzlage für all diese Parameter zum aktuellen Zeitpunkt noch nicht aussagekräftig genug ist (siehe Hintergrundtext zur Empfehlung 4-33 und 4-48), benötigt die Behandlung dieser Patienten eine besondere klinische Expertise.

Empfehlungen/Statements	Empfehlungs-grad
4-50 | KINDER UND JUGENDLICHE 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.

Global Initiative for Asthma (GINA), 2018 [12].

Global strategy for asthma management and prevention; updated 2018

Leitlinienorganisation/Fragestellung

GINA – Global Initiative for Asthma

Methodik

Grundlage der Leitlinie

- LL-Committee: members are recognized leaders in asthma research and clinical practice with the scientific expertise
- Jährliches Update der LL
- Vor jedem Treffen des LL-Committee: PubMed search is performed for the previous year using filters established by the Committee
- After initial screening by the Program Director and Chair of the Science Committee, each publication identified by the above search is reviewed for relevance and quality by members of the Science Committee. Each publication is allocated to at least two Committee members, but all members receive a copy of all of the abstracts and have the opportunity to provide comments
- During Committee meetings, each publication that was assessed by at least one member to potentially impact on the GINA report is discussed. Decisions to modify the report or its references are made by consensus by the full Committee, or, if necessary, by an open vote of the full Committee

Recherche/Suchzeitraum:

LITERATURE REVIEWED FOR GINA 2018 UPDATE

The GINA report has been updated in 2018 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 424 publications, of which 324 were screened out for relevance and/or quality. The remaining 100 publications were reviewed by at least two members of the Science Committee, and 61 were subsequently discussed at a face-to-face meeting (35 'clinical trials' and 26 meta-analyses). A list of key changes in GINA 2018 can be found on p.11, and a tracked changes copy of the 2017 report is archived on the GINA website.

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 or meta-analyses 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.

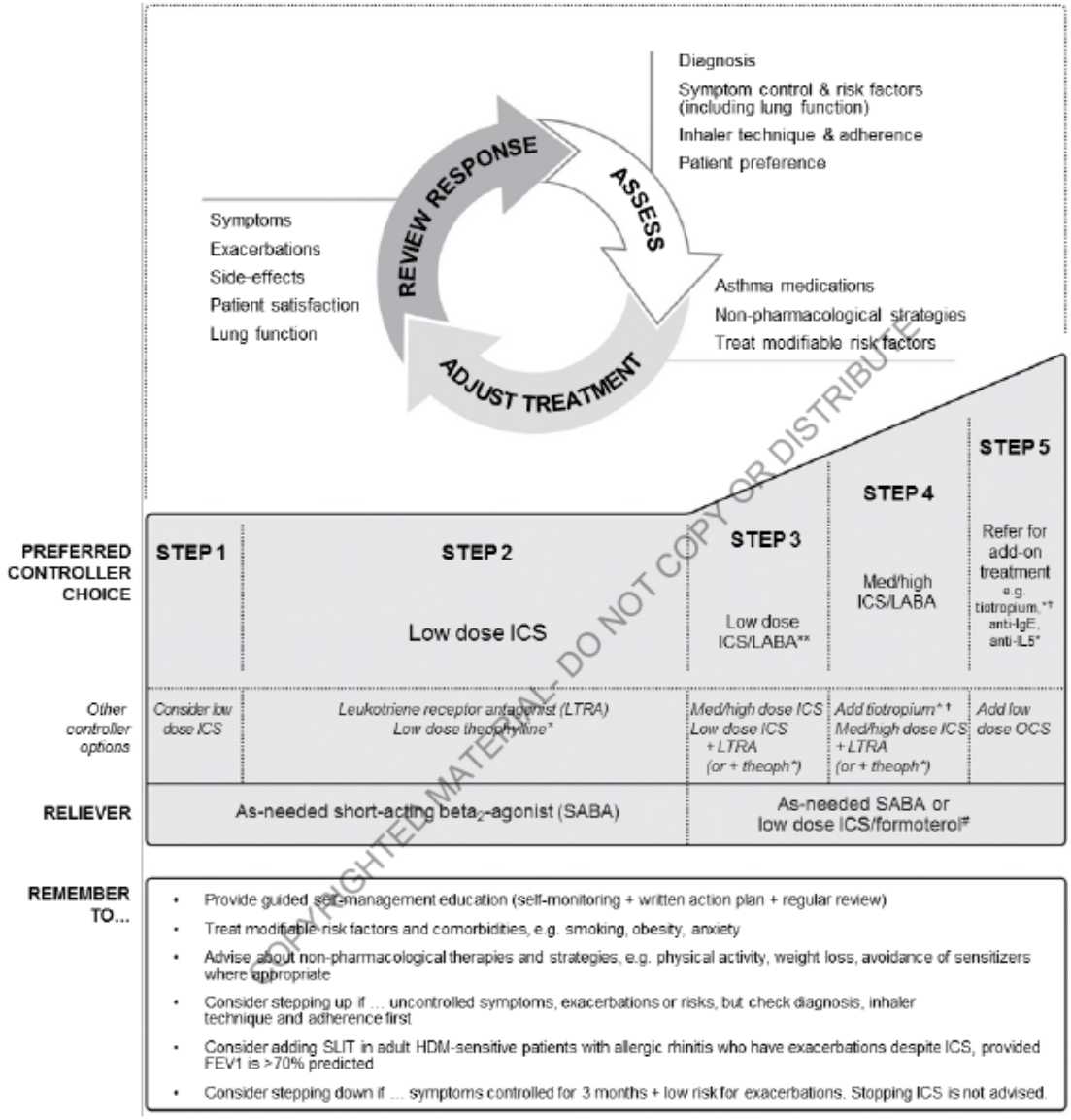
- Levels of evidence are assigned to management recommendations where appropriate.

GoR

Empfehlungen sind mit Primärquellen verknüpft. keine Angabe des GoR.

Diagnose-, Kontroll- und Therapieschema

Box 3-5. Stepwise approach to control symptoms and minimize future risk



ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids; SLIT: sublingual immunotherapy. See Box 3-6 (p.45) for low, medium and high doses of ICS for adults, adolescents and children 6–11 years. See Chapter 3 Part D (p.67) for management of exercise-induced bronchoconstriction.

* Not for children <12 years.
** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.

Medikationen

KEY POINTS

- At present, Step 1 treatment is with as-needed short-acting beta$_2$-agonist (SABA) alone. However, chronic airway inflammation is found even in patients with infrequent or recent-onset asthma symptoms, and there is a striking lack of studies of inhaled corticosteroids (ICS) in such populations.
- Treatment with regular daily low dose ICS is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization and death
- For patients with persistent symptoms and/or exacerbations despite low dose ICS, consider step up but first check for common problems such as inhaler technique, adherence, persistent allergen exposure and comorbidities
  - For adults and adolescents, the preferred step-up treatment is combination ICS/long-acting beta$_2$-agonist (LABA).
  - For adults and adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclometasone or budesonide) as both maintenance and reliever, compared with maintenance controller treatment plus as-needed SABA.
  - For children 6–11 years, increasing the ICS dose is preferred over combination ICS/LABA.
- Consider step down once good asthma control has been achieved and maintained for about 3 months, to find the patient's lowest treatment that controls both symptoms and exacerbations
  - Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit
  - Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.
- For all patients with asthma:
  - Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect
  - Encourage adherence with controller medication, even when symptoms are infrequent
  - Provide training in asthma self-management (self-monitoring of symptoms and/or PEF, written asthma action plan and regular medical review) to control symptoms and minimize the risk of exacerbations and need for health care utilization.
- For patients with one or more risk factors for exacerbations:
  - Prescribe regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients
  - Identify and address modifiable risk factors, (e.g. smoking, low lung function)
  - Consider non-pharmacological strategies and interventions to assist with symptom control and risk reduction, (e.g. smoking cessation advice, breathing exercises, some avoidance strategies)

ASTHMA MEDICATIONS

Categories of asthma medications

When compared with medications used for other chronic diseases, most of the medications used for treatment of asthma have very favorable therapeutic ratios (Appendix Chapter 5). The pharmacological options for long-term treatment of asthma fall into the following three main categories.

- *Controller medications*: these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and decline in lung function.
- *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.

- *Add-on therapies for patients with severe asthma* (Box 3-14, p.72): these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications (usually a high dose ICS and a LABA) and treatment of modifiable risk factors (see Box 3-8, p.51).

STEP 4: Two or more controllers plus as-needed reliever medication

Preferred option (adults/adolescents): combination low dose ICS/formoterol as maintenance and reliever treatment, OR combination medium dose ICS/LABA plus as-needed SABA

Preferred option (children 6–11 years): refer for expert assessment and advice

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, p22).

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 ICS[186] (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 if necessary. 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/LABA[150] (Evidence B); combination ICS/LABA medications are as for Step 3. For patients prescribed maintenance treatment and as-needed SABA, adding LABA to ICS in a combination inhaler provides additional improvements in lung function with a reduced risk of exacerbations compared with the same dose of ICS[187-189] (Evidence A) but only a small reduction in reliever use.[188,189]

For children 6–11 years, if asthma is not well controlled on moderate dose ICS (see Box 3-6, p.45), the recommendation is to refer the child for expert assessment and advice.

Other options

Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy for adult or adolescent patients with a history of exacerbations; it modestly improves lung function (Evidence A) and modestly increases time to severe exacerbation.[199] Tiotropium is not indicated in children <12 years. For adult patients with allergic rhinitis and sensitization to house dust mite, with exacerbations despite low-high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV_1 is >70% predicted.[190,191] (see p.52).

Combination high-dose ICS/LABA may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit[115,123,195,200] (Evidence A), and there is an increased risk of side-effects, including adrenal suppression.[201] 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 theophylline,[169,177,202] Evidence B). Theophylline should not be used in children. For medium or high dose budesonide, efficacy may be improved with dosing four times daily[203,204] (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 LTRA[202,205-208] (Evidence A), or low dose sustained-release theophylline[177] (Evidence B).

***STEP 5*: Higher level care and/or add-on treatment**

Preferred option: referral for specialist investigation and consideration of add-on treatment

Patients 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 management of severe asthma[131] (Evidence D)

Treatment options that may be considered at Step 5 (if not already tried) are described in Box 3-14 (p.72). They include:

- Add-on tiotropium (long-acting muscarinic antagonist) in patients aged ≥12 years whose asthma is not well-controlled 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).[199] There is no evidence for other LAMA preparations.[199]
- 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 treatment[209,210] (Evidence A).
- Add-on anti-interleukin-5 treatment (subcutaneous mepolizumab for patients aged ≥12 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 treatment (Evidence A).[211-214]
- Sputum-guided treatment: for patients 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 ICS[152] (Evidence A).
- Add-on treatment with bronchial thermoplasty: may be considered for some adult patients with severe asthma [131] (Evidence B). Evidence is limited and in selected patients (see p.52 and Appendix Chapter 6). 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 asthma[131] (Evidence D); but are often associated with substantial side effects[215,216] (Evidence B). 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. Patients should be counseled about potential side-effects (Evidence D).[216] 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).[217]

NICE, 2017 [17].

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.

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 und Evidenz

Empfehlung

Treatment in patients not on regular preventers

Review question: In children, young people and adults with asthma who have not been treated previously, is it more clinically and cost-effective to start treatment with a reliever alone (SABA) or with a reliever (SABA) and a preventer (such as ICS)?

1. Offer a short-acting beta2 agonist (SABA) as reliever therapy to adults (aged 17 and over) with newly diagnosed asthma.
2. For adults (aged 17 and over) with asthma who have infrequent, short-lived wheeze and normal lung function, consider treatment with SABA reliever therapy alone.
3. Offer a SABA as reliever therapy to children and young people (aged 5 to 16) with newly diagnosed asthma.
4. For children and young people (aged 5 to 16) with asthma who have infrequent, short-lived wheeze and normal lung function, consider treatment with SABA reliever therapy alone.
5. Offer a SABA as reliever therapy to children under 5 with suspected asthma. This should be used for symptom relief alongside all maintenance therapy.

Quality of evidence: No clinical evidence was identified.

Other considerations:

The committee noted that there may be additional benefit from starting ICS early in the treatment pathway if it prevents long-term harmful effects of untreated inflammation. These benefits would be difficult to capture in any conventional RCTs.

The population of interest for this recommendation was people with newly

diagnosed asthma or people with asthma who are treatment naïve. People with asthma who had not received any treatment for the previous month were also included, as the committee acknowledged that people may have received asthma medication sporadically in the past or during a diagnosis of asthma. The committee did not consider studies in people with asthma who are already controlled on SABA treatment to be relevant for this review. This population would be pre-selecting people who already have good asthma control on SABA alone, and therefore may not gain much further benefit from receiving additional preventer treatment.

The committee recognised that there is ongoing research into the treatment of different asthma phenotypes, and that certain groups (such as people with high FeNO) may be shown to benefit from starting on both SABA and ICS rather than SABA alone. The committee felt that this was an area where a research recommendation is appropriate.

Empfehlung 2

Choice of first-line preventer in patients with poor asthma control

Review question: What is the most clinically and cost effective first-line preventer drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are uncontrolled on SABA alone (preventer-naïve or no preventer for at least 1 month)?

6. Take into account the possible reasons for uncontrolled asthma before

starting or adjusting medicines for asthma in adults, young people and

children. These may include:

- alternative diagnoses
- lack of adherence
- suboptimal inhaler technique
- smoking (active or passive)
- occupational exposures
- psychosocial factors
- seasonal or environmental factors.

7. After starting or adjusting medicines for asthma, review the response to treatment in 4 to 8 weeks (see section 1.14 of the NICE guideline on asthma: diagnosis, monitoring and chronic asthma management).

8. Offer a low dose of an ICS as the first-line maintenance therapy to adults (aged 17 and over) with:

- symptoms at presentation that clearly indicate the need for maintenance therapy (for example, asthma-related symptoms 3

times a week or more, or causing waking at night) or -asthma that is uncontrolled with a SABA alone.

9. Offer a paediatric low dose of an ICS as the first-line maintenance therapy to children and young people (aged 5 to 16) with:

- symptoms at presentation that clearly indicate the need for maintenance therapy (for example, asthma-related symptoms 3 times a week or more, or causing waking at night) or
- asthma that is uncontrolled with a SABA alone.

10. Consider an 8-week trial of a paediatric moderate dose of an ICS in children under 5 with:

- symptoms at presentation that clearly indicate the need for maintenance therapy (for example, asthma-related symptoms 3 times a week or more, or causing waking at night) or
- suspected asthma that is uncontrolled with a SABA alone.

11. After 8 weeks, stop ICS treatment and continue to monitor the child's symptoms:

- if symptoms did not resolve during the trial period, review whether an alternative diagnosis is likely
- if symptoms resolved but then reoccurred within 4 weeks of stopping ICS treatment, restart the ICS at a paediatric low dose as first-line maintenance therapy
- if symptoms resolved but then reoccurred beyond 4 weeks after stopping ICS treatment, repeat the 8-week trial of a paediatric moderate dose of ICS.

12. Adjust the dose of ICS maintenance therapy over time, aiming for the lowest dose required for effective asthma control.

13. Ensure that a person with asthma can use their inhaler device:

- at any asthma review, either routine or unscheduled
- whenever a new type of device is prescribed.

Quality of evidence:

The evidence for the majority of outcomes at each age group were Low or Very Low quality by GRADE criteria, due to risk of bias and imprecision. There were a number of exceptions with Moderate quality evidence in the 16 years and over group reported for quality of life, reliever medication use and lung function outcomes. For children and young people 5–16 years old the outcomes AQLQ, reliever medication use (puffs/day) and FEV1 (% of predicted) also produce a set of Moderate quality evidence. Reliever medication use (daytime use) in the comparison between low dose ICS and placebo in children aged 1–5 produced High quality evidence. High quality evidence was again reported in the <1 strata in both the comparisons low dose ICS versus placebo, and moderate dose ICS versus low dose ICS for the outcome reliever medication use (number of days). However, only one study contributed to the evidence for each outcome found to produce Moderate or High quality evidence.

The quality and breadth of the evidence in the under 5 stratum was low and limited. The recommendation in this population is consensus and experience driven.

Empfehlung 3

Escalating pharmacological treatment in patients poorly controlled on low dose IC

Review question: In people with a clinician diagnosis of asthma who are uncontrolled on low dose ICS, what is the most clinically and cost-effective second-line preventer?

14. 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.

15. 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.

16. 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 LTRA7 in addition to the ICS and review the response to treatment in 4 to 8 weeks.

17. 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 LABA8 in combination with the ICS.

18. If suspected asthma is uncontrolled in children under 5 on a paediatric low dose of ICS as maintenance therapy, consider an LTRA9 in addition to the ICS.

19. If suspected asthma is uncontrolled in children under 5 on a paediatric low dose of ICS and an LTRA as maintenance therapy, stop the LTRA and refer the child to a healthcare professional with expertise in asthma for further investigation and management.

Quality of the clinical evidence:

The quality of the evidence ranged from High to Very Low, but the majority was either Low or Very Low quality. In most cases this was due to either risk of bias or imprecision, or a combination of the two. The majority of the evidence compared possible additional preventers (or higher doses of ICS) with low dose ICS/placebo.

There was limited evidence directly comparing additional preventers.

There was little evidence in the 5–16 population. Much of the evidence from this population was derived from one study with a low number of participants (around 50 with fewer available for certain outcomes).

There was no evidence in the under 5 age group

Empfehlung 4

Review question: What is the clinical and cost effectiveness of using ICS + LABA as preventer and reliever therapy compared to using ICS + LABA as preventer and a SABA as reliever therapy?

20. 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.

21. 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).

22. 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 regimen10 with a paediatric low maintenance ICS dose. Ensure that the child or young person is able to understand and comply with the MART regimen.

23. If asthma is uncontrolled in children and young people (aged 5 to 16) on a MART regimen11 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).

Quality of the clinical evidence:

The quality of the evidence ranged from High to Very Low quality. The majority of the evidence was either Moderate or High quality.

There was limited evidence regarding the total steroid dose, with only one study, one of the smaller studies, reporting this particular outcome.

The committee noted that 2 of the studies163 ,185 compared MART versus ICS + LABA as maintenance and SABA as reliever where the doses were in the same category (i.e. low dose ICS + LABA) but there were differences in precise dosing or within class drug choice. The conclusions of these studies were similar to the overall body of evidence.

Empfehlung 5

Review question: What is the most clinically and cost-effective drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are currently taking optimal preventer therapy beyond ICS low dose when this fails to provide adequate control?

24. 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.

25. If asthma is uncontrolled in children and young people (aged 5 to 16) on a paediatric moderate maintenance ICS dose with LABA (either as MART12 or a fixed-dose regimen), consider seeking advice from a healthcare professional with expertise in asthma and consider either:

- increasing the ICS dose to a 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).

Quality of the clinical evidence:

The quality of the evidence for this review ranged from Very Low to High quality. The majority of the evidence was either Low or Moderate quality. Most of the studies compared adding a new agent or increasing ICS dose against continuing on previous treatment with or without a placebo. The majority of the evidence was in people uncontrolled on ICS moderate dose. None of the evidence addressed the addition of treatment in people uncontrolled on ICS and LTRA.

Studies were found in which the baseline population were on treatment not recommended by the committee in this guideline. This included studies in people who were using a high or moderate dose ICS (without first adding in a LABA or LTRA). The committee included this population as it represents a group who are uncontrolled despite preventer treatment beyond the first line of low dose ICS, and because there will be patients currently on this treatment.

SIGN, 2016 [22].

British guideline on the management of asthma

Leitlinienorganisation/Fragestellung

SIGN = Scottish Intercollegiate Guidelines Network in Kooperation mit British Thoracic Society

Methodik

Grundlage der Leitlinie

This guideline was issued in 2014 and sections of the guideline will be updated on a biennial basis. The evidence base for this guideline was synthesised in accordance with SIGN methodology. 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.

Recherche/Suchzeitraum:

- 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 2016. All updates were made available on both the BTS (www.brit-thoracic.org.uk) and SIGN (www.sign.ac.uk) websites. Any updates to the guideline in the period between scheduled updates will be noted on the SIGN and BTS websites.
- The 2016 version includes a complete revision of the section on diagnosis, a major update to the section on pharmacological management of asthma, and updates to the sections on supported self-management, non-pharmacological management of asthma, acute asthma, difficult asthma, occupational asthma, and organisation and delivery of care.

LoE/GoR:

KEY TO EVIDENCE STATEMENTS AND GRADES OF 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 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 evidence on which the recommendation 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* 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* 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* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2^{+}
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

Empfehlungen

Empfehlung 1 (Empfehlungsgrad)

MAINTENANCE AND RELIEVER THERAPY

A	**In adults over the age of 18, combined maintenance and reliever therapy can be considered for patients who have a history of asthma attacks on medium dose ICS or ICS/LABA**

ADDITIONAL ADD-ON THERAPIES

If there is no improvement when a LABA is added, stop the LABA and try:

- an increased dose of ICS
- an LTRA
- a LAMA (LAMA are not licensed for this indication)

Increased dose of ICS

If there is a response to LABA, but control remains suboptimal, continue with the LABA and increase the dose of ICS to medium (adults) or low dose (children 5–12 years).[456] | >12 years

If, as occasionally happens, there is no response to inhaled long-acting β_2 agonist, stop the LABA and increase the dose of ICS to medium (adults) or low dose (children) if not already on this dose.[456] | 4

D D **If asthma control remains suboptimal after the addition of an inhaled long-acting β_2 agonist then the dose of inhaled corticosteroids should be increased 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.**

An LTRA

Evidence to support the use of leukotriene receptor antagonists (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.[435,464,465] | >12 years 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.[453] | 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.[466] | 1+

A LAMA

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, although it was not possible to draw conclusions about the effect of tiotropium in those taking different doses of ICS plus LABA.[467] | >12 years 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.[468] 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.[469 470] | >12 years 1++ 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 say whether adding tiotropium to ICS ('off-label' use) is safer or more effective than increasing the dose of ICS.[471] | 1+

OTHER APPROACHES

Theophyllines may improve lung function and symptoms, but side effects occur more commonly.[444]	>12 years 1+
Slow-release β_2 agonist tablets may also improve lung function and symptoms, but side effects occur more commonly.[443]	1++
Addition of short-acting anticholinergics is generally of no value.[445,472] Addition of nedocromil is of marginal benefit.[438,446]	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, theophyllines, slow-release β_2 agonist tablets (in adults only)

HIGH-DOSE THERAPIES

In a small proportion of patients asthma is not adequately controlled on a combination of short-acting β_2 agonist as required, medium-dose ICS, and an additional drug, usually a LABA. There are very few clinical trials in this specific patient group to guide management.

In adults, the addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit although results are currently inconclusive *(see section 7.4.3)*. Further research is needed to confirm possible benefits or harms of tiotropium in combination with different doses of ICS/LABA.[467] The following recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone *(see section 7.4)*.

>12 years
1++

D D

If control remains inadequate on medium dose (adults) **or low dose** (children) **of an inhaled corticosteroid plus a long-acting β_2 agonist, the following interventions can be considered:**

- **increase the inhaled corticosteroids to high dose** (adults) **or medium dose** (children 5-12 years)* ***or***
- **add a leukotriene receptor antagonist** ***or***
- **add a theophylline** ***or***
- **add slow-release β_2 agonist tablets, although caution needs to be used in patients already on long-acting β_2 agonists,** ***or***
- **add tiotropium** (adults).

There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines and β_2 agonist tablets.

✓ 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).

✓ Before proceeding to continuous or frequent use of oral steroid therapy, refer patients with inadequately controlled asthma, especially children, to specialist care.

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

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Bermejo I et al., 2018 [1].

Mepolizumab for Treating Severe Eosinophilic Asthma: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

NICE issued a final scope to appraise the clinical and cost effectiveness of mepolizumab, within its licensed indication, for the treatment of severe eosinophilic asthma. The main comparator was SoC, which, for patients with severe asthma, includes the use of high-dose ICS and other controllers, such as long-acting b-agonists, leukotriene antagonists or theophyllines, and finally daily oral corticosteroids (OCS) at the lowest possible dose to achieve adequate control. For people with severe persistent allergic IgE-mediated eosinophilic asthma, the intervention was also compared with omalizumab (brand name Xolair ®), a drug recommended by NICE for patients with severe IgE-mediated asthma who ‘‘need continuous or frequent treatment with oral corticosteroids.’’ The marketing authorisation of omalizumab states that 16 weeks after the start of treatment, physicians should assess the effectiveness of the treatment and should continue the treatment only in patients whose asthma has markedly improved. A confidential PAS is also in place for omalizumab.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2018) am 24.09.2018

#	Suchfrage
1	[mh Asthma]
2	asthma*:ti (Word variations have been searched)
3	#1 or #2
4	#3 with Cochrane Library publication date from Sep 2013 to Sep 2018, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 24.09.2018

#	Suchfrage
1	„asthma/therapy"[mh]
2	asthma*[ti]
3	(#2) AND (treatment*[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 treating[tiab] OR treated[tiab] OR management[tiab] OR drug*[tiab])
4	#1 OR #3
5	(#4) AND ((Meta-Analysis[ptyp] OR systematic[sb] 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]))))))
6	(#5) AND ("2013/09/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[ta]
8	(#7) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 24.09.2018

#	Suchfrage
1	asthma[majr]
2	asthma*[ti]
3	#1 OR #2
4	(#3) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
5	(#5) AND ("2013/09/01"[PDAT] : "3000"[PDAT])

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Anhang

Abbildung 1:Abbildungsbeschriftung