Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2014-B-121 Mepolizumab

Stand: Mai 2015

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

Mepolizumab
zur Behandlung des schweren unkontrollierten eosinophilen Asthma

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht: II* Zugelassene Arzneimittel im Anwendungsgebiet:
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Therapiehinweise zu Omalizumab
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	Geplantes Anwendungsgebiet (gekürzt): Mepolizumab ist indiziert als Zusatztherapie bei erwachsenen Patienten mit schwerem eosinophilen Asthma.
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. Hinweis: Eine längerfristige Behandlung soll symptomorientiert und nur in Verbindungmit einer entzündungshemmenden Dauertherapie erfolgen.
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: - Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen.
Beta-2-Sympathomimetika (inhalativ; langwirkend) (LABA)	
Salmeterol R03AC12 Serevent®	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 Therapiemit entzündungshemmenden Arzneimitteln (inhalative und/ oder orale Kortikoide) sichergestellt werden, da Serevent kein Ersatz hierfür ist. Diese Behandlung mit Kortikoiden ist regelmäßig weiterzuführen. <u>Warnhinweis:</u>

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Serevent Dosier-Aerosol und Serevent Diskus sollen nicht für die Akutbehandlung eines Asthmaanfalls eingesetzt werden.
Formoterol R03AC13 Formoterol CT®	– Symptomatische Langzeitbehandlung des chronischen masigen bis schweren Asthma bronchiale in Kombination mit einer entzündungshemmenden Dauertherapie (z. B. Kortikosteroide). 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.
Beta-2-Sympathomimetika (oral; kurz-, langwirkend)	
Terbutalin R03AC03 Terbutalin-ratiopharm®	Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z.B. Asthma bronchiale, chronische Bronchitis und Blählunge (Lungenemphysem). Hinweis: Terbutalin-ratiopharm ist für Patienten, die nicht symptomorientiert mit inhalativen ®2-Sympathomimetika behandelt werden können, geeignet. Eine Behandlung mit Terbutalinratiopharm sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie mit Kortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen.
Salbutamol R03CC02 Salbubronch®	Symptomatische Behandlung von Erkrankungen mit rückbildungsfähiger (reversibler) Verengung (Obstruktion) der Atemwege, wie z.B. Asthma bronchiale oder chronisch obstruktive Lungenkrankheit (COPD) mit reversibler Komponente.
Bambuterol R03CC12 Bambec®	Verhütung und Behandlung von Atemwegserkrankungen, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen) einhergehen. Hinweise zu den Anwendungsgebieten - Das Arzneimittel 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 mit Glukokortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen.
Clenbuterol R03CC63 MUCOSPAS Saft ®	Akute und chronische Atemwegserkrankungen, die mit spastischen Verengungen, veränderter Sekretbildung und gestörtem Sekrettransport einhergehen, insbesondere spastische Bronchitiden, Emphysembronchitiden und Asthma bronchiale. Hinweise zu den Anwendungsgebieten Das Arzneimittel ist nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Sofern eine Dauerbehandlung von Asthma bronchiale erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen.

II. Zugelassene Arzneimittel im Anwendungsgebiet

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. Hinweise zu den Anwendungsgebieten Das Arzneimittel ist nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Sofern eine Dauerbehandlung von Asthma bronchiale erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen.
Anticholinergika (inhalativ)	
Ipratropiumbromid R03BB01 Atrovent®	leichtem bis mittelschwerem Asthma bronchiale im Erwachsenen- und Kindesalter, wenn β2-Mimetika nicht indiziert sind oder als Ergänzung zu β2-Mimetika im akuten Asthmaanfall.
Tiotropiumbromid R03BB04 *Sp*iriva® Respimat®	Spiriva Respimat ist indiziert als ein zusätzlicher dauerhaft einzusetzender Bronchodilatator bei erwachsenen Asthma-Patienten, die als Dauertherapie eine Kombination aus inhalativen Kortikosteroiden (≥ 800 µg Budesonid/Tag oder Äquivalent) und langwirksamen Beta2-Agonisten erhalten, und die im Vorjahr mindestens eine schwere Exazerbation erfahren haben.
Inhalative Corticosteroide (ICS)	
Beclometason R03BA01 Junik®	zur Behandlung von Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei: Asthma bronchiale, chronisch obstruktiver Bronchitis
Budesonid R03BA02 BUDECORT®	Zur Behandlung persistierender Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei: - Asthma bronchiale - Chronisch obstruktiver Bronchitis.
Ciclesonid R03BA08 ALVESCO®	Zur Behandlung von persistierendem Asthma bei Erwachsenen und Jugendlichen (ab 12 Jahren).
Fluticason R03BA05 FLUTIDE®	Dauerbehandlung eines persistierenden Asthma bronchiale aller Schweregrade. Hinweis:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Fluticason-17-propionat ist nicht für die Akutbehandlung eines Asthmaanfalles geeignet.
Mometason R03BA07 ASMANEX®	Bei Erwachsenen und Jugendlichen ab 12 Jahren zur regelmäßigen Behandlung, um anhaltendes Asthma bronchiale zu kontrollieren.
Corticosteroide (systemisch, oral)	
Prednisolon, Prednisolon ratiopharm®	Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren.
Prednison, Prednison ratiopharm®	Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren.
Weitere	
Theophyllin (systemisch) R03DA04 z.B. Theophyllin retard-ratiopharm®	Bronchospasmolytikum/Antiasthmatikum Behandlung und Verhütung von Atemnotzuständen aufgrund von Verengung der Atemwege (Bronchokonstriktion) bei Patienten mit persistierendemAsthmabronchiale 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.
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). Xolair® wird als Zusatztherapie zur verbesserten Asthmakontrolle bei Patienten mit schwerem persistierendem allergischem Asthma angewendet, die einen positiven Hauttest oder In-vitro -Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und sowohl eine reduzierte Lungenfunktion (FEV1 <80%) haben als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und trotz täglicher Therapie mit hoch dosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta2-Agonisten mehrfach dokumentierte, schwere Asthma-Exazerbationen hatten
Kombinationspräparate (ICS/LABA)	
Beclometason/	Das Arzneimittel ist angezeigt für die regelmäßige Behandlung von Asthma, bei der die Anwendung eines Kombinationsprodukts (von

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Formoterol R03AK08 Foster®	inhalativem Kortikosteroid und langwirksamem Beta-2-Agonisten) angezeigt ist: - Patienten, die mit inhalativen Kortikosteroiden und inhalativen schnellwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind, oder - Patienten, die mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination bereits ausreichend eingestellt sind.
Budesonid/ Formoterol R03AK07 DUORESP Spiromax®	Zur regelmäßigen Behandlung von Asthma, bei der die Anwendung eines inhalativen Kortikosteroids und eines langwirksamen Beta-Agonisten in Kombination angezeigt ist: - bei Patienten, die mit inhalativen Kortikosteroiden und kurzwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind, oder - bei Patienten, die bereits mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination ausreichend eingestellt sind.
Salmeterol/ Fluticason Viani® R03AK06	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.
Formoterol/ Fluticason R03AK11 FLUTIFORM®	Die Fixkombination aus Fluticason-17-propionat und Formoterolfumarat-Dihydrat wird bei Erwachsenen und Jugendlichen ab 12 Jahren angewendet zur regelmäßigen Behandlung von Asthma bronchiale in Fällen, in denen ein Kombinationspräparat (ein inhalatives Kortikosteroid und ein langwirksamer Beta-2-Agonist) angezeigt ist: - Bei Patienten, die mit inhalativen Kortikosteroiden und bedarfsweise angewendeten, kurzwirksamen inhalativen Beta-2-Agonisten nicht ausreichend eingestellt sind. oder - Bei Patienten, die bereits mit einem inhalativen Kortikosteroid und einem langwirksamen Beta-2-Agonisten adäquat eingestellt sind.
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.

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

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche bei 2014-B-121 (Mepolizumab):

Mepolizumab ist indiziert als Zusatztherapie bei erwachsenen Patienten mit schwerem eosinophilen Asthma.

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, siehe: Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet.

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Asthma bronchiale“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***04.05.2015*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP.
Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die erweiterten Empfehlungen der GINA Leitlinie in Stufe 4 und 5 um Tiotropium basieren auf drei Primärstudien, die ebenfalls in der Evidenzsynopse dargestellt wurden.

Die Recherche ergab **1066** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 19 Quellen eingeschlossen. Insgesamt ergab dies **15** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BDP	Beclometasone
CS	corticosteroids
DAHTA	Deutsche Agentur für Health Technology Assessment
FENO	fraction of expired nitric oxide
FEV1	Forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of recommendation
ICS	Inhalatives Corticosteroid
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LABA	Langwirkendes Beta-2-Sympathomimetikum (long-acting beta2-agonist)
LoE	Level of Evidence
LTRA	Leukotrienrezeptorantagonist
MDI	metered dose inhaler
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
PEFR	Peak expiratory flow rate
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

IQWiG, 2014 [9]. Systematische Leitlinienrecherche und -bewertung sowie Extraktion neuer und relevanter Empfehlungen für das DMP Asthma bronchiale [V12-03]	Fragestellung/Ziele: Ziel der vorliegenden Untersuchung war es, durch eine systematische Recherche nach neuen thematisch relevanten evidenzbasierten Leitlinien und durch die Synthese der Leitlinienempfehlungen einen potenziellen Aktualisierungs- und Ergänzungsbedarf des bestehenden DMP Asthma zu spezifizieren. Die Untersuchung gliedert sich in folgende Arbeitsschritte: – Recherche und Auswahl aktueller Leitlinien zum Thema Asthma bronchiale, – Bewertung der methodischen Qualität der ausgewählten Leitlinien, – Extraktion und Synthese von Leitlinienempfehlungen, die für das bestehende DMP Asthma relevant sind, – Kennzeichnung von Empfehlungen, die einen potenziellen Aktualisierungs- und Ergänzungsbedarf des DMP Asthma begründen. Ziel der Untersuchung war es nicht, Empfehlungen im Sinne einer Nutzenbewertung des IQWiG abzugeben. Methoden Es wurde eine systematische Recherche im Internet nach themenspezifischen Leitlinien über die Leitliniendatenbanken der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), des Guidelines International Network (G-I-N), des National Guideline Clearinghouse (NGC) sowie aufseiten von fachübergreifenden und fachspezifischen Leitlinienanbietern durchgeführt. Die Recherche umfasste daher den Zeitraum ab November 2007 bis August 2013. *Potenzieller Aktualisierungs- bzw. Ergänzungsbedarf* Die DMP-Richtlinie enthält Anforderungen an die Versorgung von Erwachsenen sowie Kindern und Jugendlichen im Alter von 5 bis einschließlich 17 Jahren. Zu fast allen in der DMP-Richtlinie genannten Versorgungsaspekten der medizinischen Versorgung von Asthma-Patienten fanden sich Empfehlungen in den 12 eingeschlossenen Leitlinien. Inhaltlich stimmen sie weitestgehend mit den Aussagen der DMP-Richtlinie überein, es wurden nur wenige Diskrepanzen aufgefunden. Allerdings sind die meisten extrahierten Empfehlungen im Vergleich zum Text der DMP-Richtlinie ausführlicher. Weiterhin sprechen einige Leitlinien Themen an, die in der aktuellen DMP-Richtlinie keine Berücksichtigung gefunden haben.
G-BA, 2011 [6] Beschluss des Gemeinsamen Bundesausschusses über Empfehlungen zur Aktualisierung von	Anforderungen an strukturierte Behandlungsprogramme für Patientinnen und Patienten mit chronischen obstruktiven Atemwegserkrankungen - Teil I Asthma bronchiale (ab 5 Jahre) Medikamentöse Maßnahmen Zur medikamentösen Therapie sind mit der Patientin oder dem

Anlage 9 und 10 zur Risikostruktur-Ausgleichsverordnung (Anforderungen an strukturierte Behandlungsprogramme für Patientinnen und Patienten mit chronischen obstruktiven Atemwegserkrankungen - Teil 1 Asthma bronchiale)	Patienten ein individueller Therapieplan zu erstellen und Maßnahmen zum Selbstmanagement zu erarbeiten (siehe auch strukturierte Schulungsprogramme (Ziffer II 4)). Vorrangig sollen unter Berücksichtigung der Kontraindikationen und der Patientenpräferenzen Medikamente verwendet werden, deren positiver Effekt und Sicherheit im Hinblick auf die unter Ziffer II 1.3 genannten Therapieziele in prospektiven, randomisierten, kontrollierten Studien nachgewiesen wurde. Dabei sollen diejenigen Wirkstoffe/Wirkstoffgruppen oder Kombinationen bevorzugt werden, die diesbezüglich den größten Nutzen erbringen. Sofern im Rahmen der individuellen Therapieplanung andere Wirkstoffgruppen oder Wirkstoffe als die in dieser Anlage genannten verordnet werden sollen, ist die Patientin oder der Patient darüber zu informieren, ob für diese Wirksamkeitsbelege bezüglich der unter Ziffer II 1.3 genannten Therapieziele vorliegen. In der medikamentösen Behandlung des Asthma bronchiale werden Dauertherapeutika (Medikamente, die regelmäßig eingenommen werden) und Bedarfstherapeutika (Medikamente, die bei Bedarf, z. B. bei zu erwartenden körperlichen Belastungssituationen, zur Behandlung von Dyspnoe und insbesondere bei Asthma-Anfällen eingesetzt werden) unterschieden. In der Inhalationstherapie ist nur die im Bronchialsystem deponierte Medikamentenmenge wirksam. Diese hängt stark ab von der individuellen Anatomie der Atemwege, dem Atemmuster, der Partikelgröße und dem Inhalationssystem. Es sollte daher das Inhalationssystem und die Instruktion bezüglich der Anwendung individuell an die Bedürfnisse und Fähigkeiten (insbesondere Alter und Koordination) angepasst werden. Darüber hinaus ist es sinnvoll, bei Verwendung mehrerer inhalativer Medikamente für alle Präparate den leichen Typ von Inhalationssystem einzusetzen. Nach einer initialen Einweisung in die Inhalationstechnik sollte diese in jedem Dokumentationszeitraum mindestens einmal überprüft werden. Bei guter Asthma-Kontrolle über einen längeren Zeitraum (z.B. über drei Monate bei Einsatz inhalativer Glukokortikosteroide) soll die Reduktion der Therapie erwogen werden. Dauertherapie bei Erwachsenen Vorrangig sollen zur Dauertherapie die folgenden Wirkstoffgruppen verwendet werden: 1. Basistherapie - inhalative Glukokortikosteroide, 2. als Erweiterung dieser Basistherapie kommen in Betracht: - inhalative lang wirksame Beta-2-Sympathomimetika

	- in begründeten Fällen - systemische Glukokortikosteroide - Leukotrien-Rezeptor-Antagonisten - Theophyllin (Darreichungsform mit verzögerter Wirkstofffreisetzung) - Anti-IgE Antikörper Bei Patientinnen und Patienten mit, trotz Ausschöpfung einer erweiterten Basistherapie nicht ausreichend kontrollierbarem, schwerem persistierendem allergischem Asthma bronchiale kann eine Behandlung mit Anti-IgE Antikörper geprüft werden. Bei Undurchführbarkeit einer Therapie mit inhalativen Glukokortikosteroiden (z. B. Ablehnung oder Unverträglichkeit) als Basismedikation ist vor Verordnung einer unterlegenen, alternativen antientzündlichen Therapie ein Aufklärungsgespräch über Risiken dieser Therapieoptionen zu führen.
G-BA, 2011 [5] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) in Anlage IV: Therapiehinweis zu Omalizumab	Wirkstoff: Omalizumab (Xolair®) Zugelassene Anwendungsgebiete Omalizumab ist zugelassen als Zusatztherapie zur verbesserten Asthmakontrolle bei: 1. Erwachsenen und Jugendlichen (ab 12 Jahren) – mit schwerem persistierendem allergischem Asthma, – die einen positiven Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und – sowohl eine reduzierte Lungenfunktion (FEV1 < 80%) haben – als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und – trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta-2-Agonisten mehrfach dokumentierte, schwere Asthma - exazerbationen hatten. – Die Behandlung mit Omalizumab sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE-vermittelten Asthma ausgegangen werden kann. Empfehlungen zur wirtschaftlichen Verordnungsweise Die Verordnung von Omalizumab ist als Zusatztherapie bei Jugendlichen ab 12 Jahren und Erwachsenen nur wirtschaftlich, die kumulativ folgende Voraussetzungen erfüllen: – schweres persistierendes allergisches Asthma, – reduzierte Lungenfunktion (FEV1 < 80%), – positiver Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes und vom Patienten nicht vermeidbares Aeroallergen, – das Asthma ist IgE-vermittelt mit IgE-Werten zwischen ≥ 76 und ≤ 1500 I.E./ml vor Beginn der Behandlung,

	– häufige dokumentierte Symptome während des Tages oder nächtliches Erwachen, – trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden (entsprechend > 1000 µg pro Tag Beclometason oder Äquivalent) und mindestens einem lang wirkenden inhalativen Beta-2-Agonisten als Kontroller traten – in den letzten 12 Monaten mindestens zwei unabhängige, dokumentierte schwere Asthmaexazerbationen, die mit systemischen Kortikosteroiden behandelt wurden, oder – eine Exazerbation, die systemische Kortikosteroidgabe notwendig machte und zur Krankenhausaufnahme bzw. Notfallbehandlung führte, auf. – das Körpergewicht liegt innerhalb der Grenzen der Dosierungstabelle also ≥ 20 kg und ≤ 150 kg. – Nichtraucher
G-BA, 2012 [7] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) in Anlage IV: Therapiehinweis zu Montelukast vom 19. Januar 2012.	Montelukast (Singulair®) Empfehlungen zur wirtschaftlichen Verordnungsweise Die Therapie der ersten Wahl des Asthmas ist im Erwachsenenalter die Kombination von inhalativen Kortikosteroiden (ICS) mit langwirksamen Betasympathomimetika, wenn ICS in niedriger bis mittlerer Dosis beim mittelgradig persistierenden Asthma nicht ausreichend ist. Es stehen neben der Erhöhung der ICS-Dosis weitere Alternativen zur Verfügung. Die Auswahl richtet sich in primär nach dem Nebenwirkungsprofil und sekundär nach dem Preis. Montelukast verteuert die Therapie erheblich und ist von daher nur angezeigt, wenn eine Monotherapie mit ICS nicht ausreichend ist oder eine Kombinationstherapie von ICS mit langwirksamen Betasympathomimetika nicht in Betracht kommt. Der Einsatz ist nur wirtschaftlich in Kombination mit ICS, wenn eine Monotherapie mit ICS in niedriger bis mittlerer Dosis beim mittelgradig persistierenden Asthma nicht ausreichend ist. Montelukast ist im Erwachsenenalter weder zur Behandlung des Asthmas - auch nicht des Belastungs-asthmas - noch der saisonalen allergischen Rhinitis als Komorbidität des Asthmas Therapie der ersten Wahl. Der Einsatz von Montelukast als Monotherapie des Asthmas ist ab einem Alter von 15 Jahren nicht zugelassen. Das Gleiche gilt für schwergradiges persistierendes Asthma in allen Altersstufen und die chronisch obstruktive Lungenerkrankung (COPD). Vor dem Hintergrund, dass eine Überlegenheit gegenüber ICS bei Kindern nicht belegt ist und auch das Längenwachstum in der Regel nur unerheblich verzögert wird bei ansonsten vergleichbaren Nebenwirkungen, ist die Monotherapie mit Montelukast im Alter zwischen 2 und 14 Jahren mit leichtem persistierendem Asthma nur indiziert, wenn die Kinder nicht in der Lage sind, Kortikosteroide zu inhalieren oder Nebenwirkungen auftreten, wie zum Beispiel ein erheblich verzögertes Längenwachstum, die gegen den Einsatz von ICS sprechen. Dies entspricht der aktuellen Zulassung des Arzneimittels. Angesichts der heutigen Möglichkeiten zur Inhalation

	dürfte diese Ausnahme sehr selten sein. Für alle Altersgruppen gilt, dass beim Belastungsasthma der hohe Preis in der Regel nur gerechtfertigt ist bei Unverträglichkeit gegen inhalative kurzwirksame Betasympathomimeti-ka. Indikation Montelukast ist zugelassen als Zusatzbehandlung bei Patienten, die unter einem leichten bis mittelgradigen persistierenden Asthma leiden, das mit einem ICS nicht ausreichend behandelt und das durch die bedarfsweise Anwendung von kurzwirksamen Betasympatho-mimetika nicht ausreichend unter Kontrolle gebracht werden kann. Es kann auch eine Behandlungsalternative zu niedrig dosierten ICS bei Patienten zwischen 2 und 14 Jahren mit leichtem persistierenden Asthma sein, die in letzter Zeit keine schwerwiegenden, mit systemischen Kortikosteroiden zu behandelnden Asthmaanfälle hatten und zeigten, dass sie nicht imstande sind, ICS anzuwenden. Bei den Patienten ab 15 Jahren, für die Montelukast bei Asthma angezeigt ist, können die 10-mg-Filmtabletten auch die Symptome einer saisonalen allergischen Rhinitis lindern. Außerdem kann Montelukast zur Vorbeugung von Belastungsasthma eingesetzt werden, dessen überwiegende Komponente die durch körperliche Belastung ausgelöste Broncho-konstriktion darstellt. Die Dosierung für Erwachsene und Jugendliche ab 15 Jahren mit Asthma oder mit allergischer Rhinitis und Asthma beträgt eine 10-mg-Filmtablette täglich am Abend. Bei Kindern zwischen 6 und 14 Jahren liegt die Dosis bei einer 5-mg-Kautablette, für Kinder von 2 bis 5 Jahren bei einer 4-mg-Kautablette und für Kinder zwischen 6 Monaten und 5 Jahren beträgt sie einen Beutelinhalt mit 4 mg Granulat.

Cochrane Reviews

<table>
<tr><td>Normansell, 2014 [12]
Omalizumab for asthma in adults and children</td><td>1. Fragestellung

To assess the effects of omalizumab versus placebo or conventional therapy for asthma in adults and children.</td></tr>
<tr><td></td><td>2. Methodik

Population: Adults and children with chronic asthma from all referral sources. We included studies in which populations were receiving maintenance therapy and those in which anti-IgE was administered without background therapy. These study populations were analysed separately.
Intervention: Anti-IgE therapy at any dose or route versus.
Komparator: Placebo
Endpunkt 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. The order of the primary outcomes changed from protocol.
Suchzeitraum der syst. Recherche: bis Juni 2013
Anzahl eingeschlossene Studien/Patienten (Gesamt): 25 (n=6382)
Qualitätsbewertung der Studien: nach Cochrane Handbook for Systematic Reviews of Interventions</td></tr>
<tr><td></td><td>3. Ergebnisdarstellung

sc.omalizumab + steroid VS. placebo + steroid (stable steroid)
Asthma exacerbations
<table>
<tr><th>outcome</th><th>No of participants (studies)</th><th>Relative effect (95%CI)</th><th>Quality of the evidence (GRADE)</th></tr>
<tr><td>Number of participants with at least one exacerbation
All asthmatic participants (16 to 60 w)</td><td>3261 (10studies)</td><td>OR 0.55 (0.46 to 0.65)</td><td>moderate</td></tr>
<tr><td>Number of participants with at least one exacerbation
Moderate to severe asthma (16 to 60 w)</td><td>2889 (7 studies)</td><td>OR 0.5 (0.42 to 0.6)</td><td>moderate</td></tr>
<tr><td>Number of participants with at least one exacerbation
Severe asthma (16 to 32 w)</td><td>277 (2 studies)</td><td>OR 1 (0.5 to 1.99)</td><td>low</td></tr>
<tr><td>Mortality
16 to 60 w</td><td>4245 (9 studies)</td><td>OR 0.19 (0.02 to 1.67)</td><td>low</td></tr>
<tr><td>Hospitalisations
28 to 60 w</td><td>1824 (4 studies)</td><td>OR 0.16 (0.06 to 0.42)</td><td>moderate</td></tr>
<tr><td>Adverse event-serious
16 to 60 w</td><td>5713 (15 studies)</td><td>OR 0.72 (0.57 to 0.91)</td><td>moderate</td></tr>
</table>
<u>Inhaled steroid withdrawal</u> (4 trials,n=529)
Participants treated with subcutaneous omalizumab were</td></tr>
</table>

	significantly more likely to be able to withdraw their ICS completely than those treated with placebo (OR 2.50, 95% CI 2.00 to 3.13). Most of the evidence comes from trials in participants with moderate to severe asthma, and considerable uncertainty remains about whether benefit is seen in the **severe asthma subgroup (OR 1.55, 95% CI 0.80 to 2.98; one trial, 45 participants**). **Inhaled steroid reduction** Change from baseline in ICS dose (3 studies, n=1188) A small but statistically significant reduction in daily steroid dose was seen among omalizumab-treated participants compared with those given placebo (WMD -118 mcg BDP equivalent per day, 95%CI -154 to -84). Although a high degree of heterogeneity was observed (I^2 = 67.2%), random-effects modelling did not alter the direction of the effect but widened the confidence interval (MD -141.24 mcg, 95% CI -221 to -61). The reduction in ICS dose was greater in the trial with severe asthma than in the two trials with moderate to severe asthma, although this difference did not reach statistical significance (test for subgroup differences: Chi^2 = 3.33, df = 1 (P = 0.07), I^2 = 70.0%). **Oral steroid withdrawal** (1 Study, N=95) No significant difference was noted in the number of participants who were able to withdraw from oral steroid therapy between omalizumab and placebo treatment (OR 1.18, 95% CI 0.53 to 2.63; one study, 95 participants). Oral steroid reduction No significant difference in the median reduction of daily oral steroid dose was noted between omalizumab- and placebo-treated participants in (69% vs 75%; P = 0.675). **Adverse event-any** (14 studies,n=5167) In terms of all adverse events, no significant difference was seen between subcutaneous omalizumab and placebo (OR 0.92, 95% CI 0.81 to 1.06;). However, the level of heterogeneity among these studies (I^2 = 22%) was pronounced. **Adverse event-injection site reactions** Significantly more injection site reactions were reported among participants assigned to subcutaneous omalizumab than among those receiving placebo (OR 1.72, 95% CI 1.33 to 2.24; 9 studies,n= 3577), and the level of heterogeneity among these studies (I^2 = 42%) was considerable. This represents an absolute increase from 6% on placebo to 9% on omalizumab. No differences were reported in headache, urticaria, number of participants with any adverse events or number of withdrawals due to adverse events
	4. Anmerkungen/Fazit der Autoren • 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. • 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 from omalizumab over placebo for those withdrawing or reducing their steroid treatment. • Insufficient evidence of benefit has been found in participants specifically with severe OCS-dependent asthma.

Systematische Reviews

<table>
<tr>
<td>CADTH, 2015: [1] Omalizumab Treatment for Adults and Children with Allergic Asthma: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines</td>
<td>
1. Fragestellung
1. What is the clinical effectiveness of omalizumab for the treatment of allergic asthma in adults and children who are not responsive to other therapies?
2. What is the cost-effectiveness of omalizumab for the treatment of allergic asthma in adults and children who are not responsive to other therapies?
3. What are the international evidence-based guidelines regarding the use of omalizumab for the treatment of allergic asthma in adults and children?
</td>
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<td></td>
<td>
2. Methodik
Population: Patients with moderate to severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids
Intervention: Omalizumab
Komparator: Any comparator
Endpunkte: Clinical improvement of allergic asthma symptoms, improved asthma exacerbation management, cost-effectiveness, guidelines and recommendations
Suchzeitraum: 01/2011 – 02/2015
Anzahl eingeschlossene Studien/Patienten: 3 Systematische Reviews (Lai, 2015: 6 RCTs; Normansell, 2014: 25 double-blind, parallel-group RCTs; Norman, 2013: 11 RCTs)
Qualitätsbewertung der Studien: The included systematic reviews were critically appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) tool
</td>
</tr>
<tr>
<td></td>
<td>
3. Ergebnisdarstellung
What is the clinical effectiveness of omalizumab for the treatment of allergic asthma in adults and children who are not responsive to other therapies?
Summary of Findings of Included Systematic Reviews and Meta-Analyses:
<table>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td colspan="2">Lai, 2015</td></tr>
<tr><td><u>Exacerbations</u>
Omalizumab-treated patients experienced statistically significantly lower rates of clinically significant asthma exacerbations compared to patients who received placebo during the stable phase (RR 0.69; 95% CI 0.53 to 0.90). This reduction in exacerbation rates remained</td><td>"Based on the pooled analyses, we found that omalizumab significantly reduced the incidence of asthma</td></tr>
</table>
</td>
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</table>

		statistically significant over a period of 52 weeks (RR 0.63; 95% CI 0.55 to 0.71). ICS reduction ICS doses were statistically significantly decreased in omalizumab-treated patients compared with the placebo group (RR 1.86; 95% CI 1.51 to 2.29). Asthma symptoms Two RCTs demonstrated greater reductions in asthma symptom scores with omalizumab than placebo. Safety Patients reporting adverse events were similar in both treatment groups (RR 0.97; 95% CI 0.93 to 1.01). There were fewer serious adverse events reported among omalizumab-treated patients than patients who received placebo (RR 0.55; 95% CI 0.37 to 0.82).	exacerbations and ICS use...Additionally, omalizumab was well tolerated and demonstrated an acceptable safety profile." (pp. 4-5)
		Normansell, 2014	
		Exacerbations Treatment with omalizumab resulted in a significant reduction in the odds of having one of more exacerbations compared to placebo in all groups except for the subgroup analysis in studies looking at patients with severe asthma. Steroid-stable (10 studies, N = 3261): OR 0.55; 95% CI to 0.65 Steroid-tapering (4 studies, N = 1631): OR 0.46; 95% CI 0.36 to 0.59 Moderate/severe asthma (7 studies; N = 1889): OR 0.50; 95% CI 0.42 to 0.60 Severe asthma (2 studies, N = 277): OR 1.00; 95% CI 0.50 to 1.99 Hospitalizations Treatment with omalizumab resulted in a significant reduction in the odds of experiencing one or more hospitalization. Moderate/severe asthma (4 studies, N = 1824): OR 0.16; 95% CI 0.06 to 0.42 ICS withdrawal and reduction Patients treated with omalizumab were statistically significantly more likely to be able to withdraw from their ICS completely than those treated with placebo. Moderate/severe asthma (4 studies, N = 529): OR 2.50; 95% CI 2.00 to 3.13 There was a small but statistically significant reduction in daily steroid dose seen among omalizumab-treated patients compared with placebo-treated patients (3 studies, N = 1188): WMD -118 mcg BDP equivalent per day; 95% CI -154 to -84). A high degree of heterogeneity was observed. Asthma symptoms A significant difference favouring omalizumab was observed with regard to end of treatment symptom scores for moderate to severe patients in 4 of 7 studies reporting data on this outcome, and in severe patients in 2 out of 4 studies. Due to heterogeneity among outcome reporting, no statistical aggregation of data was done. Mortality There was no significant difference between	"Data from the included trials have shown that omalizumab is both effective and safe in patients with moderate to severe asthma that is uncontrolled on moderate to high doses of inhaled steroids with or without long-acting beta2-agonists. Insufficient evidence of benefit has been found in participants specifically with severe OCS-dependent asthma. Very few studies have explored efficacy in children with moderate to severe asthma." (p. 28)

	omalizumab and placebo with respect to mortality (9 studies, N = 4245): OR 0.19; 95% CI 0.02 to 1.67). Safety Statistically significantly fewer serious adverse events occurred in patients treated with omalizumab than those treated with placebo (15 studies, N = 5713): OR 0.72; 95% CI 0.57 to 0.91. There was no significant difference between omalizumab and placebo with respect to any adverse event (14 studies, N = 5167): OR 0.92; 95% CI 0.81 to 1.06.	
	Norman, 2013	
	Exacerbations Included trials showed a consistent finding of benefit with omalizumab for both incidence rate and proportion of adult patients with no exacerbations in the follow-up period. *Rate ratios (95% CI) – adult trials* INNOVATE: 0.738 (0.552 to 0.998) EXALT: 0.570 (0.417 to 0.778) IA-04 EU subgroup: 0.41 (0.288 to 0.583) In children, data from a post-hoc subgroup analysis (IA-05-EUP) showed a statistically significant treatment benefit for omalizumab in terms of a reduced clinically significant exacerbation rate. One supportive trial reported a statistically significant benefit of omalizumab in the number of patients with zero exacerbations in children and adolescents. Hospitalizations Hospitalization data for adult populations were reported in three trials. Relative treatment effect for hospitalization rate favoured omalizumab in INNOVATE and EXALT, but was statistically significant only in EXALT. In children, the IA-05 EUP showed no evidence of a difference in hospitalization rates between the groups or in the number of patients with zero hospitalizations. OCS withdrawal and reduction There is limited evidence from RCTs on the oral steroid-sparing effect of omalizumab and the results were mixed. Only two RCTs were identified, and both reported data from small adult subgroups. The results were heterogeneous and limited by design flaws (EXALT) and insufficient OCS dose adjustment during the run-in phase of the trial (011 OCS). In the EXALT trial at both16 and 32 weeks, omalizumab patients stopped or reduced the use of OCSs around twice as often as those on best supportive care alone and this difference was statistically significant at 32 weeks. Week 16: Relative Risk 2.04 (95% CI 0.81 to 5.12) Week 32: Relative Risk 2.06 (1.08 to 3.94)	"Omalizumab for the treatment of severe persistent asthma has been studied in a number of RCTs and observational studies. Overall, the evidence base indicates a clear treatment benefit in adults and children on the primary outcome of clinically significant exacerbations. There is also evidence of benefit in reducing hospitalisations and other unscheduled health-care use, symptoms and lung function, and improved QoL in adults. However, evidence for these secondary outcomes is limited or lacking in children. There is some evidence that omalizumab reduces requirements for OCSs in patients who are treated at step 5, but this is also considerably more robust for adults than for children." (p. 84)

	4. Anmerkungen/ Fazit der Autoren The systematic reviews demonstrated that omalizumab was associated with a reduction of clinically significant asthma exacerbations and hospitalizations compared to placebo or standard of care in adults and adolescents. In addition, omalizumab was found to be associated with a reduction in inhaled corticosteroid use and improved asthma symptoms compared to placebo in adults and adolescents. One systematic review analyzed children 6 to 11 years old separately and found limited data demonstrating reduction in exacerbation rate with omalizumab compared to placebo in this population, but no difference in other clinical outcomes.
	5. Hinweise FBMed: Die 2. Und 3. Fragestellung wurde nicht erarbeitet.
Dennis, 2011 [4]. Asthma in adults	1. Fragestellung Most guidelines about the management of asthma follow stepwise protocols. This review does not endorse or follow any particular protocol, but presents the evidence about specific interventions: What are the effects of treatments for chronic asthma?
	2. Methodik 1. Methodik a) Systematische Literaturrecherche im Suchzeitraum bis 2010 b) Vergleiche/Komparatoren: alle Behandlungen c) Endpunkte: keine Angaben d) Insgesamt eingeschlossene Studien und systematische Übersichtsarbeiten: 54 (keine Angaben zur Anzahl an Patienten) e) Bewertung der eingeschlossenen Evidenz nach GRADE
	3. Ergebnisdarstellung (ausschließlich zum relevanten Anwendungsgebiet) Adding anti-IgE treatment versus adding placebo to inhaled corticosteroids plus long-acting beta2 agonists plus either leukotriene antagonists, theophylline, or oral corticosteroids, alone or in any combination: • 1 systematic review (search date 2006; 14 parallel RCTs; 3143 adults, adolescents, and children with mild-to-severe allergic asthma). 7 trials in the review compared the anti-IgE monoclonal antibody omalizumab as an adjunct to treatment with inhaled and oral corticosteroids versus treatment with corticosteroids alone.

	• 1 RCT from Japan comparing anti-IgE monoclonal antibody omalizumab as an adjunct to treatment with inhaled and oral corticosteroids and other treatments. We also found one additional RCT from Brazil that specifically assessed the safety of the anti-IgE monoclonal antibody omalizumab in people with asthma at risk of geohelminth infection. <u>Symptom severity (excluding lung function)</u> Compared with on-going asthma therapy including inhaled and oral corticosteroids: The anti-IgE monoclonal antibody omalizumab seems more effective at improving symptoms and reducing exacerbations and the need for short-acting bronchodilators in people with moderate or severe asthma, both as an adjunctive or corticosteroid-sparing strategy. (moderate-quality evidence) <u>Lung function</u> Compared with on-going asthma therapy including inhaled and oral corticosteroids: Addition of the anti-IgE monoclonal antibody omalizumab does not seem to improve lung function (FEV1 and PEFR) in people with moderate or severe asthma. (moderate-quality evidence) <u>Hospital admission</u> Compared with on-going asthma therapy including inhaled and oral corticosteroids: Addition of the anti-IgE monoclonal antibody omalizumab may reduce asthma exacerbations requiring hospital admission in people with moderate or severe asthma. (moderate-quality evidence) <u>Quality of life</u> Compared with on-going asthma therapy including inhaled and oral corticosteroids: Addition of the anti-IgE monoclonal antibody omalizumab may be more effective at improving asthma-related quality of life. (low-quality evidence) →Anti-IgE treatment (omalizumab) as an adjunct to treatment with inhaled and oral corticosteroids improves symptom severity, decreases exacerbation frequency, decreases the use of inhaled corticosteroid therapy, and may decrease hospital admission rates in people with chronic moderate to severe asthma.

Leitlinien

<table>
<tr>
<td>SEPAR, 2015 [3].
Guidelines for Severe Uncontrolled Asthma</td>
<td>SEPAR (Spanish Society of Pulmonology and Thoracic Surgery) Guidelines on Difficult-to-Control Asthma (DCA)</td>
</tr>
<tr>
<td></td>
<td>Methodik
Grundlage der Leitlinie: MethodologyThese guidelines were drawn up following SEPAR recommendations for the development of guidelines.
Literaturrecherche: k.A.
Quality of evidence was classified as high, moderate, low and very low, based on different considerations for presence of direct bias (and the direction), consistency and directness of the estimates.
Grading and quality of evidence and implication of recommendations according to GRADE:
<table>
<tr><th colspan="2">Quality of evidence</th><th>Definition and interpretation of grades of evidence</th></tr>
<tr><td>A</td><td>High ++++</td><td>High are are very confident that the true effect lies close to that of the estimate of the effect.</td></tr>
<tr><td>B</td><td>Moderate +++</td><td>We are moderately confident in the effect estimate: the true effect islikely to be close to the estimate of the effect but there is a possibilitythat it is substantially different.</td></tr>
<tr><td>C</td><td>Low ++</td><td>Our confidence in the effect estimate is limited: the true effect may besubstantially different from the estimate of the effect.</td></tr>
<tr><td>D</td><td>Very low +</td><td>We have very little confidence in the effect estimate: the true effect islikely to be substantially different from the estimate of effect.</td></tr>
</table>
Grading of quality of evidence according to type od the study design
<table>
<tr><th>Study design</th><th>Quality of initialevidence</th><th>Reduced in case of</th><th>Increased in case of</th></tr>
<tr><td rowspan="2">Randomized clinical trials</td><td rowspan="2">High</td><td>Limitations in design or implementationImportant (–1)Very important (–2)</td><td>Strength of associationStrong (+1)Very strong (+2)</td></tr>
<tr><td>Important inconsistency (–1)Very important (–2)</td><td>Dose response gradientPresent (+1)</td></tr>
<tr><td rowspan="3">Observational studies</td><td rowspan="2">Low</td><td>Uncertainty that evidence is directImportant (–1)Very important (–2)</td><td>Consideration of possibleconfounding factors thatmay have reduced theeffect (+1)Would suggest a spuriouseffect if there is no effect (+1)</td></tr>
<tr><td>Lack of precisionImportant (–1)Very important (–2)</td><td></td></tr>
<tr><td></td><td>Publication biasImportant (–1)Very important (–2)</td><td></td></tr>
</table>
Implications of a strong recommendation (R1):</td>
</tr>
</table>

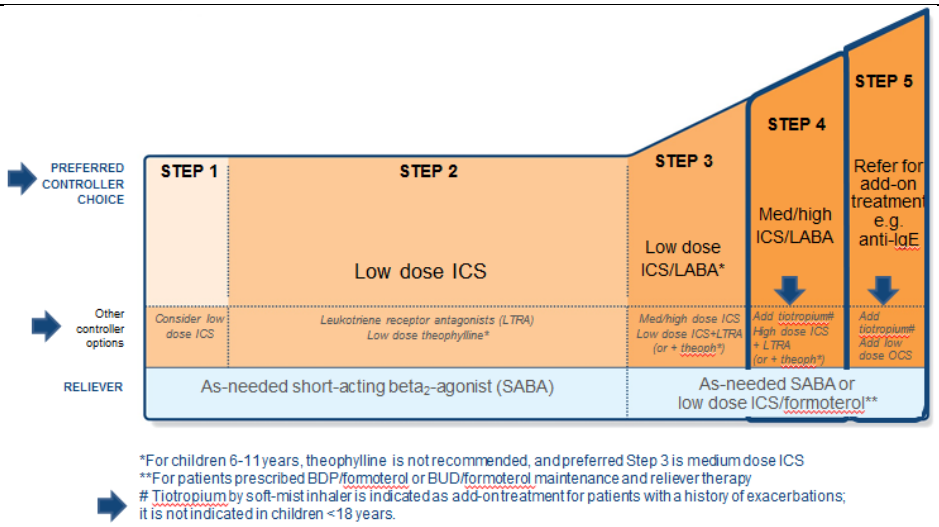
	For patients: Most people in your situation would want the recommended course of action and only a small proportion would not. For clinicians: Most patients should receive the recommended course of action. For policy makers: The recommendation can be adopted as a policy in most situations. *Implications of a weak recommendation (R2):* For patients: Most people in your situation would want the recommended course of action, but many would not. For clinicians: You should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with his or her values and preferences. For policy makers: Policy making will require substantial debate and involvement of many stakeholders.
	Empfehlungen **Treatment of Severe Uncontrolled Asthma** *Corticosteroid Insensitivity:* • In a study of 102 SUCA children, only 11% did not respond to an intra-muscular (IM) dose of triamcinolone, suggesting that 89% had some degree of response to SC (evidence D-R2). • From a clinical point of view, SC-insensitive asthma is defined by forced expiratory volume in the first second (FEV1) less than75% of the predicted value and a response <15% and 200 ml after the administration of a 2-week cycle of 40 mg/day prednisone or prednisolone (evidence D-R2). • Some studies report weak associations between certain genetic changes and environmental factors (continuous exposure to allergens, smoking, NSAID intolerance, low vitamin D levels, and chlamydia, mycoplasma or viral infections), but these can-not be considered as clearly established risk factors. The most significant environmental factor in SC insensitivity is exposure to tobacco smoke. This may act by various mechanisms: by altering the inflammatory pattern (increased neutrophils and CD8 lymphocytes and reduced eosinophil levels), by impairing mucociliary function, thus allowing excessive mucous deposition in the air-ways, or by tobacco-induced oxidative stress, which inactivates histone deacetylase, reducing nuclear translocation and the number of corticosteroid receptors and their affinity (evidence D-R2). • Lack of sensitivity to SC cannot be explained by pharmacokinetic changes or malabsorption, and is probably due to a range of different mechanisms (evidence C-R2) *Inhaled Corticosteroids:* • Response to IC varies notably among individuals (evidence C-R2) • However, there is some evidence to suggest that SUCA patients may respond to higher doses than normally recommended (evidence A-R1) • Although some studies support the greater therapeutic efficacy of

	fine particle IC (related with their effect on the peripheral airways), there is no evidence of their superiority in SUCA (evidence C-R2) • Among the new glucocorticoids, ciclesonide has fewer local and systemic side effects since it is a prodrug converted to its active form in the lung parenchyma (evidence B-R2). • New steroids, known as “dissociated” compounds (mapracorat), that aim to separate the anti-inflammatory mechanisms from the side effects, are currently under development (evidence D-R2). *Systemic Corticosteroids:* • The best time for introducing maintenance treatment with SC is not well defined, nor is there evidence that continuous treatment with low-dose SC is more effective than cycles of SC in reducing the number of exacerbations. • IM triamcinolone administration (Trigon®depot 40 mg) in asthmatics with corticosteroid insensitivity improves control, reduces eosinophils in sputum, increases FEV1and prevents exacerbations. • Reasons for its efficacy may include reinforced compliance or the higher dosage of triamcinolone com-pared to other corticosteroids used in the clinicC-R2). *Long-Acting β2-Adrenergic Agonists:* • Adding a LABA to an IC has been shown to be more effective than doubling the dose of the IC or adding an antileukotriene, although there may be notable variability in response, which needs to be monitored (evidence A-R1). • Formoterol as a complete agonist has greater intrinsic efficacy and causes a greater number of adverse effects (evidence D-R2), the most common of which are tachycardia and hypokalemia, which can be more pronounced in individuals homozygous for arginine in position 16 of β2-AR. *Long-Acting Anticholinergics:* • Recent studies have shown that long-acting anticholinergics (LAMA) may be useful in patients with severe asthma and concomitant CAFL (evidence B-R2), in cases of ACOS, in severe asthma with a non-eosinophilic inflammatory profile (evidence D-R2), and in asthmatics with the ArgGly variant in codon 16 of the β2-receptor (evidence B-R2). • There is an increasing trend in the use of LAMA as a treatment for bronchial asthma, and some CPG suggest their use in the higher stages of severity, when control cannot be achieved. *Antileukotrienes:* • Patients with AERD generally have excessive basal leukotriene production, so would appear to be ideal candidates for antileukotriene treatment (evidence C-R2). • Some recent studies report findings in air trapping and radiological changes on CT that suggest montelukast may be useful, in general, in patients with severe asthma, so it may tried as an add-on therapy in these patients (evidence C-R2). *Omalizumab:* • Omalizumab is indicated for improving asthma control when administered as add-on treatment in adults and older children(over 6

	years of age) with persistent severe uncontrolled allergic asthma with perennial allergies, reduced lung function and documented severe exacerbations, despite appropriate treatment for their level of severity (evidence B-R2). • Data from non-atopic patients receiving omalizumab have been published, which could open a new avenue for treatment in this patient group (evidenceD-R2). *Theophylline and Phosphodiesterase-4 Inhibitors:* • Although no controlled trials have been performed in severe asthma, theophylline as a single agent has relatively weak anti-inflammatory activity, but at low doses it can markedly enhance the action of corticosteroids on the expression of inflammatory genes (evidence D-R2). • Data are also available on the utility of the newphosphodiesterase-4 inhibitors (roflumilast) in asthmatics (evidence B-R2) and the 2014 Spanish COPD Guidelines (GesEPOC) update continues to suggest these drugs as add-on treatment in ACOS patients with uncontrolled symptoms (evidence D-R2CPG). **Severe Uncontrolled Asthma in Childhood** • Less than 5% of asthmatic children have SUCA • However, the care of children with SUCA accounts for more than twice the direct (medication, visit to the emergency room, hospitalization) and indirect resources (missing school, parents' absenteeism from work, etc.) used by the others (evidence B-R1). • To confirm corticosteroid response, and since there is no agreement as regards the optimal dose, duration and routeof administration in children, we suggest using triamcinolone, 40–80 mg IM, depending on age and weight (evidence D-R2). • Responders are patients who improve in all 3 domains, non-responders are those who do not improve in any domains, and partial responders are those who improve in 1 or 2 domains. • Patients who respond to SC may benefit from omalizumab, which has been shown to be safe and effective in comparative trials in children over the age of 6. • Any other treatment should also be maintained, including SC, until symptoms are controlled. • Non-responders who have persistent neutrophilic airway inflammation may benefit from macrolides, although there is insufficient evidence. Use of azithromycin has been suggested with the same regimen as for cystic fibrosis: 250 mg/day for children weighing <40 kg and 500 mg/day for those >40 kg, 3 times a week for6 months, followed by a reevaluation of efficacy (evidence A-R1). • Low-dose oral theophylline may also be tried: target blood concentrations are 5–10 mg/l.
GINA, 2015 [8]. Global strategy for asthma management and prevention	GINA = Global Initiative for Asthma Methodik 1. Internationale aktuelle Leitlinie; Update Recherche: jährliches Update (letzte Aktualisierung in 2014) 2. GoR: Nicht angegeben (jedoch Nutzung von GRADE erwähnt) 3. LoE:

	Evidence A: RCTs, rich body of data. Evidence B: RCTs, limited body of data Evidence C: Nonradomized trials. Observational studies. Evidence D: Panel consensus judgement
	Empfehlungen **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** The selection of Step 4 treatment depends on the prior selection at Step 3. For adult and adolescent patiens.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 (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 (Evidence B); combination ICS/LABA medications are as for Step 3, or once daily fluticasone furoate/vilanterol. *Other options* Tiotropium by soft-mist inhaler may be used as add-on therapy for adult patients with a history of exacerbations (Evidence B), it is not indicated in children <18 years. – Add-on tiotropium by soft-mist inhaler is a new 'other controller option' for Steps 4 and 5, in patients ≥18 years with history of exacerbations • Tiotropium was previously described in GINA as an add-on option on the basis of clinical trial evidence. • It is now included in recommendations and the stepwise figure following approval for asthma by a major regulator. *Zugrundeliegende Primärstudien (siehe Evidenzsynopse Seite 33-40):* • Kerstjens HA. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. J Allergy Clin Immunol. 2011;128(2):308-14. • Kerstjens HA. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012; 367(13):1198-207. • Peters SP. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010; 363(18):1715-26. Combination high-dose ICS/LABA may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit (Evidence A), and there is an increased risk of side-effects. 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 Evidence B). For medium or high dose budesonide, efficacy may be im[proved with dosing four times daily (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 L TRA (Evidence A), or low dose sustained-release theophylline (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 should be referred to a specialist with expertise in management of severe asthma (Evidence D) Treatment options… include: • Anti-immunoglobulin E (anti-lgE) treatment (omalizuimab): this is suggested for patients with moderate or severe allergic asthma that is uncontrolled on Step 4 treatrnent (Evidence A). • 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. ln severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS (Evidence A). • Bronchial thermoplasty: may be considered for some adult patients with severe asthma (Evidence B). Evidence is limited and in selected patients. The long term effects arenot known. • Add-on low dose oral corticosteroids (≤ 7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma (Evidence D); but are often associated with substantial side effects (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). 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). *GINA 2015, Box 3-5, Steps 4 and 5:*

	 *For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS **For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy # Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years. --- **Stepping up asthma treatment** Asthma is a variable condition, and periodic treatment adjustments by the clinician and/or the patient may be needed. • Sustained step up (for at least 2-3 months): some patients may fail to respond adequately to initial treatment. A step up in treatment may be recommended, if the symptoms are confirmed to be due to asthma; inhaler technique and adherence are satisfactory; and modifiable risk factors such as smoking have been addressed. Any step-up should be regarded as a therapeutic trial, and the response reviewed after 2-3 months. If there is no response, treatment should be reduced to the previous level, and alternative treatment options or referral considered. • Short-term step up (for 1-2 weeks): an occasional short-term increase in maintenance ICS dose for 1-2 weeks may be necessary; for example, during viral infections or seasonal allergen exposure. This may be initiated by the patient according to their written asthma action plan, or by the health care provider. • Day-to-day adjustment: for patients prescribed combination budesonide/formoterol or beclometasone/formoterol as maintenance and reliever treatment, the patient adjusts the number of as-needed doses of ICS/formoterol from day to day according to their symptoms, while continuing the maintenance dosage. Anmerkung FB Med: GINA differenziert nicht zwischen adults und adolescents; es gibt children (bis 11 Jahre) und adults & adolescents (ab 12 Jahre)
Chung, 2014 [2]. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma	European Respiratory Society (ERS) and American Thoracic Society (ATS) This guideline represents a collaborative effort between the ATS and ERS. The Committee consisted of clinicians and researchers with recognised expertise in severe asthma and in the guideline development following the GRADE approach Fragestellung: The purpose of this document is to revise the definition of severe asthma, discuss the possible phenotypes and provide guidance

	about the management of patients with severe asthma.
	Committee composition and processes of disclosing and managing potential conflicts of interest, evidence synthesis, developing recommendations and peer review of the guidelines are described in detail in the online-only full-text document of these guidelines. – Suchzeitraum der syst. Recherche: bis Juli 2012 (Informationen dazu in einem gesonderten Dokument online only) LoE und GoR: nach GRADE (ausführlichen Evidenzbewertung in einem gesonderten Dokument online)
	Definition of severe asthma for patients aged > 6 years Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for > 50% of the previous year to prevent it from becoming ‘‘uncontrolled’’ or which remains ‘‘uncontrolled‘‘ despite this therapy Uncontrolled asthma defined as at least one of the following: a. Poor symptom control: ACQ consistently >1.5, ACT <20 (or ‘‘not well controlled’’ by GINA guidelines) b. Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year c. Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year d. Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal) Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics) --- ***Question*: Should treatment guided by sputum eosinophil count, rather than treatment guided by clinical criteria alone, be used in patients with severe asthma?** *Recommendation* In adults with severe asthma, we suggest treatment guided by clinical criteria and sputum eosinophil counts performed in centres experienced in using this technique rather than by clinical criteria alone (conditional recommendation, very low quality evidence). *Values and preferences* The recommendation to use sputum eosinophil counts to guide therapy in adults places a higher value on possible clinical benefits from adjusting the treatment in selected patients and on avoidance of inappropriate escalation of treatment and a lower value on increased use of resources. The recommendation not to use sputum eosinophil counts to guide therapy in children places higher value on avoiding an intervention that is not standardised and not widely available and lower value on the uncertain and possibly limited clinical benefit. *Remarks* Because at the present time, measurement of sputum eosinophils has not yet been sufficiently standardized and is not widely available we suggest such an approach be used only in specialised centres experienced in this technique. Patients who are likely to benefit from this approach are those who can produce sputum, demonstrate persistent or at least intermittent eosinophilia and have severe asthma with frequent

	exacerbations. Clinicians should recognise that different choices will be appropriate for different patients. ***Question:*** **Should a monoclonal anti-IgE antibody be used in patients with severe allergic asthma?** *Recommendation* In patients with severe allergic asthma we suggest a therapeutic trial of omalizumab both in adults (conditional recommendation, low quality evidence) and in children (conditional recommendation, very low quality evidence). *Values and preferences* This recommendation places higher value on the clinical benefits from omalizumab in some patients with severe allergic asthma and lower value on increased resource use. *Remarks:* Adults and children (aged o6 years) with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance, if their total serum IgE level is 30–700 IU mL^{-1} (in three studies the range was wider at 30–1300 IU mL^{-1}). Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilisation, and improvement in quality of life. If a patient does not respond within 4 months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial. ***Question:*** **Should methotrexate be used in the treatment of severe asthma?** *Recommendation* We suggest that clinicians do not use methotrexate in adults or children with severe asthma (conditional recommendation, low quality evidence). *Values and preferences* This recommendation places a relatively higher value on avoiding adverse effects of methotrexate and a relatively lower value on possible benefits from reducing the dose of systemic corticosteroids. *Remarks:* Evidence from randomised trials is only available for adults. Because of the probable adverse effects of methotrexate and need for monitoring therapy we suggest that any use of methotrexate is limited to specialised centres and only in patients who require daily OCS. If a decision to use methotrexate is made, a chest radiograph, complete blood count with differential and platelets, liver function tests, serum creatinine and DLCO, are recommended prior to and after commencing therapy.
SIGN, 2014 [14]. British guideline on the management of asthma	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.

Systematische Literaturrecherche in 2013 (erste Version aus 2003, seit 2008 jährliche Updates)

LoE	
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
GoR	
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

	STEP 4: POOR CONTROL ON MODERATE DOSE OF INHALED STEROID + ADD-ON THERAPY: addition of fourth drug In a small proportion of patients asthma is not adequately controlled on a combination of shortacting β2 agonist as required, inhaled steroid (800 micrograms BDP daily), and an additional drug, usually a long-acting β2 agonist. There are very few clinical trials in this specific patient group to guide management. The following recommendations are largely based on extrapolation from trials of add-on therapy to inhaled steroids alone. If control remains inadequate on 800 micrograms BDP daily (adults) of an inhaled steroid plus a long-acting $\beta_2$agonist, consider the following interventions: - increasing inhaled corticosteroids to 2,000 micrograms BDP/day (adults) or 800 micrograms BDP/day (children 5-12 years)* - leukotriene receptor antagonists - theophyllines - slow release β_2 agonist tablets, though caution needs to be used in patients already on long-acting β_2 agonists. * at high doses of inhaled corticosteroid via pMDI, a spacer should be used. (Empfehlungsgrad D). Long-acting muscarinic antagonists appear to be as effective as salmeterol in the short term and may be superior to doubling the dose of ICS in fixed airways obstruction. Longer term studies are required to confirm this evidence. There would also appear to be benefit in adding tiotropium to ICS and salmeterol in patients who remain symptomatic despite these medications. There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines and β2 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 step 5, 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 doses ICS (greater than 800 micrograms/ day) before moving to step 5. (Good Practice Points) STEP 5: continuous or frequent use of oral steroids - The aim of treatment is to control asthma using the lowest possible doses of medication. - Some patients with very severe asthma not controlled at step 4 with high dose inhaled corticosteroids, and who have also been tried on or are still taking Long-acting β-agonists, leukotriene antagonists or theophyllines, require regular long term steroid tablets. - In adults, the recommended method of eliminating or reducing the dose of steroid tablets is inhaled steroids, at doses of up to 2,000 micrograms/day, if required. (Empfehlungsgrad A) - In children aged 5–12, consider very carefully before going above an inhaled corticosteroid dose of 800 micrograms/day. (Empfehlungsgrad D)

- There is a role for a trial of treatment with long-acting β2 agonists, leukotriene receptor antagonists, and theophyllines for about six weeks. They should be stopped if no improvement in steroid dose, symptoms or lung function is detected. (Empfehlungsgrad D)

Anti IgE monoclonal antibody

Omalizumab is a humanised monoclonal antibody which binds to circulating IgE, markedly reducing levels of free serum IgE. In adults and children over 6 years of age, it is licensed in the UK with the following indication; patients on high-dose inhaled steroids and long-acting β2 agonists who have impaired lung function are symptomatic with frequent exacerbations, and have allergy as an important cause of their asthma. Omalizumab is given as a subcutaneous injection every two to four weeks depending on dose. The total IgE must be <1,300 international units (IU)/ml for children over six years of age. In adults and children >12 years, the licensed indication is a IgE up to 1,500 IU/ml but there is no published data to support its efficacy and safety above 700 IU/ml.

➔ Omalizumab treatment should only be initiated in specialist centres with experience of evaluation and management of patients with severe and difficult asthma. (Good Practice Points)

Patients on oral steroids not previously tried on inhaled therapy

For patients who are on long term steroid tablets and have not been tried on adequate doses of inhaled medication an aim is to control the asthma using the lowest possible dose of oral steroid or, if possible, to stop long term steroid tablets completely.

Inhaled steroids are the most effective drug for decreasing requirement for long term steroid tablets.

There is limited evidence for the ability of long-acting β_2 agonists, theophyllines, or leukotriene receptor antagonists to decrease requirement for steroid tablets, but they may improve symptoms and pulmonary function

➔ In adults, the recommended method of eliminating or reducing the dose of steroid tablets is inhaled steroids, at doses of up to 2,000 micrograms/day, if required. (Empfehlungsgrad A)

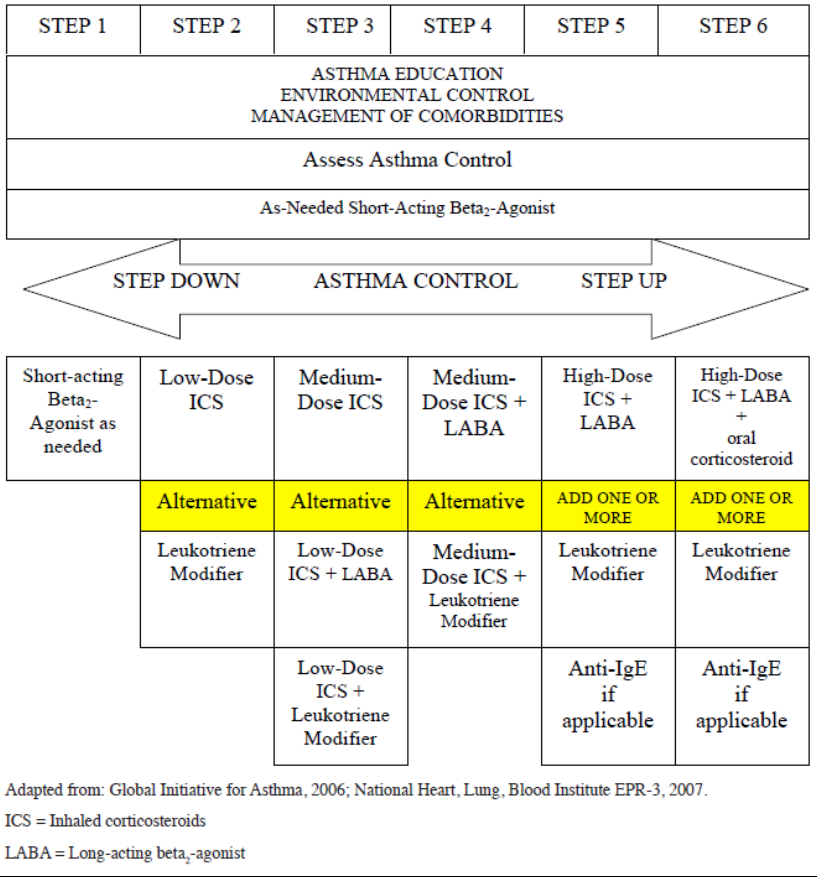
➔ There is a role for a trial of treatment with long-acting β2 agonists, leukotriene receptor antagonists, and theophyllines for about six weeks. They should be stopped if no improvement in steroid dose, symptoms or lung function is detected. (Empfehlungsgrad D)

ASTHMA IN ADOLESCENTS

Adolescence is the transitional period of growth and development between puberty and adulthood, defined by the World Health Organisation (WHO) as between 10 and 19 years of age

PHARMACOLOGICAL MANAGMENT

Specific evidence about the pharmacological management of adolescents with asthma is limited and is usually extrapolated from paediatric and adult studies. Recommendations for pharmacological

	management of asthma in children and adults can be found in section 6. Anmerkung FB Med: Die Patienten werden nach Alter in 3 Gruppen eingeteilt: <5 Jahre, 5-12 und >12 Jahre. ➔ Keine Differenzierung zwischen 12-18 und erwachsenen Patienten.
ICSI, 2012 [15]. Diagnosis and management of asthma	ICSI = Institute for Clinical Systems Improvement
	Methodik 1. Syst. Literaturrecherche im Suchzeitraum 2009-2011, Stand Juli 2012 als Update einer älteren Version 2. LoE (nach GRADE) **High Quality Evidence** = Further research is very unlikely to change our confidence in the estimate of effect. **Moderate Quality Evidence** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low Quality Evidence** = 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 or any estimate of effect is very uncertain 3. GoR – keine Angaben
	Empfehlungen  Adapted from: Global Initiative for Asthma, 2006; National Heart, Lung, Blood Institute EPR-3, 2007. ICS = Inhaled corticosteroids LABA = Long-acting beta$_2$-agonist

Primärstudien zu Tiotropium

GINA Update 2015: Die erweiterten Empfehlungen in Stufe 4 und 5 um Tiotropium basieren auf drei RCTs (Evidenz B: RCTs, limited body of data)

Kerstjens, 2012 [11]. Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy.	**Zielsetzung/Fragestellung** ClinicalTrials.gov numbers: *NCT00772538 and NCT00776984* The primary objective of each trial is to evaluate the long term efficacy of tiotropium over placebo on top of usual care in patients with severe persistent asthma as determined by pulmonary function testing, effects on asthma exacerbations, effects on quality of life, on asthma control and health care resource utilisation. The secondary objective of each trial is to compare the long term safety of tiotropium with placebo in this patient population. **Methodik:** - The two replicate trials had a randomized, doubleblind, placebo-controlled, parallel-group design, with a 48-week study period. - They were conducted between October 2008 and July 2011 in 15 countries (listed in the Supplementary Appendix) and were performed in accordance with the provisions of the Declaration of Helsinki. - The protocols were approved by the institutional review board at each participating center. **Population:** - Eligible patients were between the ages of 18 and 75 years and had a 5-year or longer history of asthma that was diagnosed before the age of 40 years. - N=912 patients underwent randomization - N=409 patients receiving tiotropium (211 in trial 1 and 198 in trial 2) and 405 patients receiving placebo (202 in trial 1 and 203 in trial 2) **Vergleich:** - tiotropium 5mcg/day over placebo on top of usual care (individual pretrial maintenance asthma therapy consisting of high-dose inhaled glucocorticoids and LABAs) - An open-label metered-dose inhaler of salbutamol (100 µg per puff) or albuterol (90 µg per puff) was provided as rescue medication for use during the trials **Endpunkte:** *Primary Outcome Measures:* - Peak Forced Expiratory Volume in 1 Second (FEV1) Response Within 3 Hours Post Dosing (0-3h) After a Treatment Period of 24 Weeks. [Time Frame: Baseline and 24 weeks]

	Peak FEV1 0-3h response was defined as the difference between the maximum FEV1 measured within the first 3 hours post dosing after a treatment period of 24 weeks and the FEV1 baseline measurement (10 minutes before the first dose of trial medication). Mixed Model Repeated Measure (MMRM) results. Means are adjusted for treatment, centre, visit, baseline, treatment*visit and baseline*visit. - Trough FEV1 Response Determined After a Treatment Period of 24 Weeks. [Time Frame: Baseline and 24 weeks] The trough FEV1 is defined as the pre-dose FEV1 measured 10 minutes before the last administration of randomised treatment. Trough FEV1 response was defined as the difference between the trough FEV1 measured after a treatment period of 24 weeks and the FEV1 baseline measurement. MMRM results. Means are adjusted for treatment, centre, visit, baseline, treatment*visit and baseline*visit. - Time to First Severe Asthma Exacerbation During the 48-week Treatment of the Pooled Data From the Two Twin Trials NCT00772538 and NCT00776984 [Time Frame: 48 weeks] Severe asthma exacerbations were pre-defined as all asthma exacerbations that required treatment with systemic (including oral) corticosteroids for at least 3 days or (in case of ongoing and pre-existing systemic corticosteroid therapy) that required at least a doubling of the previous daily dose of systemic corticosteroids for at least 3 days. *Secondary Outcome Measures:* - Peak (Within 3 Hours Post-dosing) Forced Vital Capacity (FVC) Response at the End of the 24-week Treatment Period. [Time Frame: Baseline and 24 weeks] - Trough FVC Response at the End of the 24-week Treatment Period. [Time Frame: Baseline and 24 weeks] - FEV1 Area under the Curve (AUC0-3h) Response at the End of the 24-week Treatment Period. [Time Frame: Baseline and 24 weeks] - FVC (AUC0-3h) Response at the End of the 24-week Treatment Period. [Time Frame: Baseline and 24 weeks] - Peak FEV1 0-3h Response at the End of the 48-week Treatment Period. [Time Frame: Baseline and 48 weeks] - Trough FEV1 Response at the End of the 48-week Treatment Period. [Time Frame: Baseline and 48 weeks] - AUC0-3h FEV1 Response at the End of the 48-week Treatment Period. [Time Frame: Baseline and 48 weeks] - Peak FVC 0-3h Response at the End of the 48-week Treatment Period. [Time Frame: Baseline and 48 weeks] - Trough FVC Response at the End of the 48-week Treatment Period. [Time Frame: Baseline and 48 weeks] - FVC AUC0-3h Response at the End of the 48-week

	Treatment Period. [Time Frame: Baseline and 48 weeks] - Mean Pre-dose Morning Peak Expiratory Flow (PEFa.m.) Response (Diary Data) of Last-7-days-before-week-24-visit [Time Frame: Baseline and last 7 days before week 24 visit] - Mean Pre-dose Evening Peak Expiratory Flow (PEFp.m.) Response (Diary Data) of Last-7-days-before-week 24-visit. [Time Frame: Baseline and last 7 days before week 24 visit] - Mean Pre-dose FEV1 a.m. Response (Diary Data) of Last-7-days-before-week 24-visit. [Time Frame: Baseline and last 7 days before week 24 visit] - Mean Pre-dose FEV1-p.m.Response (Diary Data) of Last-7-days-before-week 24-visit. [Time Frame: Baseline and last 7 days before week 24 visit] - Mean PEF Variability Response (Absolute Difference Between Morning and Evening PEF Value Divided by Their Mean) of Last-7-days-before-week 24-visit. [Time Frame: Baseline and last 7 days before week 24 visit] - Time to First Severe Asthma Exacerbation During the 48-week Treatment. [Time Frame: 48 weeks] - Number of Asthma Exacerbations Per Patient During the 48-week Treatment Period. [Time Frame: 48 weeks] - Number of Severe Asthma Exacerbations Per Patient During the 48-week Treatment Period. [Time Frame: 48 weeks] - Number of Patients with at Least One Asthma Exacerbation During the 48-week Treatment Period. [Time Frame: 48 weeks] - Number of Patients With at Least One Severe Asthma Exacerbation During the 48-week Treatment Period. [Time Frame: 48 weeks] - Time to First Hospitalisation for Asthma Exacerbation During the 48-week Treatment Period. [Time Frame: 48 weeks] - Number of Hospitalisations for Asthma Exacerbations Per Patient During the 48-week Treatment Period. [Time Frame: 48 weeks] - Number of Patients with at Least One Hospitalisation for Asthma Exacerbation During the 48-week Treatment Period. [Time Frame: 48 weeks] - Quality of Life as Assessed by Standardised Asthma Quality of Life Questionnaire (AQLQ(S)) at the End of the 24-week Treatment Period. [Time Frame: 24 weeks] - AQLQ(S) Total Score at the End of the 48-week Treatment Period. [Time Frame: 48 weeks] - Asthma Control as Assessed by Asthma Control Questionnaire (ACQ) at the End of the 24-week Treatment Period. [Time Frame: 24 weeks] - ACQ at the End of the 48-week Treatment Period. [Time Frame: 48 weeks] - Asthma Symptom Free Days Response During the Last-7-days-before-week-24-visit. [Time Frame: Baseline and last 7 days before week 24 visit]

- Mean Pro Re Nata (as Needed, PRN) Rescue Medication Use Response during the Last-7-days-before-week-24-visit. [Time Frame: Baseline and last 7 days before week 24 visit]

Ergebnisdarstellung:
Primary End Points
Lung Function:

- Airflow obstruction was significantly reduced with the addition of tiotropium, as compared with the addition of placebo.
- At 24 weeks, the mean (±SE) difference between the tiotropium group and the placebo group in the change in the adjusted peak FEV1 from baseline in the first 3 hours after the administration of tiotropium was 86±34 ml in trial 1 (P = 0.01) and 154±32 ml in trial 2 (P<0.001) (Fig. 2A and 2B).
- The between-group difference in change from baseline in the trough FEV1 at 24 weeks was also significantly greater for patients in the tiotropium group than for those in the placebo group: 88±31 ml in trial 1 (P = 0.01) and 111±30 ml in trial 2 (P<0.001)

Fig 2A:

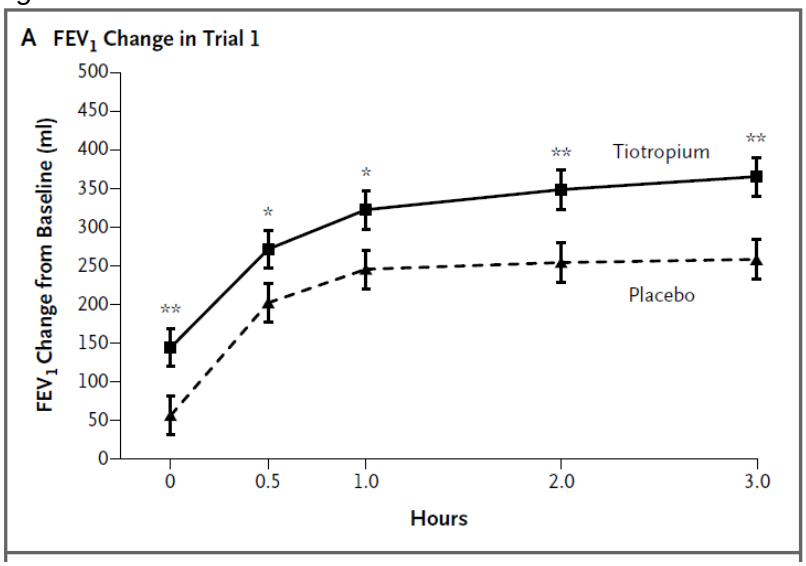
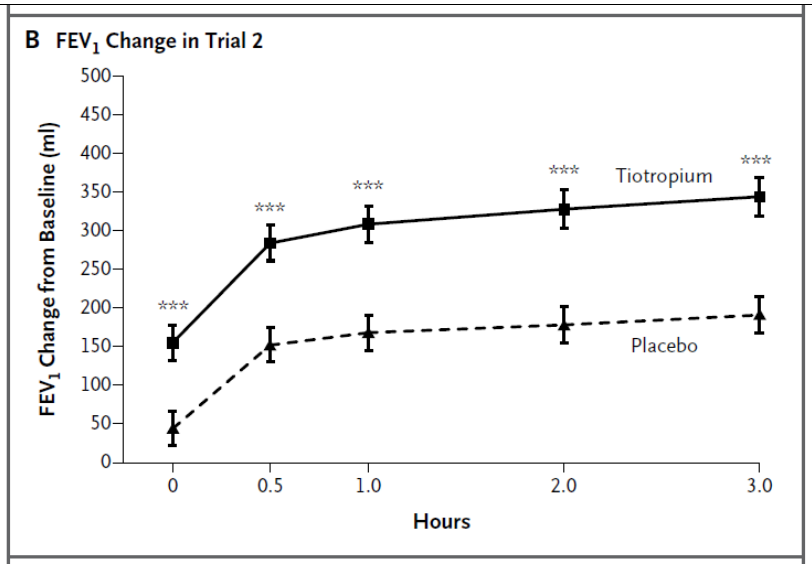


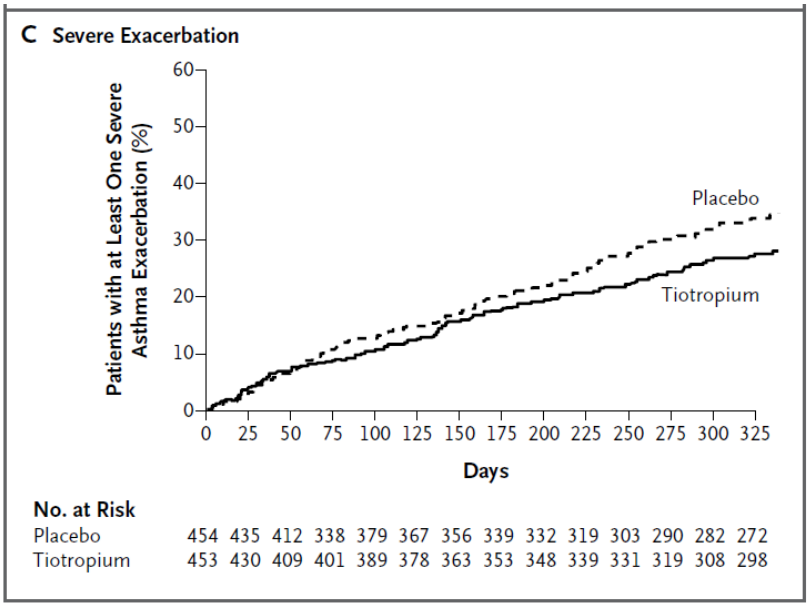
Fig 2B:



Severe Exacerbations:

- The time to the first exacerbation (the primary end point) was increased by 56 days with tiotropium as compared with placebo (282 days vs. 226 days, representing the time until at least 25% of the patients [first quartile] had a first severe exacerbation), corresponding to a reduction of 21% in risk (hazard ratio, 0.79; 95% confidence interval [CI], 0.62 to 1.00; P = 0.03) (Fig. 2C).

FIG 2C:



Key Prespecified Secondary End Points

- At week 24, there was significant improvement in spirometric measurements among patients in the tiotropium group, as compared with those in the placebo group

Adverse Events

- Adverse events were reported in 73.5% of patients in the

	tiotropium group and 80.3% of patients in the placebo group - Serious adverse events were reported for 77 patients: 37 (8.1%) in the tiotropium group and 40 (8.8%) in the placebo group **Fazit der Autoren:** In patients with poorly controlled asthma despite the use of inhaled glucocorticoids and LABAs, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation.
Kerstjens, 2011 [10]. Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial.	**Zielsetzung/Fragestellung:** ClinicalTrials.gov numbers: *NCT00365560* To compare the efficacy and safety of 2 doses of tiotropium (5 and 10 mg daily) administered through the Respimat inhaler with placebo as add-on therapy in patients with uncontrolled severe asthma (Asthma Control Questionnaire score, >1.5; postbronchodilator FEV1, <80% of predicted value) despite maintenance treatment with at least a high-dose inhaled corticosteroid plus a long-acting β_2-agonist. **Methodik:** - This randomized, double-blind, placebo-controlled, crossover study with three 8–week treatment periods was conducted in accordance with the Declaration of Helsinki. - After a 2-week run-in period, eligible patients were randomized and entered a 24–week, double-blind treatment period. - Visits occurred at the start of the trial (screening), at randomization (baseline), and at the end of each treatment period. - There was no washout period between treatments. **Population:** Patients were outpatients aged 18 to 75 years with at least a 5-year history of asthma and a current diagnosis of severe persistent asthma (GINA step 4). - N=107 patients were randomized - N=100 patients completed all 3 treatment periods **Vergleich:** - 5 or 10 mg of tiotropium or matching placebo administered as 2 actuations once daily through the Respimat inhaler as add-on therapy in patients with uncontrolled severe asthma (Asthma Control Questionnaire score, >1.5; postbronchodilator FEV1, <80% of predicted value) despite maintenance treatment with at least a high-dose inhaled corticosteroid plus a long-acting β_2-agonist - A salbutamol metered-dose inhaler (100 mg per puff) was provided as rescue medication throughout the trial **Endpunkte:** *Primary Outcome Measures:* - The primary efficacy endpoint is the FEV_1 response (within

3 hours post dosing) determined at the end of the 8-week treatment period

Secondary Outcome Measures:

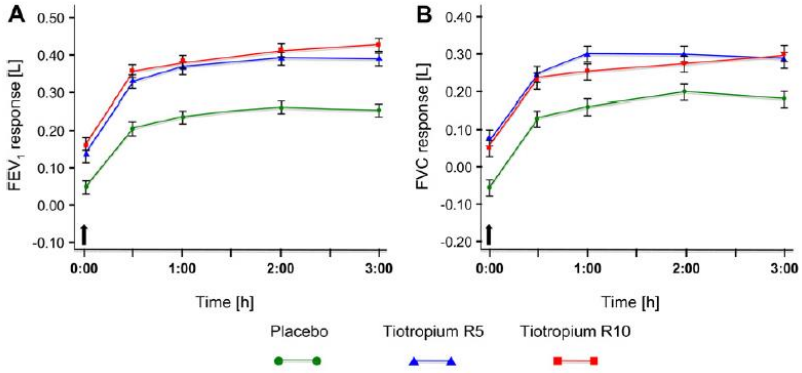
- FEV1 and FVC AUC 0-3h (in a subset 0-24h) PEF, use of rescue medication, daytime and nocturnal symptoms etc.

Ergebnisse:

FEV_1 response:

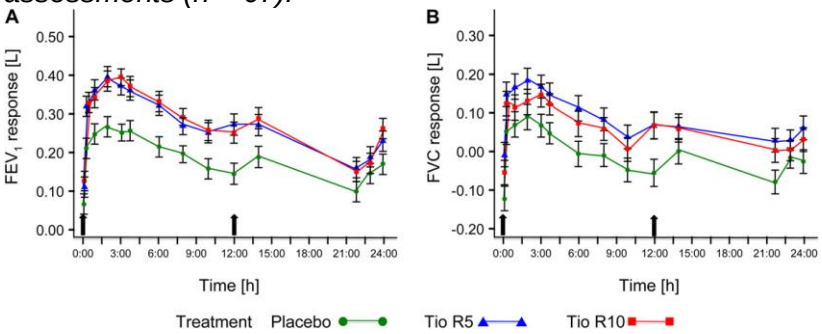
- The adjusted mean peak FEV1 response in the first 3 hours after dosing at the end of the 8–week treatment period was significantly superior to placebo with both tiotropium doses (5-µg difference from placebo, 139 mL [95% CI, 96-181 mL], P <.0001

FIG 2: FEV1 (A) and FVC (B) responses relative to baseline values within 3 hours after dosing after 8 weeks of treatment:



- 24-hour spirometric assessments in a subgroup of patients (n 5 67) also showed significant improvements in FEV1 for both active treatments compared with placebo (Fig 3).
- FEV1 AUC0-24h was significantly greater with both doses compared with placebo (5- µ g difference from placebo, 86 mL [95% CI, 41-132 mL], P5 .0012; 10-mg difference from placebo, 90 mL [95% CI, 38-142 mL], P <.001).
- no statistical difference between the active treatments.

FIG 3: Twenty-four-hour FEV1 (A) and FVC (B) responses as shown in Fig 2 in the subgroup of patients with 24-hour assessments (n = 67):



Adverse events:

	- Adverse events were reported in 40%, 42%, and 50% of patients receiving placebo, 5 mg of tiotropium, and 10 µg of tiotropium, respectively. - Serious adverse events were reported for 5 patients: 2 while receiving placebo (osteoarthritis and an asthma exacerbation), 2 while receiving 5 mg of tiotropium (pneumonia/pleurisy, treatment discontinued, and gastritis), and 1 while receiving 10 µg of tiotropium (angioedema) **Fazit der Autoren:** The addition of once-daily tiotropium to asthma treatment, including a high-dose inhaled corticosteroid plus a long-acting β_2-agonist, significantly improves lung function over 24 hours in patients with inadequately controlled, severe, persistent asthma.
Peters, 2010 [13]. Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma	– Nicht dargestellt aufgrund Studiendesign und Dosierung

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 30.04.2015**

#	Suchfrage
1	MeSH descriptor: [Asthma] explode all trees
2	asthma*:ti (Word variations have been searched)
3	#1 or #2
4	#1 or #2 Publication Year from 2010 to 2015, in Cochrane Reviews (Reviews only), Other Reviews and Technology Assessments

SR, HTAs in Medline (PubMed) am 30.04.2015

#	Suchfrage
1	"asthma/therapy"[MeSH Major Topic]
2	asthma*[Title]
3	((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract]) OR drug*[Title/Abstract]
4	(#2) AND #3
5	(#1) OR #4
6	(#5) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	(#5) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	(#6) OR #7
9	(#8) AND ("2010/04/01"[PDAT] : "2015/04/30"[PDAT])

Leitlinien in Medline (PubMed) am 30.04.2015

#	Suchfrage
1	asthma[MeSH Major Topic]
2	asthma*[Title]
3	(#1) OR #2
4	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR

	Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title])
5	(#3) AND #4
6	(#5) AND ("2010/04/01"[PDAT] : "2015/04/30"[PDAT])

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