Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

# und

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

# Vorgang: 2020-B-177 Beclometason/ Formoterol/ Glycopyrronium

Stand: August 2020

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

**Beclometason/Formoterol/Glycopyrronium**
**zur Behandlung von Asthma**

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
|---|---|
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | *siehe Übersicht II:* Zugelassene Arzneimittel im Anwendungsgebiet: |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | Nicht angezeigt |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL):<br>- Mepolizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 21. Juli 2016)<br>- Reslizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 6. Juli 2017)<br>- Benralizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 2. August 2018)<br>- Dupilumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 20. Februar 2020)<br>Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL) - Anlage IV: Therapiehinweis zu Omalizumab (Beschluss vom 17. Dezember 2015)<br><br>DMP-Richtlinie (DMP-RL): Asthma |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigenTherapie im Anwendungsgebiet gehören. | *siehe Evidenzsynopse* |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Beclometason/Formoterol/Glycopyrronium<br>R03AL09<br>Trimbow® | Geplantes Anwendungsgebiet laut Beratungsanforderung:<br>Maintenance treatment in adult patients with asthma who are not adequately treated by a com-bination of an inhaled corticosteroid and a long-acting beta2-agonist or who are already treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist plus a long-acting muscarinic antagonist |
| **Beta-2-Sympathomimetika (inhalativ; kurzwirkend) (SABA)** | |
| Salbutamol<br>R03AC02<br>Salbutamol CT | Zur Verhütung und Behandlung von Atemwegserkrankungen mit reversibler Obstruktion, wie z. B. Asthma bronchiale oder chronische Bronchitis.<br>Hinweis:<br>Eine längerfristige Behandlung soll symptomorientiert und nur in Verbindung mit einer entzündungshemmenden Dauertherapie erfolgen.<br>(FI Salbutamol CT, Stand 04/2015) |
| Fenoterol<br>R03AC04<br>Berotec N® | - Symptomatische Behandlung von akuten Asthmaanfällen.<br>- Prophylaxe von belastungsinduziertem Asthma bronchiale.<br>- Symptomatische Behandlung von Asthma bronchiale allergischer und nichtallergischer Ursache und/oder anderen Erkrankungen, die mit einer reversiblen Obstruktion der Atemwege einhergehen, z.B. chronisch obstruktive Bronchitis mit und ohne Lungenemphysem.<br>Hinweis:<br>- Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen.<br>(FI Berotec, Stand 09/2015) |
| **Beta-2-Sympathomimetika (systemisch; kurzwirkend) (SABA)** | |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Reproterol<br>R03CC14 Bronchospasmin | Zur kurzfristigen Behandlung des schweren bronchospastischen Anfalls und des Status asthmaticus.<br>(FI Bronchospasmin, Stand 02/2016) |
| **Beta-2-Sympathomimetika (inhalativ; langwirkend) (LABA)** | |
| Salmeterol<br>R03AC12<br>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).<br>Gleichzeitig soll beim Asthma bronchiale eine regelmäßige Therapie mit entzündungshemmenden Arzneimitteln (inhalative und/ oder orale Kortikoide) sichergestellt werden, da Serevent kein Ersatz hierfür ist. Diese Behandlung mit Kortikoiden ist regelmäßig weiterzuführen.<br><u>Warnhinweis:</u><br>Serevent Dosier-Aerosol und Serevent Diskus sollen nicht für die Akutbehandlung eines Asthmaanfalls eingesetzt werden.<br>(FI Serevent ® Dosier-Aerosol, Stand 02/2015) |
| Formoterol<br>R03AC13<br>Formoterol CT® | - Symptomatische Langzeitbehandlung des chronischen mäßigen bis schweren Asthma bronchiale in Kombination mit einer entzündungshemmenden Dauertherapie (z. B. Kortikosteroide).<br>- […]<br>Hinweis:<br>Bisher liegen keine Hinweise darauf vor, dass Formoterol eine Behandlung mit Kortikosteroiden ersetzen kann. Bei Asthma bronchiale muss Formoterol in jedem Fall mit Kortikosteroiden zur Inhalation kombiniert werden.<br>(FI Formoterol-CT, Stand 06/2015) |
| **Beta-2-Sympathomimetika (oral; kurz-, langwirkend)** | |
| Terbutalin<br>R03AC03<br>Aerodur Turbohaler® | Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z.B. Asthma bronchiale, chronische Bronchitis und Blählunge (Lungenemphysem).<br>(FI Aerodur Turbohaler, Stand 07/2015) |
| Salbutamol | Verhütung und Behandlung von Atemwegserkrankungen bei Erwachsenen und Kindern ab 2 Monaten, |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| R03CC02<br>Salbubronch® | die mit einer Verengung der<br>Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen), wie z. B. bei Asthma<br>bronchiale, chronischer Bronchitis und Blählunge (Lungenemphysem).<br><br>Hinweis<br>SALBUBRONCH Elixier ist nur für Patienten, die nicht symptomorientiert mit inhalativen β2-Sympathomimetika behandelt werden<br>können, geeignet. Eine Behandlung mit SALBUBRONCH Elixier sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie<br>mit Glukokortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen. (FI SALBUBRONCH® Elixier, Stand 02/2014) |
| Bambuterol<br>R03CC12<br>Bambec® | Verhütung und Behandlung von Atemwegserkrankungen, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur<br>einhergehen (obstruktive Atemwegserkrankungen).<br>Hinweis:<br>Bambec ist nur für Patienten, die nicht symptomorientiert mit inhalativen Beta-2-Sympathomimetika behandelt werden können, geeignet. Bei Patienten mit Asthma bronchiale sollte eine Behandlung mit Bambuterol in Ergänzung zu einer entzündungshemmenden Dauertherapie, z. B. mit Glukokortikoiden zur Inhalation oder Leukotrien- Rezeptor-Antagonisten, erfolgen.<br>(FI Bambec®, Stand 05/2016) |
| Clenbuterol<br>R03CC13<br>Spiropent® | Symptomatische Behandlung chronisch obstruktiver Atemwegserkrankungen mit reversibler Atemwegsverengung, wie z. B. Asthma bronchiale oder chronisch obstruktive Bronchitis mit und ohne Emphysem.<br>Hinweis<br>Spiropent Tabletten sind nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Eine Behandlung mit Spiropent Tabletten sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie mit Kortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen.<br>(FI Spiropent®, Stand 03/2014) |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Clenbuterol/ Ambroxol<br>R03CC63<br>Spasmo Mucosolvan Saft® | Akute und chronische Atemwegserkrankungen, die mit spastischen Verengungen, veränderter Sekretbildung und gestörtem Sekrettransport einhergehen, insbesondere spastische Bronchitiden, Emphysembronchitiden und Asthma bronchiale.<br>Hinweis<br>Spasmo-Mucosolvan Saft ist nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Sofern eine Dauerbehandlung eines Asthma bronchiale mit Spasmo-Mucosolvan Saft erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie (z. B. mit Kortikoiden) erfolgen. (FI Spasmo-Mucosolvan® Saft, Stand 03/2016) |
| **Anticholinergika (inhalativ)** | |
| Tiotropiumbromid<br>R03BB04<br>Spiriva® Respimat® | […]<br>Spiriva Respimat ist indiziert als zusätzlicher dauerhaft einzusetzender Bronchodilatator bei Patienten ab 6 Jahren mit schwerem<br>Asthma, die im Vorjahr mindestens eine schwere Exazerbation erfahren haben (siehe Abschnitte 4.2 und 5.1). (FI Spiriva® Respimat®, Stand 10/2018) |
| **Inhalative Corticosteroide (ICS)** | |
| Beclometason<br>R03BA01<br>Junik® | zur Behandlung von Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei: Asthma bronchiale, chronisch obstruktiver Bronchitis<br>[…]<br>(FI Junik®, Stand 03/2013) |
| Budesonid<br>R03BA02<br>BUDECORT® | Zur Behandlung persistierender Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei:<br>- Asthma bronchiale<br>- Chronisch obstruktiver Bronchitis.<br>(FI Budecort® 200 Novolizer®, Stand 06/2014) |
| Ciclesonid<br>R03BA08<br>ALVESCO® | Zur Behandlung von persistierendem Asthma bei Erwachsenen und Jugendlichen (ab 12 Jahren).<br><br>(FI Alvesco®, Stand 04/2016) |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Fluticason<br>R03BA05<br>FLUTIDE® | Dauerbehandlung eines persistierenden Asthma bronchiale aller Schweregrade.<br>Hinweis:<br>Fluticason-17-propionat ist nicht für die Akutbehandlung eines Asthmaanfalles geeignet.<br>(FI Flutide®, Stand 07/2016) |
| Mometason<br>R03BA07<br>ASMANEX® | Bei Erwachsenen und Jugendlichen ab 12 Jahren zur regelmäßigen Behandlung, um anhaltendes Asthma bronchiale zu kontrollieren.<br><br>(FI ASMANEX® Twisthaler®, Stand 10/2014) |
| **Corticosteroide (systemisch, oral)** | |
| Prednisolon,<br>Prednisolon ratiopharm® | […]<br>Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren.<br>(FI Prednisolon-ratiopharm®, Stand 08/2010) |
| Prednison,<br>Prednison ratiopharm® | […]<br>Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren.<br>FI Prednison-ratiopharm®, Stand 09/2011) |
| **Weitere** | |
| Theophyllin (systemisch)<br>R03DA04<br>z.B. Theophyllin retard-ratiopharm® | Bronchospasmolytikum/Antiasthmatikum<br>Behandlung und Verhütung von Atemnotzuständen aufgrund von Verengung der Atemwege (Bronchokonstriktion) bei Patienten mit persistierendem Asthma bronchiale oder mittel- bis schwergradiger obstruktiver Atemwegserkrankung (z. B. chronische Bronchitis und Lungenemphysem).<br>Hinweis:<br>Es wird empfohlen die Dauertherapie dieser Erkrankungen mit Theophyllin in Kombination mit anderen die Bronchien erweiternden und entzündungshemmenden Arzneimitteln, wie z. B. lang wirksamen β-Sympathomimetika und Glukocortikoiden durchzuführen. Arzneimittel mit verzögerter Theophyllin-Freisetzung, wie Theophyllin retardratiopharm®, sind nicht zur Akutbehandlung des Status asthmaticus oder der akuten Bronchospastik bestimmt. Theophyllin sollte nicht als Mittel der ersten Wahl zur Behandlung von Asthma bei Kindern angewendet werden.<br>(FI Theophyllin retard-ratiopharm®, Stand 04/2014) |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Omalizumab R03DX05<br>Xolair® | Xolair wird angewendet bei Erwachsenen, Jugendlichen und Kindern (6 bis < 12 Jahre). Die Behandlung mit Xolair sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE- (Immunglobulin E-) vermittelten Asthma ausgegangen werden kann (siehe Abschnitt 4.2).<br>Erwachsene und Jugendliche (ab 12 Jahren)<br>Xolair wird als Zusatztherapie zur verbesserten Asthmakontrolle bei Patienten mit schwerem persistierendem allergischem Asthma angewendet, die einen positiven Hauttest oder in vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und sowohl eine reduzierte Lungenfunktion (FEV1 < 80 %) haben als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und trotz täglicher Therapie mit hoch dosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta2-Agonisten mehrfach dokumentierte, schwere Asthma-Exazerbationen hatten.<br>(FI Xolair®, Stand 09/2016) |
| Mepolizumab<br>R03DX09<br>Nucala® | Nucala ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei Erwachsenen, Jugendlichen und Kindern ab 6 Jahren (siehe Abschnitt 5.1).<br>(FI Nucala , Stand 08/2018) |
| Reslizumab<br>R03DX08<br>CINQAERO® | CINQAERO wird angewendet als Zusatztherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus einem anderen Arzneimittel zur Erhaltungstherapie nur unzureichend zu kontrollieren ist (siehe Abschnitt 5.1).<br>(FI CINQAERO, Stand 08/2016) |
| Benralizumab<br>R03DX10<br>Fasenra | Fasenra ist angezeigt als Add-on-Erhaltungstherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist (siehe Abschnitt 5.1).<br>(FI Fasenra, Stand 02/2019) |
| Dupilumab<br>D11AH05<br>Dupixent | Dupixent ist angezeigt als Add-on-Erhaltungstherapie bei Erwachsenen und Jugendlichen ab 12 Jahren mit schwerem Asthma mit Typ-2-Inflammation, gekennzeichnet durch eine erhöhte Anzahl der Eosinophilen im Blut und/oder erhöhtes FeNO (siehe Abschnitt 5.1), das trotz hochdosierter inhalativer Kortikosteroide (ICS) plus einem weiteren zur Erhaltungstherapie angewendeten Arzneimittel unzureichend kontrolliert ist. (FI Dupixent, Stand 05/2019) |
| **Kombinationspräparate (ICS/LABA)** | |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Beclometason/ Formoterol R03AK08<br>Foster® | Foster ist angezeigt für die regelmäßige Behandlung von Asthma, bei der die Anwendung eines Kombinationsprodukts (von inhalativem Kortikosteroid und langwirksamem Beta-2-Agonisten) angezeigt ist:<br>• Patienten, die mit inhalativen Kortikosteroiden und inhalativen schnellwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation<br>nicht ausreichend eingestellt sind oder<br>• Patienten, die mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination bereits ausreichend<br>eingestellt sind. (FI Foster, Stand 12/2016) |
| Budesonid/ Formoterol R03AK07<br>DUORESP Spiromax® | DuoResp® Spiromax® wird nur bei Erwachsenen ab 18 Jahren angewendet. 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. (FI DuoResp® Spiromax®, Stand 07/2016) |
| Salmeterol/ Fluticason R03AK06<br>Viani® | Viani Diskus ist indiziert für die regelmäßige Behandlung von Asthma bronchiale, bei der die Anwendung von langwirksamem Beta2- Agonisten und inhalativem Kortikoid in Kombination angezeigt ist: – 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. (FI Viani®, Stand 04/2015) |
| Formoterol/ Fluticason R03AK11<br>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. (FI flutiform®, Stand 06/2015) |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Vilanterol/ Fluticason R03AK10<br>Relvar® Ellipta® | Relvar Ellipta ist angezeigt für die regelmäßige Behandlung von Asthma bei Erwachsenen und Jugendlichen ab 12 Jahren, bei denen ein Kombinationspräparat (langwirksamer Beta2-Agonist und inhalatives Kortikosteroid) angezeigt ist. Patienten, die mit inhalativen Kortikosteroiden und einer Bedarfsmedikation mit inhalativen kurzwirksamen Beta2-Agonisten nicht ausreichend eingestellt sind. […] (FI Relvar® Ellipta®, Stand 10/2016) |
| **Kombinationspräparate: Anticholininergika/ Beta-2-Sympathomimetikum** | |
| Ipratropiumbromid/ Fenoterol R03AL01<br>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. (FI Berodual®, Stand 10/2014) |

Quellen: AMIS-Datenbank, Fachinformationen

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

## Inhaltsverzeichnis

## Abkürzungsverzeichnis

| | |
|---|---|
| ACQ | Asthma Control Questionnaire |
| AE | adverse events |
| anti-IL-5 | anti-interleukin-5 |
| AQLQ | Asthma Quality of Life Questionnaire |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| BUD | budesonide |
| CI | confidence interval |
| F | formoterol |
| FEV1 | forciertes exspiratorisches Volumen (engl. Forced Expiratory Volume in 1 second) |
| FP | fluticasone |
| FVC | Forced vital capacity |
| GIN | Guidelines International Network |
| GINA | Global Initiative for Asthma |
| GoR | Grade of Recommendations |
| HR | Hazard Ratio |
| ICS | Inhaled Corticosteroid |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| IV | intravenous |
| KI | Konfidenzintervall |
| LABA | long-acting beta2-agonists |
| LAMA | long-acting muscarinic antagonist |
| LoE | Level of Evidence |
| NICE | National Institute for Health and Care Excellence |
| NMA | Netzwerkmetaanalyse |
| OCS | orales Glucocorticosteroid |
| OR | Odds Ratio |
| PEF | Peak expiratory flow |
| RCTs | randomized controlled trials |

| | |
|---|---|
| RR | Relatives Risiko |
| SABA | short-acting beta-agonist |
| SAE | Serious adverse events |
| SAL | salmeterol |
| SC | subcutaneous |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SiT | single inhaler therapy |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |

# 1 Indikation

Erhaltungstherapie bei erwachsenen Patienten mit Asthma, die nicht adäquat durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten behandelt werden oder die bereits durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten plus einem langwirkenden Muskarin-Antagonisten behandelt werden

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Asthma* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.04.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1370 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 35 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

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# 3 Ergebnisse

## 3.1 G-BA-Beschlüsse/IQWiG-Berichte

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**G-BA, 2015 [12].**

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

**Anwendungsgebiet**

I. Der Therapiehinweis zu Omalizumab in Anlage IV der AM-RL wird wie folgt geändert:

1. In der Überschrift werden nach der Angabe „(Xolair®)“ die Wörter „bei Asthma bronchiale“ eingefügt.

2. Der Abschnitt „Zugelassene Anwendungsgebiete“ wird wie folgt geändert:

a. Absatz 1 wird in Ziffer 2. „Kindern (6 bis < 12 Jahre)“ wie folgt geändert:

aa. Dem Wortlaut im zweiten Spiegelstrich wird das Wort „und“ angefügt.

bb. Im dritten Spiegelstrich werden die Wörter „als auch“ gestrichen.

b. Nach Absatz 1 wird folgender Absatz 2 eingefügt:

„Omalizumab (150 mg Injektionslösung) ist zugelassen als Zusatztherapie für die Behandlung der Jugendlichen (ab 12 Jahren) mit unzureichendem Ansprechen Behandlung mit H1-Antihistaminika.1“

c. Der Erläuterungstext zu Fußnote „1“ wird wie folgt gefasst: „Dieses Indikationsgebiet ist nicht Gegenstand dieses Therapiehinweises.“

d. Der bisherige Absatz 2 wird zu Absatz 3.

e. Nach Absatz 3 (neu) wird folgender Absatz 4 angefügt:

„Ein im Juni 2000 gestellter Antrag auf Zulassung für die Behandlung der saisonalen allergischen Rhinitis ist aufgrund der negativen Bewertung durch die europäische Zulassungsbehörde vom Hersteller zurückgezogen worden. In diesem Anwendungsgebiet ist ein Off-Label-Use grundsätzlich Rechtsprechung des Bundessozialgerichts ausgeschlossen.

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

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

**Anwendungsgebiet**

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

**Vergleichstherapie**

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

inhalativen Corticosteroiden und langwirksamen Bronchodilatatoren (LABA) und ggf. der oralen Corticosteroidtherapie.

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

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

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

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**G-BA, 2017[17].**

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

**Anwendungsgebiet**

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

**Zweckmäßige Vergleichstherapie**

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

eine patientenindividuelle Therapieeskalation:

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

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

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

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

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

**G-BA, 2018 [16].**

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

**Anwendungsgebiet**

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

**Vergleichstherapie**

eine patientenindividuelle Therapieeskalation:

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

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

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

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

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

Ein Zusatznutzen ist nicht belegt.

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

Anhaltspunkt für einen geringen Zusatznutzen.

**G-BA, 2019 [14].**

Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL) zuletzt geändert am 17. Januar 2019, Inkrafttreten: 01. April 2019

**Fazit**

1.5.8.1 Dauertherapie bei Erwachsenen

Vorrangig sollen zur Dauertherapie die folgenden Wirkstoffgruppen verwendet werden:

1. Basistherapie

- inhalative Glukokortikosteroide,

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

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

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

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

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**G-BA, 2019 [15].**

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

**Zugelassene Anwendungsgebiete**

Omalizumab ist zugelassen als Zusatztherapie zur verbesserten Asthmakontrolle bei:

<u>Erwachsenen und Jugendlichen (ab 12 Jahren)</u>

- 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:

Der Therapiehinweis bezieht sich ausschließlich auf die Indikation Asthma bronchiale.

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

- schweres persistierendes allergisches Asthma,
- reduzierte Lungenfunktion (FEV1 < 80%),
- positiver Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes und vom Patienten nicht vermeidbares Aeroallergen,
- das Asthma ist IgE-vermittelt mit IgE-Werten zwischen ≥ 76 und ≤ 1500 I.E./ml vor Beginn der Behandlung,
- häufige dokumentierte Symptome während des Tages oder nächtliches Erwachen,
- trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden (entsprechend > 1000 µg pro Tag Beclometason oder Äquivalent) und mindestens einem lang wirkenden inhalativen Beta-2-Agonisten als Kontroller traten
- in den letzten 12 Monaten mindestens zwei unabhängige, dokumentierte schwere Asthmaexazerbationen, die mit systemischen Kortikosteroiden behandelt wurden, oder
- eine Exazerbation, die systemische Kortikosteroidgabe notwendig machte und zur Krankenhausaufnahme bzw. Notfallbehandlung führte, auf.
- das Körpergewicht liegt innerhalb der Grenzen der Dosierungstabelle also ≥ 20 kg und ≤ 150 kg.
- Nichtraucher

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**G-BA, 2020 [13].**

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

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

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

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

**Zweckmäßige Vergleichstherapie**

eine patientenindividuelle Therapieeskalation unter Berücksichtigung der Vortherapie unter Auswahl von:

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

**Fazit / Ausmaß des Zusatznutzens**

Ein Zusatznutzen ist nicht belegt

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

**Zweckmäßige Vergleichstherapie**

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

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

oder

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

**Fazit / Ausmaß des Zusatznutzens**

Ein Zusatznutzen ist nicht belegt

## 3.2 Cochrane Reviews

**Farne HA et al., 2017 [11].**

Anti-IL5 therapies for asthma.

**Fragestellung**

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

**Methodik**

Population:

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

Intervention:

- anti-IL-5 therapy

Komparator:

- Placebo

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

**Ergebnisse**

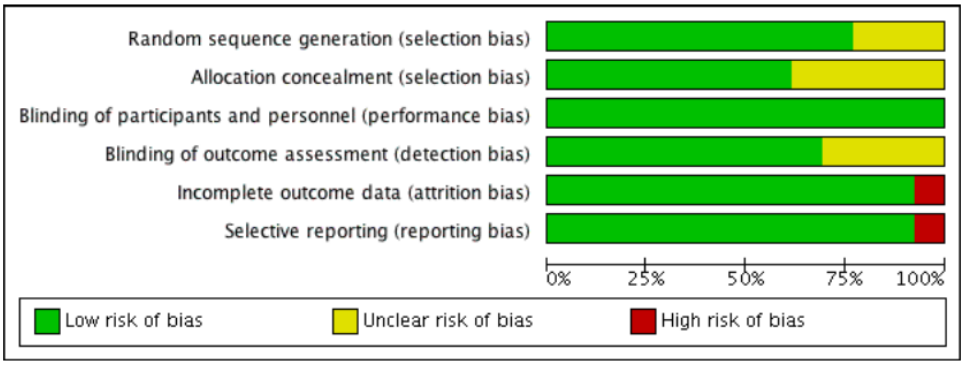
Anzahl eingeschlossener Studien:

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

Qualität der Studien:

- The evidence included in this review is provided by very well-designed studies. We consider these studies to be at low risk of bias in the following important respects: the

procedure that determined who received which treatment, the blinding processes and the clarity of detail concerning participants who did not complete the study. Overall the evidence was high to moderate quality.

- 


Studienergebnisse:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### Anmerkung/Fazit der Autoren

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

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**Kew KM et al., 2015 [23].**

Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting $beta_2$- agonists (LABA) for adults with asthma.

### Fragestellung

To assess the efficacy and safety of adding a LAMA to ICS compared with adding a LABA for adults whose asthma is not well controlled on ICS alone.

### Methodik

Population: adults (aged 18 years or older) whose asthma is not well controlled with ICS alone

Intervention: LAMA add-on

Komparator: LABA add-on

→ Studies involving the addition of the following LAMAs at any dose:

tiotropium (Spiriva HandiHaler or Respimat);

aclidinium bromide (Eklira Genuair);

glycopyrronium bromide (Seebri Breezhaler).

→ Eligible comparison groups were randomised to receive the same dose of ICS as the intervention group, with the addition of any of the following LABAs:

formoterol 12 or 24 mcg twice daily

salmeterol 50 mcg twice daily

vilanterol 22 mcg once daily

Endpunkte:

(1) primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); Any serious adverse event.

(2) sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (in particular, trough forced expiratory volume in one second (FEV1)); Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events

Suchzeitraum (Aktualität der Recherche): bis April 2015

Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs (n= 2049)

Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential, nicht-publizierten Daten

Heterogenität: $I^2$ nach Higgins/Thompson (greater than 30% → they reported it and explored possible causes by pre-specified subgroup analysis)

→ a priori definierte Subgruppen:

Duration of therapy (six months or less, more than six months).

Corticosteroid dose (according to GINA 2014 – defined low, medium and high cut-offs).

Dose and type of LABA (e.g. formoterol 24 mcg, salmeterol 50 mcg).

Dose and type of LAMA (e.g. tiotropium HandiHaler 18 mcg, tiotropium Respimat 5 mcg).

**Ergebnisse**

- 4 Studien eingeschlossen

Patientencharakteristika

- Baseline characteristics, with the exception of percentagemale and mean age, were generally poorly reported across studies.Mean percentage predicted FEV1 at baseline was between 66% and 76% in the three studies reporting it (NCT00350207; NCT00565266; Rajanandh 2014; Rajanandh 2015). Mean ages were all between
- 37 and 45 years.The proportion ofmen and women was fairly balanced within studies reporting this information, and across studies the percentage of men ranged between 33% (NCT00565266) and 65% (LAMA group of Rajanandh 2014).
- All of the studies compared the LAMA, tiotropium, to salmeterol or formoterol, both used as an add-on drug to ICS. NCT01172808 and NCT01172821 were multi-arm twin trials that included separate arms for two doses of tiotropium Respimat, 2.5mcg daily and 5mcg daily.NCT00350207 used tiotropium at 5 mcg daily; NCT00565266, NCT01290874,

Rajanandh 2014, and Rajanandh 2015 used tiotropium HandiHaler 18 mcg daily, but only one of these contributed data to at least one meta-analysis.

Qualitätsbewertung: several studies were given high risk of bias ratings, particularly in the blinding domains and selective reporting, and there was some uncertainty in others, mostly due to insufficient reporting. However, most of the high risk of bias judgements were associated with studies that did not contribute data to the metaanalyses.

Studienergebnisse

**Comparison 1. Long-acting muscarinic antagonists (LAMA) add-on versus long-acting beta$_2$-agonists (LABA) add-on**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations (oral corticosteroid) | 2 | | Odds Ratio (Random, 95% CI) | 1.05 [0.50, 2.18] |
| 2 Asthma Quality of Life Questionnaire (AQLQ) total | 4 | | Mean Difference (Random, 95% CI) | -0.12 [-0.18, -0.05] |
| 3 Serious adverse events (all) | 4 | | Odds Ratio (Random, 95% CI) | 0.84 [0.41, 1.73] |
| 4 Exacerbations (hospital) | 4 | | Odds Ratio (Random, 95% CI) | 0.72 [0.18, 2.92] |
| 5 Trough forced expiratory volume in 1 second ($FEV_1$) (L) | 4 | | Mean Difference (Random, 95% CI) | 0.05 [0.01, 0.09] |
| 6 Peak $FEV_1$ (L) | 3 | | Mean Difference (Random, 95% CI) | Totals not selected |
| 7 Trough peak expiratory flow (PEF) (L/min) | 4 | | Mean Difference (Random, 95% CI) | 5.78 [0.86, 10.71] |
| 8 Trough forced vital capacity (FVC) (L) | 3 | 1745 | Mean Difference (IV, Random, 95% CI) | 0.03 [-0.02, 0.07] |
| 9 Peak FVC (L) | 2 | 1483 | Mean Difference (IV, Random, 95% CI) | -0.00 [-0.04, 0.03] |
| 10 Asthma Control Questionnaire (ACQ) total | 3 | | Mean Difference (Random, 95% CI) | 0.06 [0.00, 0.13] |
| 11 ACQ response | 2 | 1563 | Odds Ratio (M-H, Random, 95% CI) | 0.91 [0.73, 1.13] |
| 12 Adverse events AEs (all) | 3 | 1839 | Odds Ratio (IV, Random, 95% CI) | 1.11 [0.92, 1.35] |
| 13 AEs classified as asthma | 3 | 1839 | Odds Ratio (M-H, Random, 95% CI) | 0.95 [0.74, 1.22] |

**Comparison 3. Long-acting muscarinic antagonists (LAMA) dose head-to-head**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations (oral corticosteroid) | 1 | 1036 | Odds Ratio (M-H, Fixed, 95% CI) | 0.69 [0.40, 1.22] |
| 2 Asthma Quality of Life Questionnaire (AQLQ) total | 2 | 973 | Mean Difference (IV, Random, 95% CI) | 0.01 [-0.09, 0.10] |
| 3 Serious adverse events (SAEs) (all) | 2 | 1036 | Odds Ratio (M-H, Random, 95% CI) | 1.09 [0.47, 2.49] |

**Comparison 4. Sensitivity analysis excluding the cross-over trial**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations (oral corticosteroid) | 1 | | Odds Ratio (IV, Random, 95% CI) | Totals not selected |
| 2 Asthma Quality of Life Questionnaire (AQLQ) total | 3 | 1745 | Mean Difference (IV, Random, 95% CI) | -0.11 [-0.19, -0.03] |
| 3 Serious adverse events (SAEs) (all) | 3 | 1839 | Odds Ratio (IV, Random, 95% CI) | 0.79 [0.30, 2.07] |

- Studies reporting exacerbations requiring OCS showed no difference between the two add-ons, but our confidence in the effect was low due to inconsistency between studies and because the confidence intervals (CI) included significant benefit of either treatment (odds ratio (OR) 1.05, 95%CI 0.50 to 2.18; 1753 participants; 3 studies);

- People taking LAMA scored slightly worse on two scales measuring quality of life (Asthma Quality of Life Questionnaire; AQLQ) and asthma control (Asthma Control Questionnaire; ACQ); the evidence was rated high quality but the effects were small and unlikely to be clinically significant (AQLQ: mean difference (MD) -0.12, 95% CI -0.18 to -0.05; 1745 participants; 1745; 4 studies; ACQ: MD 0.06, 95% CI 0.00 to 0.13; 1483 participants; 3 studies).
- some evidence support small benefits of LAMA over LABA on lung function, including on our pre-specified preferred measure trough forced expiratory volume in one second (FEV1) (MD 0.05 L, 95% CI 0.01 to 0.09; 1745 participants, 4 studies). However, the effects on other measures varied, and it is not clear whether the magnitude of the differences were clinically significant.
- More people had adverse events on LAMA but the difference with LABA was not statistically significant.

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**Kew KM et al., 2016 [22].**

Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta$_2$-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma (Review)

**Fragestellung**

To assess the effects of adding a long-acting muscarinic antagonist (LAMA) to combination long-acting beta$_2$-agonists (LABA) and inhaled corticosteroids (ICS) in adults whose asthma is not well controlled by LABA/ICS

**Methodik**

Population:

- studies in adults (aged 18 years or older) with asthma who were taking LABA/ICS combination therapy

Intervention / Komparator:

- (1) LAMA add-on to any dose of LABA/ ICS combination therapy versus the same dose of LABA/ICS alone
- (2) LAMA versus placebo (if they required participants to be taking LABA/ICS combination therapy for inclusion in the trial)
- (3) We included studies involving the addition of the following LAMA at any dose.
- Tiotropium (Spiriva Handihaler or Respimat).
- Aclidinium bromide (Eklira Genuair).
- Glycopyrronium bromide (Seebri Breezhaler).
- (4) allowed participants to continue using additional short- or long-acting medications (e.g. salbutamol, terbutaline and ipratropium, leukotriene receptor antagonists), provided they were not part of the randomised treatment.

Endpunkte:

- primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); Serious adverse events (all causes)
- sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (preferably trough forced expiratory volume in one second, or $FEV_1$); Asthma control

(measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events

Recherche/Suchzeitraum:

- bis Januar 2016

Qualitätsbewertung der Studien:

Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential, nicht-publizierten Daten und Cross-over-Studien

- Heterogenität: $I^2$ nach Higgins/Thompson

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 3 completed RCTs (n=1197)

Charakteristika der Population:

- Four studies met the inclusion criteria, one of which was withdrawn prior to enrolment (NCT02127697).The other three studies were all multicentre, parallel, double-blind, double-dummy randomised controlled trials sponsored by Boehringer-Ingelheim.
- Kerstjens 2012a and Kerstjens 2012b randomised patients to one of two groups, tiotropium Respimat at a dose of 5 µg once daily or placebo. Ohta 2014 was a three-arm study randomising people to receive one of two doses of tiotropium Respimat, 2.5 µg or 5 µg daily, or placebo.
- Inclusion criteria that were commonacross the trials were that patients were aged between 18 and 75years, diagnosed with asthma before age 40 as confirmed at screening with a range of similar lung function requirements, and had a score of at least 1.5 on the ACQ to confirm that it was symptomatic.
- The twin trials were more stringent with criteria relating to the duration and severity of asthma, requiring participants to have at least a five-year history of asthma, at least one exacerbation needing treatment with systemic glucocorticoids in the previous year, and stable high doses of LABA/ICS.
- Ohta 2014 required only a 12-week history of symptomatic asthma, and crucially that participants could be taking stablemediumdoses of ICS, “alone or in a fixed combination with a LABA, for at least four weeks”.

Qualität der Studien:

- low risk of bias across domains
  - 4 double-blind, double-dummy trials comparing LAMA to placebo, including 1197 people with asthma taking combination LABA/ICS
    - für die quanititative Analyse wurden 3 Studien eingeschlossen

**Studienergebnisse:**

LAMA + LABA/ICS vs LABA/ICS

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations requiring oral corticosteroids (patients with at least one) | 2 | 907 | Odds Ratio (M-H, Random, 95% CI) | 0.76 [0.57, 1.02] |
| 2 Exacerbations requiring oral corticosteroids (number per patient) | 2 | 907 | Rate Ratio (Random, 95% CI) | 0.79 [0.53, 1.17] |
| 3 Time to first exacerbation requiring oral corticosteroids | 2 | 907 | Hazard Ratio (Random, 95% CI) | 0.80 [0.63, 1.01] |
| 4 Quality of life (AQLQ) | 2 | 907 | Mean Difference (IV, Random, 95% CI) | 0.09 [-0.03, 0.20] |
| 5 Serious adverse events | 3 | 1197 | Odds Ratio (M-H, Random, 95% CI) | 0.60 [0.24, 1.47] |
| 6 Exacerbations requiring hospital admission | 3 | 1191 | Risk Difference (M-H, Random, 95% CI) | -0.01 [-0.04, 0.01] |
| 7 Lung function (change in trough $FEV_1$ L) | 3 | 1191 | Mean Difference (IV, Random, 95% CI) | 0.07 [0.03, 0.11] |
| 8 Lung function (change in trough FVC) | 3 | 1191 | Mean Difference (IV, Random, 95% CI) | 0.07 [0.02, 0.13] |
| 9 Asthma control (ACQ) | 2 | 907 | Mean Difference (IV, Random, 95% CI) | -0.13 [-0.23, -0.02] |
| 10 Asthma control (ACQ responder) | 2 | 1192 | Odds Ratio (M-H, Random, 95% CI) | 1.42 [0.88, 2.29] |
| 11 Any adverse events | 3 | 1197 | Odds Ratio (M-H, Random, 95% CI) | 0.70 [0.52, 0.94] |
| 12 Quality of life (AQLQ) by timeframe | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 12.1 24-26 weeks | 2 | 907 | Mean Difference (IV, Random, 95% CI) | 0.11 [-0.03, 0.24] |
| 12.2 48-52 weeks | 2 | 907 | Mean Difference (IV, Random, 95% CI) | 0.09 [-0.03, 0.20] |

- People randomised to take a LAMA add-on had fewer exacerbations requiring oral corticosteroids than those continuing to take LABA/ICS alone, although the confidence intervals included no difference (OR 0.76, 95% CI 0.57 to 1.02) = moderate quality
- Over 48 weeks, 328 out of 1000 people taking their usual LABA/ICS would have to take oral corticosteroids for an exacerbation compared with 271 if they took a LAMA as well (95%CI 218 to 333 per 1000).
- Quality of life (AQLQ) was no better for those taking LAMA add-on than those taking LABA/ICS alone when considered in light of the 0.5 minimal clinically important difference on the scale (MD 0.09, 95% CI − 0.03 to 0.20)
- evidence for whether LAMA increased or decreased serious adverse events in this population was inconsistent (OR 0.60, 95% CI 0.24 to 1.47; I2 = 76%).
- high quality evidence showing benefits to lung function (trough FEV1 and FVC) and potentially small benefits to asthma control. People taking a LAMA add-on were less likely to experience non-serious adverse events.

**Anmerkung/Fazit der Autoren**

Tiotropium add-on may have additional benefits over LABA/ICS alone to reduce the need for rescue oral steroids in people with severe asthma. The effect was imprecise, and there was no evidence for other LAMA preparations. Possible benefits on quality of life were negligible, and evidence for the effect on serious adverse events was inconsistent. There are likely to be small added benefits of tiotropium Respimat 5 µg daily on lung function and asthma control over LABA/ICS alone, and fewer non-serious adverse events. The benefit of tiotropium add-on on the frequency of hospital admission is not yet known, despite year-long trials.

*Kommentare zum Review*

- The studies added tiotropium Respimat to LABA/ICS therapy; however the exact LABA/ICS combination was not specified
- all of the studies were funded by industry

**Janjua S et al., 2019 [21].**

Inhaled steroids with and without regular formoterol for asthma: serious adverse events

**Fragestellung**

To assess the risk of mortality and non-fatal serious adverse events (SAEs) in trials that randomly assign participants with chronic asthma to regular formoterol and inhaled corticosteroids versus the same dose of inhaled corticosteroid alone.

**Methodik**

Population:

- adults with chronic asthma

Intervention/Komparator:

- ICS and formoterol with ICS alone

Endpunkte:

- Primary outcomes
  - All-cause mortality.
  - All-cause non-fatal SAEs.
- Secondary outcomes
  - Asthma-related mortality.
  - Asthma-related non-fatal SAEs.
  - Respiratory-related mortality.
  - Respiratory-related non-fatal SAEs.
  - Cardiovascular-related mortality.
  - Cardiovascular-related non-fatal SAEs.
  - Asthma-related non-fatal life-threatening events (intubation or admission to intensive care).
  - Respiratory-related non-fatal life-threatening (intubation or admission to intensive care).

Recherche/Suchzeitraum:

- The previously published version included searches up to August 2012
- We updated the search for this version from 2011 to 18 February 2019.

Qualitätsbewertung der Studien:

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

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 29 RCTs included 37,984 adults (aged 12 years and over) and 10 studies included 4035 children and adolescents.

Charakteristika der Population:

- participants with a clinical diagnosis of asthma of any age group, unrestricted by disease severity or previous or current treatment.

Qualität der Studien:

- We obtained full data on all-cause mortality and SAEs. Where data for asthma-related SAEs were not reported, we judged studies as 'high risk', and 'unclear risk' if the information provided by the authors or sponsors was insufficient.
- Quality of the evidence
  - We were moderately certain regarding the data in adults, but less certain about the effects of adding formoterol to ICS in children. Given the low number of deaths that occurred in the studies, we do not yet have enough information to be able to measure accurately the risk of adding formoterol to ICS on number of deaths.
  - Almost all trials were sponsored by drug manufacturers.
  - Other concerns were that the cause of serious adverse events (i.e. whether they were judged by the trialists to be asthma-related or not) were not independently assessed, and it may have been possible to guess which treatment group the person experiencing the adverse event was from. Although the people in the trial did not know whether they had been given a dummy drug or the active treatment, formoterol has quite a large effect on symptoms. This meant that they might have been able to guess who was taking formoterol. It was not possible for us to tell whether this occurred or not, which is why we primarily look at the all-cause events, which do not require assessment of cause.

Studienergebnisse:

- All-cause mortality Adults
  - We included 29 studies in the analysis (participants = 35,751). Three studies compared low- and high-dose formoterol plus ICS with ICS alone (O'Byrne 2001; Pauwels 1997; Peters 2016).
  - In the analysis, each treatment dose from the three studies was reported separately (resulting in 32 estimates of treatment effect), and the number of participants in the ICS only treatment group was halved (when necessary) to avoid double-counting.
  - Seventeen deaths were reported in 18,645 participants taking formoterol with ICS, and 13 deaths occurred out of 17,106 participants taking ICS alone.
  - These trials were combined with the use of the Peto odds ratio (as no continuity correction for zero cells is required).
  - The Peto OR of all-cause mortality with formoterol was 1.25 (95% confidence interval (CI) 0.61 to 2.56; 29 studies; 35, 751 participants ; $I^2$ = 0%;
- All-cause non-fatal serious adverse events
  - We included 29 studies in the analysis (35,751 participants).
  - Three studies compared low- and high-dose formoterol plus ICS with a placebo treatment (O'Byrne 2001; Pauwels 1997; Peters 2016).
  - In the analysis, each treatment dose from the three studies was reported separately (resulting in 32 estimates of treatment effect).

- The number of adults experiencing one or more non-fatal SAEs was very similar when formoterol was randomly assigned with ICS in comparison with ICS alone.
- One or more non-fatal SAEs occurred in 401 out of 18,645 (2.1%) participants on regular formoterol with ICS and in 369 out of 17,106 (2.1%) participants on ICS alone.
- The Peto OR was 1.00 (95% CI 0.87 to 1.16; 29 studies; 35,751 participants; $I^2$ = 0%

**Summary of findings for the main comparison. Regular formoterol and ICS compared to same-dose ICS in adults with asthma**

**Formoterol and ICS compared to same-dose ICS for chronic asthma**

**Patient or population:** adults with chronic asthma
**Intervention:** formoterol and ICS
**Comparison:** same-dose ICS

**Setting:** community; most were multicentre studies, of which 10 studies were conducted in the USA. Other multicentre studies were conducted in at least 2 to 27 countries including Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Chile, Finland, France, Germany, Hungary, Ireland, Luxembourg, Mexico, Norway, the Philippines, Poland, Spain, Thailand, and the UK. 2 single-centre studies were conducted in Japan and Russia.

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with same-dose ICS | Risk with formoterol and ICS | | | | |
| **All-cause mortality**<br>Follow-up: 26 weeks | 1 per 1000 | 1 per 1000 (0 to 2) | OR 1.25 (0.61 to 2.56) | 35,751 (32 RCTs) | ⊕⊕⊕⊖ MODERATE [1] | |
| **All-cause non-fatal serious adverse events**<br>Follow-up: 26 weeks | 22 per 1000 | 22 per 1000 (19 to 25) | OR 1.00 (0.87 to 1.16) | 35,751 (32 RCTs) | ⊕⊕⊕⊕ HIGH | The upper confidence interval of the absolute risk with formoterol and ICS resulted in 3 more adults per 1000 experiencing an SAE compared to ICS treatment alone (i.e. 25 minus 22). |
| **Asthma mortality**<br>Follow-up: 26 weeks | No deaths | Pooled risk difference 0.0003 (−0.0007 to 0.0013) | Not estimable | 24,022 (31 RCTs) | ⊕⊕⊖⊖ LOW [2,3] | There were 3 deaths in the LABA + ICS treatment arm for this outcome. |
| **Asthma-related non-fatal serious adverse events**<br>Follow-up: 26 weeks | 6 per 1000 | 5 per 1000 (4 to 7) | OR 0.86 (0.64 to 1.14) | 35,158 (30 RCTs) | ⊕⊕⊕⊖ MODERATE [3] | The upper confidence interval of the absolute risk with formoterol and ICS resulted in 1 more adults per 1000 experiencing an SAE compared to ICS treatment alone (i.e. 7 minus 6). |

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

**CI:** confidence interval; **ICS:** inhaled corticosteroids; **LABA:** long-acting beta$_2$-agonist; **OR:** odds ratio; **RCT:** randomised controlled trial; **SAE:** serious adverse event

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

[1]We downgraded the evidence for this outcome by 1 due to wide upper confidence interval of the absolute risk.
[2]We downgraded the evidence for this outcome by 1 due to too few events in the ICS treatment arm.
[3]We downgraded the evidence for this outcome by 1 due to lack of independent assessment of causation of SAEs.

**Summary of findings 2. Regular formoterol and ICS compared to same-dose ICS in children and adolescents with asthma**

**Formoterol and ICS compared to same-dose ICS for chronic asthma**

**Patient or population:** children and adolescents with chronic asthma
**Intervention:** formoterol and ICS
**Comparison:** same-dose ICS

**Setting:** community; all were multicentre studies, with 4 studies conducted in the USA and 1 study in the UK. Other studies were conducted in at least 7 countries including Argentina, Australia, Belgium, Brazil, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, India, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, Switzerland, and Ukraine.

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with same-dose ICS | Risk with formoterol and ICS | | | | |
| **All-cause mortality**<br>Follow-up: 12.5 weeks | No deaths | No deaths | Pooled risk difference 0.0000 (95% CI −0.0034 to 0.0034) | 4035 (10 RCTs) | ⊕⊕◯◯ LOW [1] | |
| **All-cause non-fatal serious adverse events**<br>Follow-up: 12.5 weeks | 8 per 1000 | 11 per 1000 (6 to 21) | OR 1.33 (0.71 to 2.49) | 4035 (10 RCTs) | ⊕⊕⊕◯ MODERATE [2] | The upper confidence interval of the absolute risk with formoterol and ICS resulted in 13 more children and adolescents per 1000 experiencing an SAE compared to ICS alone (i.e. 21 minus 8). |
| **Asthma-related mortality**<br>Follow-up: 12.5 weeks | No deaths | No deaths | Pooled risk difference 0.0000 (95% CI −0.0034 to 0.0034) | 4035 (10 RCTs) | ⊕⊕◯◯ LOW [1] | |
| **Asthma-related non-fatal serious adverse events**<br>Follow-up: 12.5 weeks | 3 per 1000 | 4 per 1000 (1 to 11) | OR 1.18 (0.40 to 3.51) | 4035 (10 RCTs) | ⊕◯◯◯ VERY LOW [2, 3, 4] | The upper confidence interval of the absolute risk with formoterol and ICS resulted in 8 more children and adolescents per 1000 experiencing an SAE compared to ICS alone (i.e. 11 minus 3). |

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

**CI:** confidence interval; **ICS:** inhaled corticosteroids; **OR:** odds ratio; **RCT:** randomised controlled trial; **SAE:** serious adverse event

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

[1]We downgraded the evidence for this outcome by 2 due to no deaths and uncertainty of treatment.
[2]We downgraded the evidence for this outcome by 1 due to wide confidence interval.
[3]We downgraded the evidence for this outcome by 1 due to lack of independent assessment of causation of SAEs.
[4]We downgraded the evidence for this outcome by 1 due to unexplained heterogeneity between trial results.

### Anmerkung/Fazit der Autoren

We did not find a difference in the risk of death (all-cause or asthma-related) in adults taking combined formoterol and ICS versus ICS alone (moderate- to low-certainty evidence). No deaths were reported in children and adolescents. The risk of dying when taking either treatment was very low, but we cannot be certain if there is a difference in mortality when taking additional formoterol to ICS (low-certainty evidence).

We did not find a difference in the risk of non-fatal SAEs of any cause in adults (high-certainty evidence). A previous version of the review had shown a lower risk of asthma-related SAEs in adults taking combined formoterol and ICS; however, inclusion of new studies no longer shows a difference between treatments (moderate-certainty evidence).

The reported number of children and adolescents with SAEs was small, so uncertainty remains in this age group.

We included results from large studies mandated by the FDA. Clinical decisions and information provided to patients regarding regular use of formoterol and ICS need to take into account the balance between known symptomatic benefits of formoterol and ICS versus the remaining degree of uncertainty associated with its potential harmful effects.

*Kommentare zum Review*

The majority of included studies were sponsored by manufacturers of combination products, but we did not regard sponsorship as necessarily increasing the risk of bias when studies were well designed.

## 3.3 Systematische Reviews

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

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

Siehe auch [2]; [3]

**Fragestellung**

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

**Methodik**

Population:

- patients with uncontrolled severe asthma

Intervention:

- benralizumab, dupilumab, omalizumab, mepolizumab and reslizumab

Komparator:

- standard of care/placebo

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

**Ergebnisse**

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

Qualität der Studien:

The systematic review included only English language articles; however, the risk of selection bias is probably small because we screened previous systematic reviews and

the GDG included several international experts in the field; thus, the possibility of missing results from non-English articles is unlikely. We did not include observational studies that could have been informative for some of the outcomes with low or very low-quality evidence from RCTs (eg serious AE).

Studienergebnisse:

- Severe asthma exacerbation rate
  - The annualized exacerbation rates were reported in three benralizumab trials,39-41 three dupilumab trials,42-44 three mepolizumab trials,45-47 three omalizumab trials48,50,51 and five reslizumab trials.52-55 All biologicals reduced asthma exacerbations rate compared to standard of care with high certainty of evidence: benralizumab IRR 0.53; 95% CI 0.39 to 0.72; dupilumab IRR 0.44; 95% CI 0.32 to 0.59; mepolizumab IRR 0.49 95% CI 0.38 to 0.66; omalizumab IRR 0.56; 95% CI 0.40 to 0.77; and reslizumab IRR 0.46; 95% CI 0.37 to 0.58.
- Asthma control
  - The change in asthma control following biologicals addition was evaluated using Asthma Control Questionnaires (ACQ) scores and the Total Asthma Symptoms Scores (TASS). Dupilumab, omalizumab and mepolizumab probably improve asthma control with moderate certainty of evidence: dupilumab (ACQ-5) MD −0.48; 95% −0.88 to −0.09 42-44; omalizumab (TASS) MD −0.16; 95% −0.51 to 0.19 48-51 and mepolizumab (ACQ-5) MD −0.43; 95% CI −0.56 to −0.31.45-47 Nevertheless, none of the biologicals showed an improvement above the MID threshold of 0.5.
- Quality of life
  - QoL was reported in three benralizumab trials 39-41; two dupilumab trials42,43; three mepolizumab trials45-47; one omalizumab trial 48 and three reslizumab trials.53-55 Changes in QoL were evaluated using the Asthma Quality of Life Questionnaire (AQLQ) for all biologicals, except for mepolizumab that used the St. George's Respiratory Questionnaire (SGRQ) score. All the addition of all biologicals improved QoL with moderate to high certainty, although below the MID: benralizumab MD + 0.23 (95% CI 0.11 to 0.36); dupilumab MD + 0.42 (95% CI + 0.25 to + 0.59); mepolizumab (SGRQ) MD −7.14 (95% CI −9.07 to −5.21); omalizumab MD + 0.13 (95% CI +0.11 to +0.37); and reslizumab MD + 0.17 (95% CI +0.08 to +0.25).
- Safety
  - Drug-related AE were assessed in two trials for benralizumab,40,41 one trial for dupilumab,42 three mepolizumab trials,45-47 one trial for omalizumab 48 and three trials for reslizumab.52,53,55 For mepolizumab, there is an increased likelihood of drug-related AE (RR 1.35; 95% CI 1.01 to 1.80; high certainty of evidence). Benralizumab and reslizumab probably increases drug-related AE (moderate certainty of evidence): benralizumab RR 1.41, 95% CI 0.87 to 2.27; reslizumab RR 1.18, 95% CI 0.89 to 1.56. For dupilumab and omalizumab, the RR is rather small: dupilumab RR of 1.00, 95% CI 0.88 to 1.13; and omalizumab RR 1.01, 95% CI 0.91 to 1.1.
  - There is low to very low certainty of evidence that drug-related serious AE may increase with the use of dupilumab RR 1.46 (95% 0.60 to 3.54) and reslizumab RR 4.71 (95% 0.54 to 41.31). For benralizumab and mepolizumab, results are inconclusive: benralizumab RR 0.56 (95% CI 0.22 to 1.44) and mepolizumab RR 0.98 (95% CI 0.06 to 15.63). Data were not fully reported in all trials; thus, the certainty of evidence was downgraded due to the low number of events.

- Reduction in oral corticosteroids use
  - Benralizumab, dupilumab and mepolizumab showed with high certainty of evidence, a reduction in daily OCS: benralizumab >50% (RR 1.76, 95%CI 1.26 to 2.47); dupilumab 29.4% (95% CI 43.2 lower to 15.57 lower); and mepolizumab >50% (RR 1.61; 95%CI 1.07-2.41).41,44,46 Mepolizumab showed a reduction in OCS to 5mg/day or less (crude RR 1.71; 95%CI 1.11 to 2.55, P = .01) and a reduction of 100% in daily OCS (crude RR 1.91; 95% CI 0.69 to 5.30, P = .2) compared to placebo.
- Reduction of rescue medication use
  - This end point was assessed only for mepolizumab and showed no clinically significant reduction in the daily use of rescue medication after 24 weeks (MD—0.1 puffs/day; CI 95% −0.35 to 0.15).45
- Lung function - $FEV_1$
  - The change from baseline of $FEV_1$ was assessed for benralizumab,39-41 mepolizumab,45-47 omalizumab 48 and reslizumab.52-55 Compared to standard of care, there was an increase in $FEV_1$, but below the MID agreed by the GDG (moderate certainty of evidence): benralizumab MD + 140mL (95% CI +90 to +190); mepolizumab MD + 110.9 mL (95% CI +58.91 to +162.89), reslizumab MD + 141.82 mL (95% CI +89.23 to +194.41); and omalizumab mean percentage change + 3.7% (95% CI 2.1% to 9.5%). There is low certainty of evidence that for patients with baseline eosinophils ≥300 cells/μL dupilumab may increase FEV1 compared to standard of care [MD + 180 mL (95% CI 110 to 250)].

**Anmerkung/Fazit der Autoren**

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

*Kommentare zum Review*

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

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

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

**Fragestellung**

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

**Methodik**

Population:

- Patients with Inadequately Controlled Asthma

Intervention:

- dupilumab and benralizumab

Komparator:

- placebo

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 3 RCTs

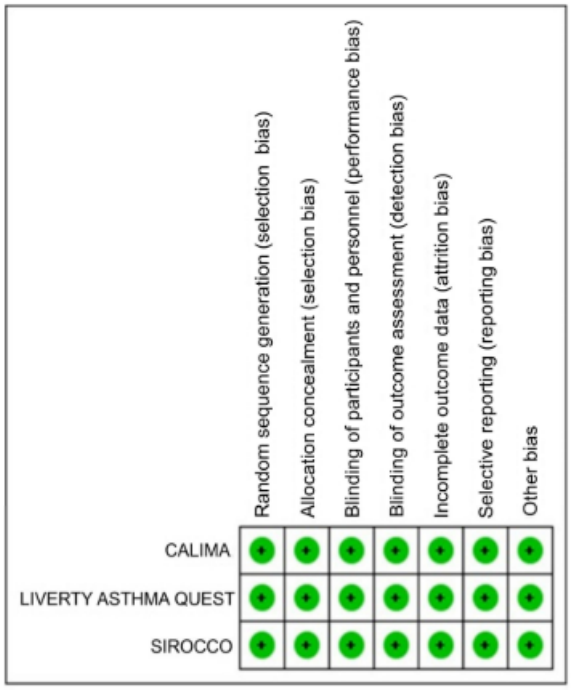
Charakteristika der Population:

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

- FEV1.0 reversibility after administration of short-acting beta-2 agonist of ≥12%, or ≥200 mL; and the ACQ score of ≥1.5 before inclusion.

Qualität der Studien:

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




Studienergebnisse:

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

population, and 0.251 (0.155–0.347) and 0.146 (0.088–0.204) in the subgroup with the blood eosinophil count of ≥300 (Figure 4A,B).

- The comparison of the two drugs showed no significant difference in the change in FEV1.0 from the baseline in the overall population and the subgroup with the blood eosinophil count of ≥300.
- The changes in AQLQ score from baseline in the dupilumab group and benralizumab group were significantly better than the placebo with respective MD and 95% CrI of 0.261(0.111 to 0.408) and 0.220 (0.106 to 0.333) in the overall population, and 0.342 (0.120 to 0.565) and 0.300 (0.161 to 0.439) in the subgroup with a blood eosinophil count of ≥300.
- The comparison between the two drugs showed no significant difference in the AQLQ score from the baseline in the overall population and the subgroup with the blood eosinophil count of ≥300 with the MD and 95% CrI of 0.041 (−0.145 to 0.227) and 0.042 (−0.220 to 0.304), respectively

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

**Anmerkung/Fazit der Autoren**

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

**Busse W et al., 2019 [7].**

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

**Fragestellung**

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

**Methodik**

Population:

- patients with SEA aged 12 years or greater

Intervention:

- mepolizumab, reslizumab, benralizumab

Komparator:

- Placebo als Brückenkomparator

Endpunkte:

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

Recherche/Suchzeitraum:

- Primary data source for this ITC was the published Cochrane by Farne et al. → siehe oben Reference [11]. Additional search on January 2018.

Qualitätsbewertung der Studien:

- Vermutlich analog Cochrane Publikation [11].

**Ergebnisse**

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

Qualität der Studien:

- K.A.

Studienergebnisse:

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

**Anmerkung/Fazit der Autoren**

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

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**Xiong XF et al., 2019 [34].**

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

**Fragestellung**

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

**Methodik**

Population:

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

Intervention:

- dupilumab

Komparator:

- placebo

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane approach

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Five studies involving 3369 patients

Charakteristika der Population:

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

Qualität der Studien:

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

Studienergebnisse:

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

**Anmerkung/Fazit der Autoren**

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

*Kommentare zum Review*

- Siehe auch Zayed Y et al. 2018 [35].

**Liu W et al., 2019 [25].**

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

**Fragestellung**

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

**Methodik**

Population:

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

Intervention:

- intervention must include benralizumab

Komparator:

- placebo

Endpunkte:

- AEs

Recherche/Suchzeitraum:

- Embase, PubMed and Cochrane from inception to September 2018

Qualitätsbewertung der Studien:

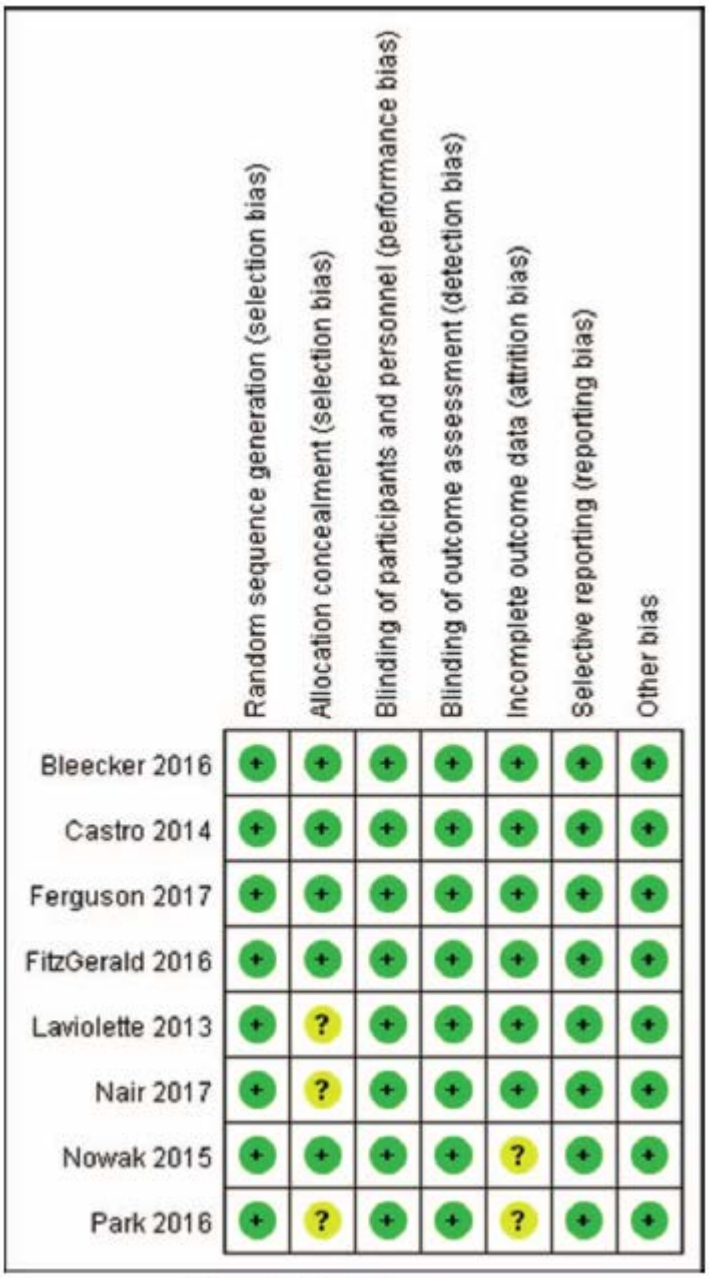


Figure 2. Risk-of-bias summary.

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Eight RCTs with 3788 patients

Charakteristika der Population:

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

Qualität der Studien:

- Cochrane Collaboration's tool

Studienergebnisse:

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

**Anmerkung/Fazit der Autoren**

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

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

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

**Fragestellung**

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

**Methodik**

Population:

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

Intervention/Komparator

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

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- risk of bias was assessed using a NICE checklist

**Ergebnisse**

Anzahl eingeschlossener Studien:

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

## Charakteristika der Population:

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

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

The highlighted cells indicate differences across the trials.

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

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

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

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

## Qualität der Studien:

- ‘‘ Only phase 3 studies were included‘‘

Studienergebnisse:

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

**Anmerkung/Fazit der Autoren**

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

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**Sobieraj DM et al., 2018 [30].**

Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

Siehe auch: **Sobieraj DM et al., 2018 [29].**

**Fragestellung**

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

**Methodik**

Population:

- patients 12 years and older with uncontrolled, persistent asthma

Intervention vs Komparator:

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

Endpunkte:

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

- health care utilization (additional medication use, additional health resource use related to the intervention)

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of BiasTool forRCTs

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 15 RCTs (n=7122)

Charakteristika der Population:

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

Qualität der Studien:

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

**Studienergebnisse:**

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

- Comparing LAMA with LABAas add-on therapy to inhaled corticosteroids, there was no statistically significant association of LAMA with
  - the risk of exacerbation requiring systemic corticosteroid (RR,0.87 [95% CI, 0.53 to 1.42]; RD, 0.00 [95% CI, −0.02 to 0.02])
  - in asthma worsening (RR, 1.00 [95% CI, 0.84 to 1.20]; RD, 0.00 [95% CI, −0.05 to 0.04]), or in the composite outcome including oral steroid use or increase in asthma medication (RR,0.60[95%CI,0.15 to2.42];RD,−0.03 [95%CI,−0.12 to 0.06]).

- No deaths occurred in 3 RCTs and in the fourth trial 3 of 532 participants (0.6%) died in the LAMAgroup, 2 of these deaths were considered asthma-related (0.4%) whereas no deaths occurred in the LABA group.
- LAMA had no significant associations with ACQ scores with 1 trial reportingACQ-6score, 2 trials reportingACQ-7 scores, and 2 trials reportingACQ-7 responder analysis.
- No significant associations were found in measures of spirometry including the most frequently reported lung function measures of FEV1 trough, FEV1% predicted, and FVC trough with LAMA use
- No significant associations were found for AQLQ score

Triple Therapy vs Inhaled Corticosteroids and LABA

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


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**Anmerkung/Fazit der Autoren**

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

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**Tian BP et al., 2017 [31].**

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

**Fragestellung**

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

**Methodik**

Population:

- Eosinophilic asthma patients

Intervention:

- benralizumab

Komparator:

- placebo

Endpunkte:

- symptom control, lung function or AEs

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

Qualität der Studien:

Table 2. Risk of bias of the included studies.

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

**Studienergebnisse:**

Asthma Exacerbations.

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

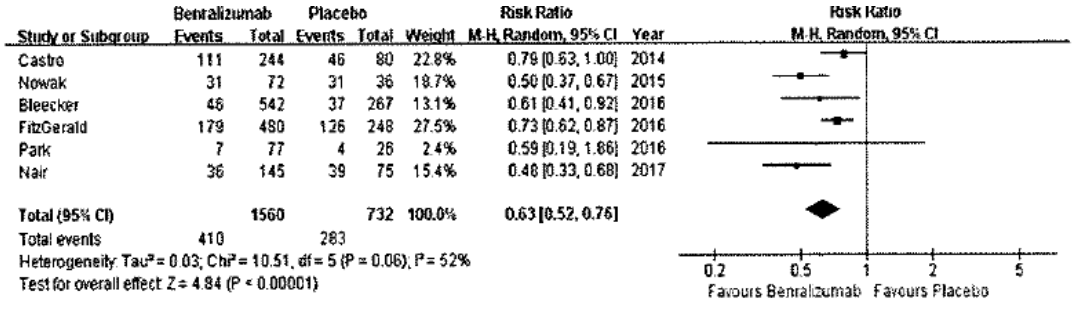


Figure 2. The effect of benralizumab versus placebo on exacerbations.

FEV1% changes from basefine

- Three studies assessed the responsiveness ofFEVl (forced expiratory volume in l sec) % of predicted value

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

Asthma Control Questionnaire IACQ) score

- Although several trials described the ACQ scores, the ACQ data of four RCTs with 755 participants (544 in the benralizumab treatment group and 217 in the placebo-control group) could be analyzed together [19, 21, 31, 32].
- The findings from the meta-analysis suggested similar outcomes for the ACQ changes from baseüne between the benralizumab and control groups (SMD: -0. 10, 95% CI: -0.26 to 0. 06, p = 0.22) in eosinophilic asthmatics.
- No significan£ heterogeneity was observed among the studies (I2 = 32%, f = 0.22) (Figure S2).

Asthma control and Quality ofLife Assessment (AQLQ)

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

Adverse events

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

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**Anmerkung/Fazit der Autoren**

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

**Wang FP et al., 2018 [33].**

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

**Fragestellung**

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

**Methodik**

Population:

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

Intervention:

anti-interleukin 5 therapy at any dose

Komparator:

others

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

12 RCTs (3340 patients)

Charakteristika der Population:

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

Qualität der Studien:

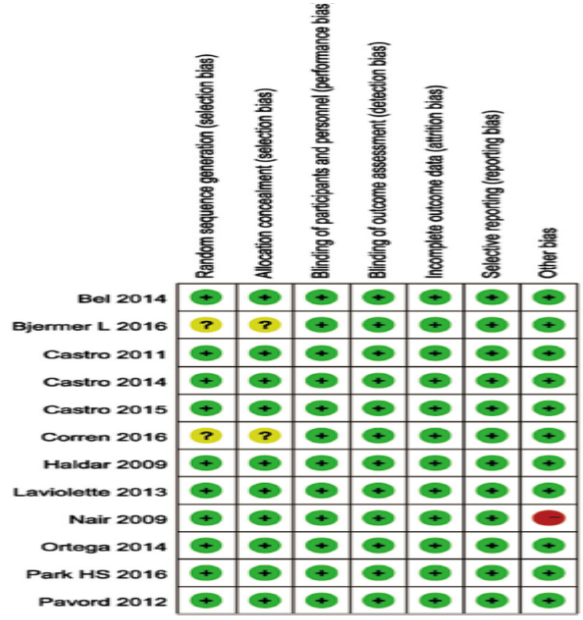

Fig. 8 Risk of bias summary of included studies

**Studienergebnisse:**

FEV1

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

Asthma Quality-of-Life Questionnaire (AQLQ)

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

Asthma Exacerbations

- Six studies were included.
- Overall, compared with placebo, asthma exacerbations risk was significantly decreased with anti-interleukin 5 treatment (RR = 0.52; 95 % CI, 0.46 to 0.59; P < 0.001), and there was no heterogeneity among studies (I2 = 0 %, P = 0.5).

- When looking at subgroups, mepolizumab (RR = 0.55; 95 % CI, 0.47 to 0.64; P < 0.001) and reslizumab (RR = 0.46; 95 % CI, 0.37 to 0.58; P < 0.001) were also linked to markedly lower asthma exacerbations.

Adverse Events

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


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36) Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID (2009) Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 360(10):973–984CrossRefPubMedPubMedCentralGoogle Scholar
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45) 12.
46) Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, Ward CK, Wu Y, Wang B, Khatry DB, Merwe R, Kolbeck R, Molfino NA, Raible DG (2014) Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2(11):878–890. doi: 10.1016/S2213-2600%2814%2970201-2 CrossRefGoogle Scholar
47) 19.
48) Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P (2011) Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 184(10):1125–1132. doi: 10.1164/rccm.201103-0396OC CrossRefPubMedGoogle Scholar
49) 20.
50) Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P (2015) Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 3(5):355–366. doi: 10.1016/S2213-2600(15)00042-9 CrossRefPubMedGoogle Scholar
51) 21.
52) Corren J, Weinstein S, Janka L, Zangrilli J, Garin M (2016) Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest. doi: 10.1016/j.chest.2016.03.018 PubMedCrossRefGoogle Scholar
53) 22.
54) Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M (2016) Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. Chest. doi: 10.1016/j.chest.2016.03.032 PubMedCrossRefGoogle Scholar
55) 23.
56) Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, Busse WW, Wenzel S, Wu Y, Datta V, Kolbeck R, Molfino NA (2013) Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J

Allergy Clin Immunol 132(5):1086–1096.e1085. doi: 10.1016/j.jaci.2013.05.020 CrossRefPubMedPubMedCentralGoogle Scholar
57) 24.
58) Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K (2016) A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. Int Arch Allergy Immunol 169(3):135–145. doi: 10.1159/000444799

**Anmerkung/Fazit der Autoren**

In summary, the current meta-analysis indicated that antiinterleukin 5 treatment was well tolerated and could significantly improve FEV1, quality of life, and reduced asthma exacerbation risk in patients with eosinophilic asthma. Therefore, the humanized anti-interleukin 5 monoclonal antibodies may be effective and safe for eosinophilic asthma. The results highlight the importance of selection asthma phenotypes could derive clinical benefit from anti-interleukin 5 therapy. Nasopharyngitis was the most frequently reported adverse event in either study involving anti-interleukin 5 treatments, and benralizumab needs more data to support its safety profile.

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**Li J et al., 2017 [24].**

**Fragestellung**

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

**Methodik**

Population:

inadequately controlled, eosinophilic asthma

Intervention vs Komparator:

Reslizumab vs. others

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

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

## Charakteristika der Population:

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

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

## Qualität der Studien:

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

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

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

Studienergebnisse:

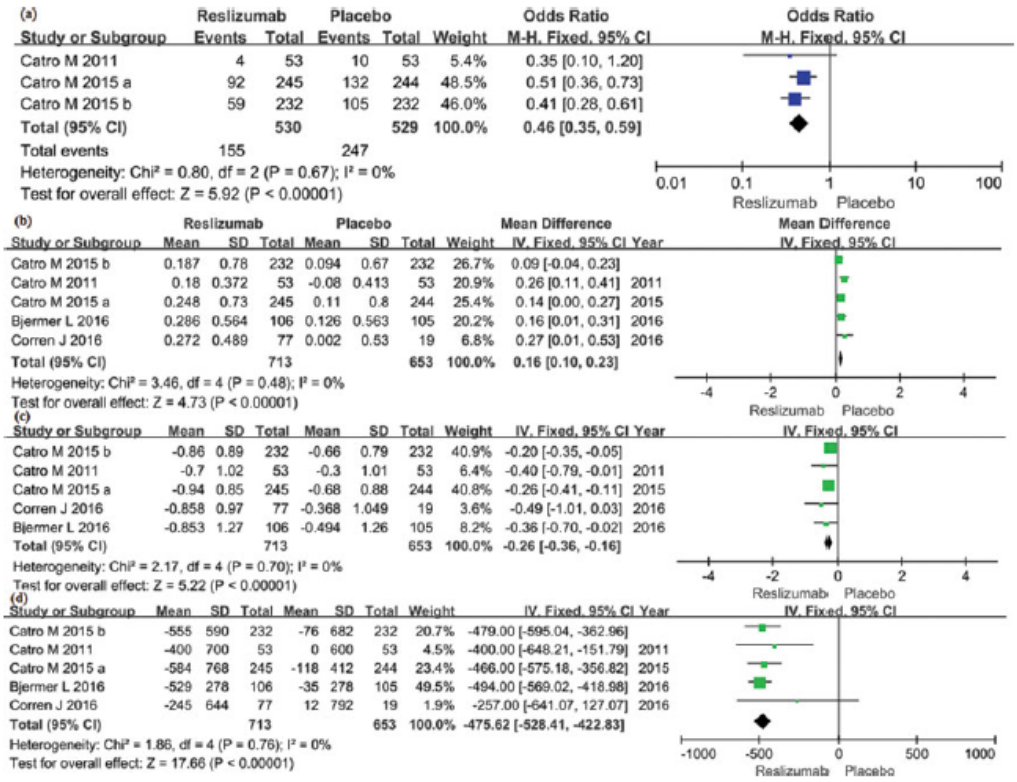


**Figure 3.** Forest plots showing changes in (a) asthma exacerbation, (b) $FEV_1$, (c) ACQ score and (d) blood eosinophil counts in the treatment studies. FEV1: a forced expiratory volume in 1 second; ACQ: Asthma Control Questionnaire; SD: standard deviation, IV: inverse variance; CI: confidence interval,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

The proportion of individuals who withdrawn due to AE

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

Upper respiratory AEs

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

16. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3(5):355–66.

17. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am Respir Crit Care Med 2011;184(10):1125–32.

18. Corren J,Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest. in press.

19. Bjermer L, Lemiere C,Maspero J,Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: A randomized phase 3 study. Chest. in press.

**Anmerkung/Fazit der Autoren**

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

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**Cockle SM et al., 2017 [10].**

Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison

**Fragestellung**

To collect all publicly available RCTs to support an indirect treatment comparison of mepolizumab and omalizumab in severe asthma

**Methodik**

Bayesian network meta-analysis (Details in Appendix B). A Frequentist network meta-analysis was also conducted.

Population:

- patients ≥12 years of age, with severe asthma (patients receiving >1000 mg/day beclomethasone dipropionate equivalent plus ≥1 additional controller, and with a documented history of exacerbations).
- This population definition was then further refined to incorporate treatment eligibility for mepolizumab and omalizumab, as far as data availability allowed. Two populations were defined,
  - 1) the Overlap population, which aimed to include patients eligible for both mepolizumab AND omalizumab, and
  - 2) the Trial population, which aimed to include patients eligible for either mepolizumab OR omalizumab

Intervention:

- mepolizumab and omalizumab

Komparator:

- placebo, in addition to SoC

Endpunkte:

- Primary pre-specified endpoints were the rate of clinically significant exacerbations and the rate of exacerbations requiring hospitalization.
- Pre-specified secondary endpoints included the change from baseline in health-related quality of life (HRQoL), measured by the St George's Respiratory Questionnaire or Asthma Quality of Life Questionnaire; change from baseline in lung function ($FEV_1$), or postbronchodilator $FEV_1$, or $FEV_1$% predicted, or morning peak expiratory flow (PEF; L/min) when these data were unavailable; change from baseline in asthma control measured by the Asthma Control Questionnaire; and the proportion of patients with any adverse events (AEs), serious AEs (SAEs), withdrawals due to AEs or fatal AEs

Recherche/Suchzeitraum:

- A systematic literature review was conducted on August 5, 2014, and updated on July 8, 2015

Qualitätsbewertung der Studien:

- Eigene Kriterien in Anlehnung an NICE: Randomisierung angemessen, allocation concealment, Gruppen vergleichbar hinsichtlich prognostisch relevanter Faktoren, Verblindung, Unterschiede bzgl. drop-outs zwischen den Gruppen, selektives Berichten von Endpunkten, ITT-Analyse

**Ergebnisse**

Anzahl eingeschlossener Studien:

- The systematic literature review identified seven mepolizumab publications corresponding to three distinct RCTs and 29 omalizumab publications, corresponding to 19 distinct RCTs
- Upon application of the ITC inclusion/exclusion criteria (PICOS), of the 22 identified RCTs, one mepolizumab study (…) and three omalizumab studies (…) were eligible for inclusion in the primary ITC analysis
  - OMA: N=527
  - Mepa: N=1298

Charakteristika der Population:

**Table 2**
Key characteristics of double-blind, randomized controlled trials included in the ITC.

| | Study duration (weeks) | Treatment arms[a] | Key inclusion criteria | Number of patients | Included in Overlap population[b] analysis | Included in Trial population[c] analysis |
|---|---|---|---|---|---|---|
| **Mepolizumab-included studies** | | | | | | |
| MENSA [12][d] | 32 | • Mepolizumab 100 mg SC every 4 weeks (n = 194)<br>• Placebo (n = 191) | • Blood eosinophil counts≥150 cells/μL at initiation of treatment or≥300 cells/μL in previous 12 months<br>• ≥2 asthma exacerbation in previous 12 months | 527 | ✓ | ✓ |
| **Omalizumab-included studies** | | | | | | |
| INNOVATE [16][d] | 28 | • Omalizumab administered every 2 or 4 weeks to provide dose of ≥0.016 mg/kg per IU/mL of IgE (n = 209)<br>• Placebo (n = 210) | • Persistent allergic asthma despite high doses of corticosteroids and long-acting $\beta_2$ agonists<br>• ≥2 asthma exacerbation (or 1 severe exacerbation) in previous 12 months | 419 | ✓ | ✓ |
| Chanez et al., 2010 [9][e] | 16 | • Omalizumab administered every 2 or 4 weeks as per EU prescribing information [9] (n = 20)<br>• Placebo (n = 11) | • Persistent allergic asthma despite high doses of corticosteroids and long-acting $\beta_2$ agonists<br>• ≥2 severe asthma exacerbations in previous 12 months | 31 | ✓ | ✓ |
| EXTRA [18][f] | 48 | • Omalizumab ≥0.008 mg/kg per IU/mL of IgE every 2 weeks or ≥0.016 mg/kg of IgE every 4 weeks (n = 427)<br>• Placebo (n = 421) | • Severe allergic asthma despite high doses of corticosteroids and long-acting $\beta_2$ agonists<br>• ≥1 asthma exacerbation in previous 12 months | 848 | – | ✓ |

IgE, immunoglobulin E; ITC, indirect treatment comparison; SCS, systemic corticosteroids.
[a] For patients included in the base case meta-analysis only.
[b] Including patients potentially eligible for both mepolizumab and omalizumab.
[c] Including all patients eligible for mepolizumab regardless of their eligibility for omalizumab.
[d] Provided data for all efficacy and safety endpoints in the primary Bayesian network meta-analysis of the Overlap and Trial populations.
[e] Provided data for all safety endpoints in the primary Bayesian network meta-analysis of the Overlap and Trial populations.
[f] Provided data for exacerbations and safety endpoints in the primary Bayesian network meta-analysis of the Trial population.

Qualität der Studien:

- die 4 ausgewerteten RCTs erfüllten fast alle Qualitätskriterien

**Studienergebnisse:**

- Although asthma control and QoL were pre-specified as efficacy endpoints for the ITC, feasibility assessment demonstrated there was insufficient data in the included studies for endpoint analysis.
- In the Overlap population, no differences between treatments in clinically significant exacerbations and exacerbations requiring hospitalization were found, although trends favored mepolizumab.

- In the Trial population, mepolizumab treatment produced greater reductions in clinically significant exacerbations (RR: 0.63 [95% CrI: 0.45,0.89]) but not exacerbations requiring hospitalization compared with omalizumab, although the trend favored mepolizumab.
- Both treatments had broadly comparable effects on lung function, and similar tolerability profiles

[59] 9 Genetech. XOLAIR® Summary of Product Characteristics. ; 2009 (accessed May 2016) - http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf

[60] 12 Ortega, H.G., Liu, M.C., Pavord, I.D. et al, Mepolizumab treatment in patients with severe eosinophilic asthma. N. Engl. J. Med. 2014;371:1198–1207.

[61] 16 Humbert, M., Beasley, R., Ayres, J. et al, Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005;60:309–316.

[62] 18 Hanania, N.A., Alpan, O., Hamilos, D.L. et al, Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann. Intern. Med. 2011;154:573–582.

**Anmerkung/Fazit der Autoren**

In summary, this ITC compared the efficacy and tolerability of mepolizumab and omalizumab. Restrictions in terms of data availability led to a number of study limitations, which have been acknowledged and which were partially tested by additional scenarios and sensitivity analyses. These additional analyses supported the results from the primary analysis, which suggested that in patients with severe asthma eligible to receive both treatments, mepolizumab seems to be at least as efficacious as omalizumab at reducing exacerbations and improving lung function, and that the tolerability profiles of the two treatments do not seem to meaningfully differentiate.

*Kommentare zum Review*

- This study was funded by GlaxoSmithKline, alle Autoren sind Angestellte bei GSK
- asthma control and HRQoL could not be included in the analysis; different measures were used in the mepolizumab and omalizumab trials, preventing comparison
- differences in the length of time between clinical visits may influence patient recall of AEs, and the existence of an extension study for the mepolizumab population may have influenced the rate of withdrawals
- average patient age was greater in the mepolizumab MENSA trial (~50 years of age) than in the omalizumab INNOVATE and EXTRA trials (43e45 years of age). consequently, the number of asthma comorbidities in these patients may have differed, suggesting that the comparison of treatment AE profiles between RCTs should be interpreted with caution.

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**Cabon Y et al., 2017 [8].**

Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo controlled trials

**Fragestellung**

Inconsistent results have been reported regarding IL-5 blockade treatment in asthma. There were no direct between-treatment comparisons.

**Methodik**

- A meta-analysis was first conducted to assess the efficacy of the IL-5 blockade strategy overall
- An indirect network meta-analysis was then performed to compare each anti-IL5 mAb efficacy and safety result using the Bayesian framework according to Cochrane's collaboration guidelines

*Hinweis*: Further eosinophilic subgroup analysis and sensitivity analysis were also conducted in case of heterogeneity.

Population:

- patients with severe asthma

Intervention:

- anti-interleukin-5 therapies (benralizumab, reslizumab and mepolizumab)

Komparator:

- Placebo (als Brückenkomparator)

Endpunkte:

- annual exacerbation rates, $FEV_1$ change from baseline and variations in asthma symptoms assessed by changes in the ACQ-5

Recherche/Suchzeitraum:

- from 1990 to September 2015

Qualitätsbewertung der Studien:

- Metaanalyse: Cochrane tool / NMA: R-AMSTAR criteria were assessed to check the overall data quality

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Of the 11 clinical trials identified, 10 were considered eligible for the meta-analysis, reported in six separate publications and two publications describing two different trials each (total: 3421 patients)

Charakteristika der Population:

- The defined exacerbation and population characteristics were quite similar in the eight studies consisting of 10 trials, which involved a total of 3421 patients (59.6% females, average age 47.3 years, average BMI 28.0 kg/ $m^2$

Qualität der Studien:

- 7 RCTs with high quality, 3 RCTs with moderate quality

**Studienergebnisse:**

Metaanalyse:

- The annual exacerbation rate ratio of the three aggregated anti-IL-5 mAbs vs. placebo was 0.60 [0.50, 0.71], $P < 0.01$. This effect was assessed by a random effect model due to heterogeneity ($I^2 = 0.61$).

- The heterogeneity noted in the exacerbation rate ratios was due to the combined rate reduction in eosinophilic and non-eosinophilic 2014 Castro's studies. When these two trials were excluded, the exacerbation rate estimates based on the fixed effect model were 0.52 [0.45, 0.60] ($P < 0.01$, $I^2 = 0$).
- The FEV1 change from baseline vs. placebo was 0.09 L [0.05; 0.12], $P < 0.01$, using a fixed effect model ($I^2 = 0.28$).
- The meta-analysis indicated an overall ACQ-5 change from baseline of -0.31 [-0.41, -0.21], $P < 0.01$, based on a fixed effect model ($I^2 = 0.11$) involving seven studies only, because of missing values in three studies.

Subgruppenanalyse:

- A specific meta-analysis was performed in the eosinophilic patient subgroup (> 300 mm3/L). For this subgroup, including five studies, the annual exacerbation rate ratio was 0.57 [0.47, 0.69], $P < 0.01$, I2 = 0.54. FEV1 increased by 0.10 L [0.06, 0.14] ($P < 0.01$, $I^2 = 0$) in this subgroup. ACQ-5 changed by -0.33 [-0.45, -0.21] ($P < 0.01$, $I^2 = 0.21$).

Netzwerkemetaanalyse:

- Accordingly, the top three treatments with the greatest probability of being ranked first for reducing the exacerbation rate were reslizumab 3 mg/kg with P1 = 51%, followed by mepolizumab 750 mg (P1 = 22%) and mepolizumab 100 mg (P1 = 13%).
- Corresponding rate ratio reductions regarding the exacerbation rate vs. placebo were 0.46 [0.3, 0.69] for reslizumab 3 mg/kg, 0.51 [0.35, 0.77] for mepolizumab 750 mg and 0.55 [0.37, 0.83] for mepolizumab 100 mg. As expected, benralizumab 2 mg did not significantly differ from placebo.
- Regarding the asthma control questionnaire (ACQ-5) findings, benralizumab 20 mg had the greatest probability of being ranked first (mean difference vs. placebo -0.38 [-0.97, 0.18], P1 = 27%). Reslizumab 3 mg/kg (0.14 L [0.05, 0.24], P1 = 37%) had the best likelihood of being ranked first for FEV1 improvement. Regarding safety concerns, we analysed non-severe adverse events first. Benralizumab 20 mg had the greatest probability of being ranked as the safest (RR = 0.94 [0.57, 1.54], P1 = 28%), which was also in favour of the treatment. For severe adverse events, reslizumab was ranked as the best SAE reducer compared to placebo (RR = 0.81 [0.22, 3.03], P1 = 37%), again in favour of the treatment.

Subgruppenalanyse:

- In the eosinophilic subgroup, the top three drugs for exacerbation rate reduction were reslizumab 3 mg/kg with a 0.46 [0.26, 0.81] rate ratio regarding the annual exacerbation rate vs. placebo, with a probability of being the best treatment P1 = 41%.
- This treatment was followed by mepolizumab 750 mg with 0.49 [0.23, 1.02] (P1 = 27%) vs. placebo, and then mepolizumab 100 mg with a 0.54 [0.31, 0.97] (P1 = 11%) rate ratio regarding the annual exacerbation rate vs. placebo.
- On average, benralizumab 20 mg had the highest probability of being the best treatment for improving the FEV1 value (0.15L [0.30, 0.60], P1 = 29%) and decreasing the ACQ-5 score (-0.36 [-2.28, 1.56], P1 = 18%).

63) 12 Castro M, Mathur S, Hargreave F et al Reslizumab for poorly controlled, eosinophili asthma: a randomized, placebo controlled study. Am J Respi Crit Care Med 2011; 184:1125–32.

64) 13 Castro M, Wenzel SE, Bleecker ERet al. Benralizumab, an anti-interleuki 5 receptor a monoclonal antibody versus placebo for uncontrolled eosinophili asthma: a phase 2b randomise dose-ranging study. Lance Respir Med 2014; 2:879–90.

65) 15 Castro M, Zangrilli J, Wechsler ME et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo- controlled, phase 3 trials. Lancet Respir Med 2015; 3:355–66.

66) 16 Bel EH, Wenzel SE, Thompson PJ et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014; 371:1189–97.

67) 17 Ortega HG, Liu MC, Pavord ID et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014; 371:1198–207.

68) 18 Pavord ID, Korn S, Howarth P et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012; 380:651–9.

69) 19 Flood-Page P, Swenson C, Faiferman Iet al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007; 176:1062–71.

70) 20 Haldar P, Brightling CE, Hargadon B et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009; 360:973–84.

**Anmerkung/Fazit der Autoren**

In conclusion, anti-IL-5 treatment had significant effects in severe asthma patients with frequent exacerbations and evidence of eosinophilic inflammation. Reslizumab appeared to be the most effective mAb in reducing exacerbation rates and improving FEV1. Nonetheless, mepolizumab 100 mg and benralizumab 20 mg appeared to be excellent alternatives. No clear significant differences between treatments in terms of efficacy and safety were found due to the limited number of studies available.

Long-term effects, best duration of treatment and the risk of relapse after withdrawal are important issues that should be addressed in further studies. A clear definition of the satisfactory clinical response and the ideal response time for its assessment would also be warranted.

*Kommentare zum Review*

- Siehe auch: Casale TB et al. [9]

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**Wang FP et al., 2016 [32].**

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

**Fragestellung**

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

**Methodik**

Population:

adults/adolescents (12 years) with diagnosis of asthma

Intervention:

anti-interleukin-5 monoclonal antibody therapy at any dose

Komparator:

placebo-controlled or standard therapy

Endpunkte:

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

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

20 RCTs

Charakteristika der Population:

Sample sizes ranged from 19 to 1306 subjects.

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

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

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

Qualität der Studien:

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

Studienergebnisse:

Subgroup analysis of asthma exacerbation and FEV1 in RCTs.

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

71) Studies including patients with severe/referactory asthma

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

73) **23.** Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009; 360(10):985±93. doi: 10. 1056/NEJMoa0805435
74) **24.** Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. The Lancet. 2012; 380 (9842):651±9. doi: 10.1016/S0140-6736(12)60988-X
75) **25.** Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoidsparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014; 371(13):1189±97. doi: 10. 1056/NEJMoa1403291
76) **26.** Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371(13):1198±207. doi: 10.1056/ NEJMoa1403290 PMID: 25199059.
77) **27.** Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. Am J Respir Crit Care Med. 2003; 167(12):1655±9. Epub 2003/03/22. doi: 10.1164/rccm.200206-525OC PMID: 12649124.
78) **28.** Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011; 184 (10):1125±32. Epub 2011/08/20. doi: 10.1164/rccm.201103-0396OC PMID: 21852542.
79) Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety o benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroid Anti-Interleukin-5 Therapy for Asthma and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3
80) trial. Lancet. 2016. doi: 10.1016/S0140-6736(16)31324-1 PMID: 27609408.
81) **37.** FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin- 5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016. doi: 10.1016/S0140-6736(16)31322-8 PMID: 27609406.

**Anmerkung/Fazit der Autoren**

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

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**Rodrigo GJ et al., 2016 [27].**

Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma. A systematic review with meta-analysis

**Fragestellung**

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

**Methodik**

Population:

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

Intervention:

- Fluticasone furoate evilanterol

Komparator:

- ICS monotherapy or ICS-LABA twice-daily combinations

Endpunkte:

- pulmonary function (forced expiratory volume in 1 second [$FEV_1$] or peak expiratory flow rate [PEF]) as a primary outcome
- rescue medication use, health status (Asthma Quality of Life Questionnaire [AQLQ] total score), asthma control, number of patients with at least 1 severe asthma exacerbation (defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥3 days or a hospitalization or emergency department visit due to asthma), withdrawals,

- safety of treatment (adverse events [AEs], serious adverse events [SAEs], cardiac events, and pneumonia). A SAE was defined as any untoward medical occurrence that sometimes results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability or incapacity

Recherche/Suchzeitraum:

- bis Januar 2016

Qualitätsbewertung der Studien:

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

Heterogenität: Statistical heterogeneity was measured by the I2 test (<25% absence, 26%-39% unimportant, 40%-60% moderate, and 60%-100% substantial).

Subruppen: a priori subgroup analysis, we explored the influence of the dose of fluticasone furoate-vilanterol (100/25 mg vs 200/25 mg once daily). Subgroups were compared using the residual $Chi^2$ test from the Peto odds ratios

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 7 RCTs (N=5.668)

Charakteristika der Population:

Characteristics of the Included Studies

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

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

Qualität der Studien:

- Qualitätsbewertung: the studies had a high methodologic quality

**Studienergebnisse:**

Fluticasone furoate-vilanterol vs. fluticasone furoate, 100 mg (3 Studien) (no statistical heterogeneity among studies)

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

Fluticasone Furoate-Vilanterol Group vs Fluticasone Propionate, 500 mg (3 Studien[27-29])

- fluticasone furoate-vilanterol significantly increased the percentage of patients symptom free and reduced the number of patients with at least 1 severe asthma exacerbation (1.3% vs 2.4%, NNTB ¼ 88).
- No statistical difference in health status. Safety outcomes revealed no significant differences in AEs (1.4% vs 2.4%) or in the occurrence of pneumonia (0.4% vs 0.2%)
- fluticasone furoate-vilanterol group had a nonsignificant small increase in the frequency of cardiac events (6.4% vs 1.8%) compared with fluticasone propionate (Ergebnis von einer Studie[27])

Fluticasone FuroateeVilanterol, 100/25 mg, vs Fluticasone Propionatee Salmeterol, 250/50 mg (1 Studie[30])

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

82) [24] Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax. 2014;69:312e319.

83) [25] Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25mg or 200/25 mg) or FF (100 mg) in persistent asthma. J Asthma. 2015;52:1073e1083.

84) [26] Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014;2:553e561.

85) [27] Busse WW, O'Byrne PM, Bleecker ER, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the b2 agonist vilanterol administered once daily for 52 weeks in patients 12 years old with asthma: a randomised trial. Thorax. 2013;68:513e520.

86) [28] Lin J, Kang J, Lee SH, et al. Fluticasone furoate/vilanterol 200/25 mg in Asian asthma patients: a randomized trial. Respir Med. 2015;109:44e53.

87) [29] O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014;43:773e782.

88) [30] Woodcock A, Bleecker ER, Lötvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013;144:1222e1229.

**Anmerkung/Fazit der Autoren**

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

## 3.4 Leitlinien

**Bundesärztekammer (BÄK), 2018 [6].**

Nationale VersorgungsLeitlinie 3. Auflage, 2018 Asthma – Langfassung

**Leitlinienorganisation/Fragestellung**

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

**Methodik**

Grundlage der Leitlinie

Primär werden die Mitgliedsgesellschaften der AWMF, die in den jeweiligen Themenbereichen aktiv sind sowie die Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) angesprochen. Zusätzlich werden Patientenvertreter nach einem festgelegten Verfahren eingeladen. Die Repräsentativität der Leitliniengruppe zur Entwicklung der NVL wird in der Auftaktsitzung durch die Leitlinien-gruppe geprüft.

Die Koordination der NVL-Entwicklung obliegt dem ÄZQ. Jede neue NVL und jede Überarbeitung einer NVL wird bei der AWMF angemeldet.

Die Recherche kann abhängig von der Fragestellung, den vorhandenen Ressourcen und der Evidenzlage auf drei verschiedenen Ebenen (Leitlinien, Aggregierte Evidenz, Primärliteratur) erfolgen.

Die systematische Berücksichtigung der Evidenz zur Formulierung und Graduierung der Empfehlungen orientiert sich an GRADE. Für die endgültige Formulierung und Graduierung von Empfehlungen bei einer Präsenzveranstaltung wurde die Technik des Nominalen Gruppenprozesses

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

Recherche/Suchzeitraum:

- Cochrane, Medline
  - Wirksamkeit und Sicherheit von Anti-IL-5-Antikörpern bei Patienten mit Asthma 28.03.2017
  - Wirksamkeit und Sicherheit von Benralizumab 26.04.2018
- Reviews: 26.03. 2016
- Leitlinien: bis 29.01.2016

LoE

- Bewertung des Biasrisikos (Risiko systematischer Fehler) in klinischen Studien: ein Manual für die Leitlinienerstellung

GoR

Tabelle 1: Einstufung von Leitlinien-Empfehlungen in Empfehlungsgrade (Grades of Recommendation) [8]

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

**Empfehlungen**

Definition schweres Asthma

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

**Stufenschema**

**Medikamentöses Stufenschema | ERWACHSENE**

| | Stufe 1 | Stufe 2 | Stufe 3 | Stufe 4 | Stufe 5 |
|---|---|---|---|---|---|
| Langzeittherapie | – ICS niedrigdosiert | – ICS niedrigdosiert | – ICS niedrigdosiert + LABA (bevorzugt)<br>oder<br>– ICS mitteldosiert | – ICS mittel- bis hochdosiert + LABA (bevorzugt)<br>oder<br>– ICS mittel- bis hochdosiert + LABA + LAMA* | – ICS in Höchstdosis + LABA + LAMA*<br>– Vorstellung bei einem in der Behandlung von schwerem Asthma erfahrenen Pneumologen<br>und<br>– Anti-IgE- oder Anti-IL-5-(R)-Antikörper |
| **Alternativen in begründeten Fällen:** | | | | | |
| | – ICS niedrigdosiert | – LTRA | – ICS niedrigdosiert + LAMA*<br>oder<br>– ICS niedrigdosiert + LTRA | – ICS mittel- bis hochdosiert + LABA + LTRA<br>oder<br>– ICS mittel- bis hochdosiert + LAMA* | – OCS (zusätzlich oder alternativ) |
| Bedarfstherapie | – SABA | | – SABA<br>oder<br>– Fixkombination aus ICS und Formoterol, wenn diese auch die Langzeittherapie darstellt | | |

Asthmaschulung, Allergie-/Umweltkontrolle, Beachtung von Komorbiditäten

Spezifische Immuntherapie (bei gegebener Indikation)

Im Stufenschema werden zur besseren Übersicht übergeordnete Arzneimittelkategorien und keine einzelnen Präparate genannt. Nicht alle Präparate und Kombinationen sind für die jeweilige Indikation zugelassen (siehe Fachinformationen), teilweise handelt es sich um einen Off-Label-Use (siehe Kapitel 4 Medikamentöse Therapie).

* aus der Gruppe der LAMA ist Tiotropium für die Behandlung des Asthmas zugelassen (Stand: September 2018)

ICS: Inhalative Corticosteroide, IgE: Immunglobulin E, IL-5: Interleukin 5, LABA: Langwirkende Beta-2-Sympathomimetika, LAMA: Langwirkende Anticholinergika, LTRA: Leukotrienrezeptorantagonisten, OCS: Orale Corticosteroide, SABA: Kurzwirkende Beta-2-Sympythomimetika

## 4.2 Allgemeine Therapieprinzipien innerhalb des Stufenschemas

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-3**<br>Ein geringer Bedarf an kurzwirkenden Beta-2-Sympathomimetika (SABA) ist ein wichtiges Ziel und ein Kriterium für den Erfolg der Therapie. | **Statement** |
| **4-4 \| ERWACHSENE**<br>Die Therapie mit inhalativen Corticosteroiden (ICS) soll bei Erwachsenen in den Therapiestufen 2 bis 5 die Basis der Langzeittherapie sein. | ⇑⇑ |

### Therapieintensivierung

| | |
|---|---|
| **4-10**<br>Bei unkontrolliertem Asthma soll eine Intensivierung der Therapie den Stufenschemata folgend empfohlen werden. | ⇑⇑ |
| **4-11**<br>Bei teilweise kontrolliertem Asthma sollte eine Intensivierung der Therapie den Stufenschemata folgend erwogen werden. | ⇑ |
| **4-12**<br>Nach einer Intensivierung der Langzeittherapie gemäß Stufenschema soll die Asthmakontrolle innerhalb von drei Monaten überprüft werden. | ⇑⇑ |

### Empfehlungen zu Stufe 4

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

Eine systematische Übersichtsarbeit [107] verglich die Kombinationstherapie von ICS plus LABA mit einer Drei-fachkombination aus ICS, LABA und langwirksamen Anticholinergika (LAMA). Exazerbationen, die mit OCS be-handelt werden mussten, traten bei Patienten, die die Dreifachkombination erhielten, seltener auf (271/1 000 vs. 328/1 000). Der Unterschied war jedoch nicht signifikant (OR 0,76 (95% KI 0,57; 1,02); $I^2$ = 1%, 2 RCTs, n = 907, Datenqualität moderat). Ebenfalls nicht signifikant waren die Unterschiede im Gruppenvergleich hinsichtlich der Lebensqualität, der schweren unerwünschten Effekte und der Exazerbationen, die eine Hospitalisierung erforder-lich machten. Die Asthmakontrolle, erhoben mit dem Asthma-Control-Questionnaire (ACQ-9), war zugunsten der Dreifachkombination verbessert (MD -0,13 (95% KI -0,23; -0,02); $I^2$ = 0%, n = 907, 2 RCTs, Datenqualität hoch). Zudem waren jegliche unerwünschte Effekte bei Erhalt der Dreifachkombination seltener (OR 0,70 (95% KI 0,52; 0,94); $I^2$ = 0%, 3 RCTs, n = 1 197, Datenqualität hoch). [107]

Die Autoren sehen eine additive Behandlung mit LAMA zu einer bereits bestehenden Medikation aus ICS in mitt-lerer oder hoher Dosis plus LABA als Therapiealternative für Patienten mit Asthma in Stufe 4. Wichtig ist, dass in der Stufe 4 alle verfügbaren Therapieoptionen ausgereizt werden, bevor die Therapie zur Stufe 5 eskaliert wird. Dabei entscheidet der Arzt individuell mit dem Patienten (siehe Kapitel 3.1 Gemeinsame Entscheidungsfindung), ob er zunächst die ICS-Dosis erhöht oder zu einer Dreifachkombination übergeht.

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

In begründeten Fällen, insbesondere wenn Kontraindikationen gegen die bisher verwendeten Medikamente vor-liegen oder unerwünschte Wirkungen bei deren Anwendung auftreten, empfehlen die Autoren auch die Kombina-tion aus ICS mittel- bis hochdosiert, LABA und LTRA oder ICS mittel- bis hochdosiert und LAMA. In der systema-tischen Recherche wurden keine Metaanalysen identifiziert, die die Wirksamkeit und Sicherheit der Dreifachkom-bination evaluierten.

### Empfehlung zu Stufe 5

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-32 \| ERWACHSENE**<br>Die Indikation zur Therapie mit monoklonalen Antikörpern sollte erst gestellt wer-den, wenn selbst unter dreimonatiger maximaler inhalativer antiobstruktiver Kom-binationstherapie mit einem ICS in Höchstdosis, einem LABA und einem LAMA (Tiotropium) keine Asthmakontrolle erreicht wird. | ⇑ |

Darüber hinaus weist die Leitliniengruppe darauf hin, dass die Therapie mit monoklonalen Antikörpern in Stufe 5 sehr aufwändig und über einen längeren Zeitraum mit hohen Kosten verbunden ist. Vor diesem Hintergrund er-achten sie es als notwendig, dass die in der Empfehlung 4-32 genannte Dreifachkombination mit ICS höchstdo-siert (siehe Tabelle 6) über drei Monate evaluiert wird, bevor die Therapie mit monoklonalen Antikörpern initiiert wird. Der Eindruck aus der

Versorgungssituation ist, dass die Kombination ICS plus LABA plus LAMA vor einer weiteren Therapieeskalation häufig nicht ausgeschöpft wird, da es sich um ein eher neueres Therapiekonzept handelt.

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-33 \| ERWACHSENE**<br>Ein Therapieversuch mit Omalizumab für mindestens vier Monate soll bei Erwachsenen in Stufe 5 empfohlen werden, wenn folgende Kriterien vorliegen:<br>• schweres IgE-vermitteltes allergisches Asthma und<br>• positiver Hauttest oder in-vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen und<br>• IgE-Serumkonzentration unter Berücksichtigung des Körpergewichts im therapierbaren Bereich und<br>• erfolgte Eliminierung vermeidbarer Allergenexpositionen. | ⇑⇑ |

Im Cochrane-Review von Normansell et al. [115] senkte Omalizumab während der kontinuierlichen Corticostero-idgabe das Risiko für eine oder mehr Exazerbationen im Vergleich zu Placebo (OR 0,55 (95% KI 0,46; 0,65); $I^2$ = 50%, 10 RCTs, n = 3 261, moderate Datenqualität) und die Häufigkeit von Hospitalisierungen (OR 0,16 (95% KI 0,06; 0,42); $I^2$ = 0%, 4 RCTs, n = 1 824, moderate Datenqualität). Bei schwererer Erkrankung war der Effekt von Omalizumab hinsichtlich der Exazerbationen nicht mehr signifikant [115].

Die Daten zur Sicherheit wurden für die steroidstabile und die Ausschleichphase gemeinsam ausgewertet [115]. Schwere unerwünschte Wirkungen waren in der Gruppe der mit Omalizumab behandelten Patienten weniger wahrscheinlich (OR 0,72 (95% KI 0,57; 0,91); $I^2$ = 7%, 15 RCTs, n = 5 713, Datenqualität moderat). Hinsichtlich jeglicher unerwünschter Wirkungen und Mortalität ergab sich kein Unterschied. Reaktionen an der Injektionsstelle waren unter Omalizumab höher (OR 1,72 (95% KI 1,33; 2,24); $I^2$ = 42%; 9 RCTs, n = 3 577, Datenqualität mode-rat). [115]

Die gepoolten Auswertungen von Daten aus Studien mit einer Dauer von 52 bis 60 Wochen von Lai et al. zeigten ähnliche Tendenzen für die oben genannten Endpunkte [118].

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-34 \| ERWACHSENE**<br>Ein Therapieversuch mit Mepolizumab, Reslizumab oder Benralizumab für mindestens vier Monate sollte bei Erwachsenen in Stufe 5 erwogen werden, wenn folgende Kriterien vorliegen:<br>• schweres eosinophiles Asthma und<br>• zweimaliger Nachweis einer Konzentration von > 300 Eosinophilen pro µl Blut außerhalb von Exazerbationen in den vergangenen zwei Jahren. | ⇑ |

Im Vergleich zu Placebo senkte die subkutanen Gabe von Mepolizumab in einem Studienzeitraum von 32 Wo-chen (MENSA) die Rate klinisch relevanter Exazerbationen (0,83 vs. 1,74; Rate Ratio 0,47 (95% KI 0,35; 0,63); 1 RCT, n = 385, Datenqualität moderat) und die Anzahl der Exazerbationen, die das Aufsuchen einer Notaufnahme oder eine Hospitalisierung nach sich zogen [122]. Des Weiteren verbesserten sich die Lebensqualität und die Symptome signifikant, letztere allerdings nicht klinisch relevant [122].

Ein RCT (SIRIUS) [123] mit 135 Teilnehmern berichtet, dass durch die subkutane Applikation von Mepolizumab über einen Zeitraum von 24 Wochen im Vergleich zu Placebo mehr OCS eingespart werden konnten (OR 2,39 (95% KI 1,25; 4,56)). Auch die jährlich Exazerbationsrate verbesserte sich durch Mepolizumab trotz der OCS-Reduktion (Rate Ratio 0,68 (95% KI 0,47; 0,99) [123]. Die niedrige Fallzahl und die fehlende Verblindung der Er-gebnisevaluation stellen allerdings ein Risiko für eine Verzerrung dar.

Die Phase-III-Studie von Corren et al. [125] prüfte die Abhängigkeit der Wirksamkeit und Sicherheit von Reslizu-mab von der Eosinophilenzahl im Blut bei Patienten der Altersgruppe von 18 bis 65 Jahren über einen Zeitraum von 16 Wochen. Bei der Ausgangserhebung wiesen 20% der eingeschlossenen Patienten eine Eosinophilenzahl ≥ 400/µl auf. Eine klinisch relevante Verbesserung der Asthmakontrolle, gemessen mit dem ACQ-7, war unter Reslizumab häufiger als in der Placebogruppe. Je höher die Eosinophilenzahl war, desto deutlicher war die Ver-besserung der Asthmakontrolle. Die Fallzahl für diese Subgruppenanalyse war jedoch gering und die Power der Studie genügte nicht, um repräsentative Ergebnisse zu generieren. [125]

Gestützt werden die Aussagen von Corren et al. [125] durch eine weitere Phase-III-Studie [126], bei der eine mindestens einmalige Erhöhung der Eosinophilenzahl auf ≥ 400/µl eines der Einschlusskriterien war. Untersucht wurden die Dosierungen 0,3 mg/kg Körpergewicht (KG) und 3,0 mg/kg KG im Vergleich zu Placebo. Sowohl die Asthmasymptome als auch die Asthmakontrolle, erhoben mit dem ACQ, verbesserten sich in beiden Interventi-onsgruppen im Vergleich zu Placebo. Die Verbesserung der Lebensqualität, gemessen mit dem AQLQ, wurde nur bei der höheren Dosierung ersichtlich, war jedoch klinisch nicht relevant (delta of least square mean 0,359 (95% KI 0,047; 0,670). [126] Die Qualität der Studie ist durch ein unklares Risiko für Selektionsbias, Performance bias, Detection bias und ein hohes Risiko für Attrition bias limitiert.

Die subkutane Anwendung von Benralizumab bei schwerem Asthma wurde in zwei Phase-III-Studien (SIROCCO und CALIMA) untersucht, die sehr ähnliche Studiendesigns, jedoch leicht differierende Beobachtungszeiträume hatten [127,128]. In der Studie CALIMA führte die subcutane Gabe von Benralizumab im 4-Wochen-Intervall (Rate Ratio 0,64 (95% KI 0,49; 0,85) und im 8-Wochen-Intervall (Rate Ratio 0,72 (95% KI 0,54; 0,95)) über einen Zeitraum von 56 Wochen im Vergleich zu Placebo zur Reduktion der jährlichen Exazerbationsrate [127]. In der Studie SIROCCO führte die subcutane Gabe von Benralizumab im 4-Wochen-Intervall (Rate Ratio 0,55 (95% KI 0,42; 0,71) und im 8-Wochen-Intervall (Rate Ratio 0,49 (95% KI 0,37; 0,64)) über einen Zeitraum von 48 Wochen im Vergleich zu Placebo zur Reduktion der jährlichen Exazerbationsrate [128]. Die Asthmasymptome verbesserten sich im Vergleich zu Placebo in beiden Studien nur in der Gruppe der im 8-Wochen-Intervall behandelten Patienten [127,128]. Unklar bleibt, ob die Ergebnisevaluation in den Studien ver-blindet erfolgte.

Eine weitere Phase-III-Studien (BISE) untersuchte die Wirksamkeit und Sicherheit von Benralizumab im Vergleich zu Placebo bei Patienten mit mildem bis moderatem Asthma: Hier ergaben sich hinsichtlich des Symptomscores und der asthmabezogenen Lebensqualität keine signifikanten Unterschiede zwischen der Interventions- und der Placebogruppe [129].

Überdies untersuchte die Studie ZONDA [130] den corticosteroidsparenden Effekt von Benralizumab über einen Zeitraum von 28 Wochen. Die Chance einer Reduktion von OCS war bei der Gabe von Benralizumab im 4-Wochen-Intervall OR 4,09 (95% KI 2,22; 7,57) und im 8-Wochen-Intervall OR 4,12 (95% KI 0,22; 7,63) höher als bei der Gabe von Placebo [130].

Ein Wirksamkeitsvergleich zwischen den einzelnen monoklonalen Antikörpern wurde in der systematischen Re-cherche nicht identifiziert.

Zu Sicherheitsaspekten von Mepolizumab, Reslizumab und Benralizumab stehen bisher nur die Zulassungsstu-dien bzw. teilweise deren Verlängerungen zur Verfügung. In einigen Studien floss der nicht näher bzw. ungenau definierte Endpunkt „Verschlechterung des Asthmas“ als unerwünschte Wirkung ein: Hier blieb meist unklar, ob zum Beispiel auch die Effektivitätsendpunkte Exazerbationen oder Symptome mit ausgewertet wurden [123–126]. Teilweise wurde in den identifizierten Studien ersichtlich, dass es sich dabei auch um Exazerbationen handelt [127–130,139]. Vor diesem Hintergrund lassen sich ähnliche oder erhöhte Raten an unerwünschten und schwe-ren unerwünschten Nebenwirkungen in der Placebogruppe erklären [122–130].

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-38 \| ERWACHSENE**<br>Die Langzeittherapie mit systemischen Corticosteroiden soll bei Erwachsenen in Stufe 5 wegen der Gefahr schwerer Nebenwirkungen nicht empfohlen werden, es sei denn, die Asthmakontrolle ist trotz des kombinierten Einsatzes der verschiedenen Therapieoptionen der vorherigen Stufe sowie zusätzlich monoklonaler Antikörper (sofern indiziert und wirksam) unzureichend. | ⇓⇓ |

Auch wenn zum aktuellen Zeitpunkt nur begrenzte Langzeiterhebungen für die Sicherheit der verschiedenen monoklonalen Antikörper vorliegen (siehe Empfehlun-gen 4-33, 4-34 bis 4-37), werden die unerwünschten Langzeitwirkungen von systemischen Corticosteroiden als so erheblich eingeschätzt, dass die Leitliniengruppe OCS als nachrangige Therapieoption für die Langzeittherapie in Stufe 5 einordnen.

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

Asthma: diagnosis, monitoring and chronic asthma management.

**Leitlinienorganisation/Fragestellung**

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

**Methodik**

Grundlage der Leitlinie

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

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

Recherche/Suchzeitraum:

- 09/2016

LoE/GoR

Overall quality of outcome evidence in GRADE

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

**Empfehlungen**

Treatment in patients not on regular preventers

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

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

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

22. If asthma is uncontrolled in children and young people (aged 5 to 16) on a paediatric low dose of ICS and a LABA as maintenance therapy, consider changing their ICS and LABA maintenance therapy to a MART regimen10 with a paediatric low maintenance ICS dose. Ensure that the child or young person is able to understand and comply with the MART regimen.

23. If asthma is uncontrolled in children and young people (aged 5 to 16) on a MART regimen11 with a paediatric low maintenance ICS dose, consider increasing the ICS to a paediatric moderate maintenance dose (either continuing on a MART regimen or changing to a fixed-dose of an ICS and a LABA, with a SABA as a reliever therapy).

Quality of the clinical evidence:

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

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

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

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

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

- increasing the ICS to a high maintenance dose (this should only be offered as part of a fixed-dose regimen, with a SABA used as a reliever therapy) or
- a trial of an additional drug (for example, a long-acting muscarinic receptor antagonist or theophylline) or
- seeking advice from a healthcare professional with expertise in asthma.

Quality of the clinical evidence:

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

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

Trade-off between clinical benefits and harms

Uncontrolled on ICS moderate dose, adults

Possible interventions identified in the evidence at this stage included the addition of a LABA, addition of a LABA and conversion to MART, increasing ICS dose, addition of an LTRA, addition of a LAMA and addition of a theophylline. Any one of the additional preventers could be accompanied by an increase or decrease in steroid dose simultaneously.

Consistent with the review of interventions for those uncontrolled on ICS low dose, the addition of a LABA appeared to have the greatest benefit for critical outcomes like severe exacerbations. Again consistent with the previous review there was little difference between addition of a LABA and addition of an LTRA when compared directly, although the addition of an LTRA had less benefit than addition of a LABA when compared to continuing on ICS moderate dose. Consistent with the evidence in the population uncontrolled on ICS + LABA, the use of MART appeared to have clinically important benefits over ICS + LABA + SABA when required.

Uncontrolled on ICS high dose, adults

Possible interventions identified in the evidence at this stage included the addition of a LABA, addition of a LABA and conversion to MART and addition of an LTRA. Any one of the additional preventers could be accompanied by a change in steroid dose.

There was evidence of a clinically important benefit of addition of LABA compared to continuation on ICS high dose in terms of reliever medication use. The direct comparison between addition of LABA and conversion to MART as opposed to just addition of LABA showed a clinically important benefit for MART in terms of severe exacerbations

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**Global Initiative for Asthma (GINA), 2020 [20].**

*GINA – Global Initiative for Asthma*

Global strategy for asthma management and prevention (2020 update)

Siehe auch [19]

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The GINA report has been updated in 2020 following the routine twice-yearly review of the literature by the GINA Science Committee.
- The literature searches for ‘clinical trial’ publication types (see above) and meta-analyses identified a total of 2,420 publications, of which 1,860 were screened out for duplicates, relevance and/or quality.
- The remaining 560 publications (377 ‘clinical trials’ and 183 meta-analyses) were reviewed by at least two members of the Science Committee; a total of 89 were subsequently discussed at face-to-face meetings in May 2019 in Dallas, USA and in September 2019 in Madrid, Spain.
- A list of key changes in GINA 2020 can be found starting on p.14, and a tracked changes copy of the 2019 report is archived on the GINA website at www.ginasthma.org/archived-reports/.

LoE

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



GoR

- keine Angabe des GoR.

Sonstige methodische Hinweise

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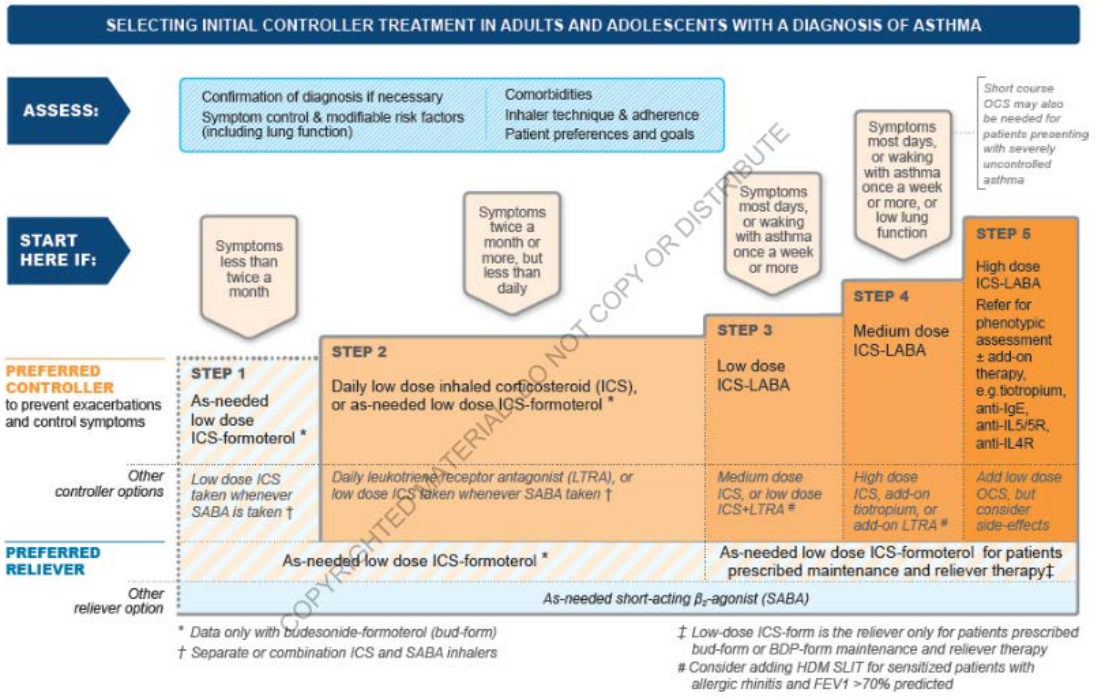
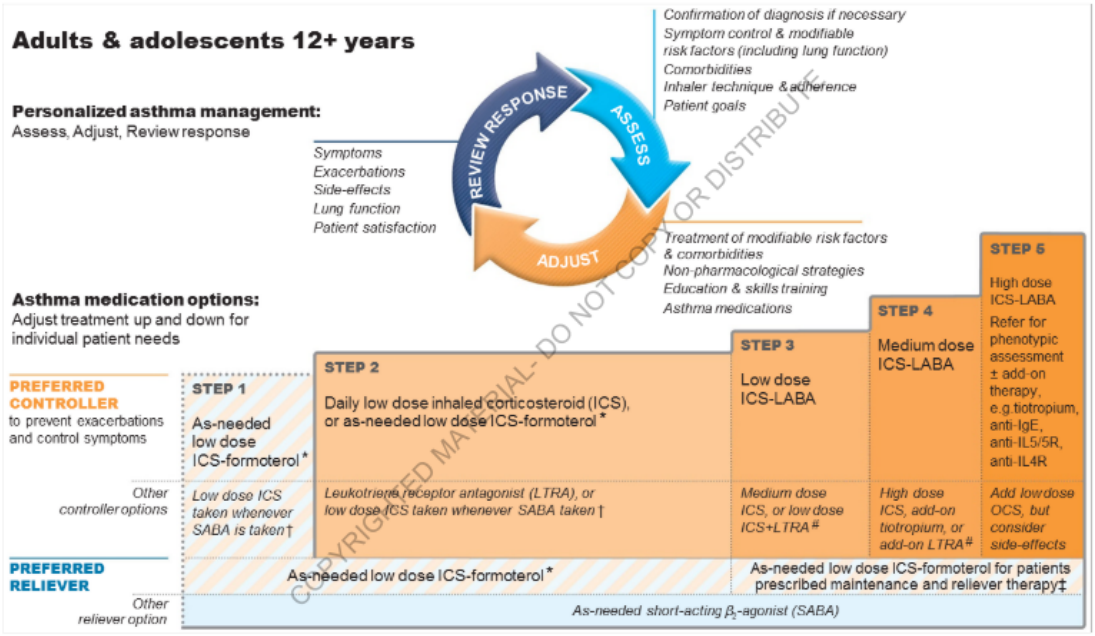
## Empfehlungen

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




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

**Box 3-5A. Personalized management for adults and adolescents to control symptoms and minimize future risk**




HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist; SLIT: sublingual immunotherapy. For recommendations about *initial* asthma treatment in adults and adolescents, see Box 3-4A (p.50) and 3-4B (p.51).

STEP 3: Preferred controller options: Low dose ICS-LABA maintenance plus as-needed SABA, OR low dose ICS-formoterol maintenance and reliever therapy (adults and adolescents); medium dose ICS plus as-needed SABA OR low-dose combination ICS-LABA plus as-needed SABA (children 6–11 years)

- Before considering a step up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p.40).

Preferred Step 3 controller options for adults and adolescents

- For adults and adolescents, there are two 'preferred' Step 3 options:
  - combination low dose ICS-LABA as maintenance treatment with as-needed SABA as reliever, and
  - low dose ICS-formoterol as both maintenance and reliever treatment.
- For patients receiving maintenance ICS treatment with as-needed SABA, adding LABA in a combination inhaler provides additional improvements in symptoms and lung function with a reduced risk of exacerbations compared with the same dose of ICS,[214,215] (Evidence A) but there is only a small reduction in reliever use.
- Currently approved combination ICS-LABA inhalers for Step 3 maintenance treatment of asthma include low doses of fluticasone propionate-formoterol, fluticasone furoate-vilanterol, fluticasone propionate-salmeterol, beclometasone-formoterol, budesonide-formoterol and mometasone-formoterol (see Box 3-6, p.56). Effectiveness of fluticasone furoate-vilanterol over usual care was demonstrated for asthma symptom control in a large real-world study, but there was no difference in risk of exacerbations.
- The ICS-formoterol maintenance and reliever regimen can be prescribed with low dose beclometasone-formoterol or budesonide-formoterol. In adult and adolescent patients with ≥1 exacerbation in the previous year, the ICS-formoterol maintenance and reliever regimen significantly reduces exacerbations and provides similar levels of asthma control at relatively low doses of ICS, compared with a fixed dose of ICS-LABA as maintenance treatment or a higher dose of ICS, both with as-needed SABA219-224 (Evidence A). Low dose ICS-formoterol is the preferred reliever for patients prescribed the maintenance and reliever treatment regimen. It should not be used as the reliever for patients taking combination ICS-LABA medications with a different LABA. For patients prescribed ICS-formoterol maintenance and reliever therapy, the maximum recommended dose of formoterol in a single day, based on product information, is 48 mcg (for beclometasone-formoterol) or 72mcg (for budesonide-formoterol)

Other Step 3 controller options for adults and adolescents

- For adult patients with allergic rhinitis and sensitized to house dust mite, with suboptimally controlled asthma despite low to high dose ICS, consider adding sublingual allergen immunotherapy (SLIT), provided FEV1 is >70% predicted.[225,226] (see p.68).
- Another option for adults and adolescents is to increase ICS to medium dose130 (see Box 3-6, p.56), but at a group level this is less effective than adding a LABA227,228 (Evidence A). Other less efficacious options are low dose ICS plus either LTRA229 (Evidence A) or low dose, sustained-release theophylline230 (Evidence B). See note above about the FDA warning for montelukast.[205]

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

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

Preferred Step 4 controller options for adults and adolescents

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

Other Step 4 controller options for adults and adolescents

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

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

- Patients of any age with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in investigation and management of severe asthma[138] (Evidence D).
- In severe asthma, as in mild-moderate asthma,245 participants in randomized controlled trials may not be representative of patients seen in clinical practice. For example, a registry

study found that over 80% of patients with severe asthma would have been excluded from recent studies evaluating biologic therapy.[246]

- The GINA Pocket Guide and decision tree on Diagnosis and Management of difficult-to-treat and severe asthma in adolescent and adult patients are included in Chapter 3E (p.94). Treatment options that may be considered after optimization of existing therapy may include the following (always check local eligibility and payer criteria): • Combination high dose ICS-LABA: this may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit122,130,228 (Evidence A), and there is an increased risk of side-effects, including adrenal suppression.247 A high dose is recommended only on a trial basis for 3–6 months when good asthma control cannot be achieved with medium dose ICS plus LABA and/or a third controller (e.g. LTRA or sustained-release theophylline208,243 Evidence B).
- Add-on tiotropium (long-acting muscarinic antagonist) in patients aged ≥6 years whose asthma is not wellcontrolled with ICS-LABA. Add-on tiotropium (mostly 5µg once daily by mist inhaler) modestly improves lung function (Evidence A) and modestly increases the time to severe exacerbation requiring oral corticosteroids (Evidence B).236,237 Results with other LAMA preparations are awaited.236
- Add-on azithromycin (three times a week) for adult patients with persistent symptomatic asthma despite moderate-high dose ICS and LABA reduced asthma exacerbations in eosinophilic248 and non-eosinophilic asthma248,249 (Evidence B) and improved asthma-related quality of life248,249 (Evidence B). Diarrhea was more common.248 Since macrolides such as azithromycin can cause ototoxicity and cardiac arrhythmia, asthma patients with hearing impairment248 or abnormal prolongation of the corrected QT interval[248,249] were excluded from the studies. Before considering add-on therapy with azithromycin in adult patients with uncontrolled or severe asthma, ECG should be checked for long QTc, sputum should be checked for atypical mycobacteria, and the risk of increasing antimicrobial resistance at the patient and the population level should be taken into account. Treatment for at least 6 months is suggested, as a clear benefit was not seen by 3 months. There is no clear evidence about how long treatment should be continued.
- Add-on anti-immunoglobulin E (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4–5 treatment[250,251] (Evidence A).
- Add-on anti-interleukin-5/5R treatment (subcutaneous mepolizumab for patients aged ≥6 years; intravenous reslizumab for ages ≥18 years) or anti-interleukin 5 receptor treatment (subcutaneous benralizumab for ages ≥12 years), with severe eosinophilic asthma that is uncontrolled on Step 4–5 treatment (Evidence A).252-256 Efficacy data for mepolizumab in children 6–11 years are limited to one very small open label uncontrolled study.[257]
- Add-on anti-interleukin-4R α treatment (subcutaneous dupilumab) for patients aged ≥12 years with severe Type 2 asthma, or requiring treatment with maintenance OCS (Evidence A).[258-260]}
- Sputum-guided treatment: for adults with persisting symptoms and/or exacerbations despite high dose ICS or ICS-LABA, treatment may be adjusted based on eosinophilia (>3%) in induced sputum. In severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS161 (Evidence A).
- Add-on treatment with bronchial thermoplasty: may be considered for some adult patients with severe asthma[138,261] (Evidence B). Evidence is limited and in selected patients (see p.69). The long-term effects compared with control patients, including for lung function, are not known.

- Add-on low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma138 (Evidence D), but are often associated with substantial side effects262,263 (Evidence A). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors and other add-on treatments including biologics where available and affordable. Patients should be counseled about potential side-effects.263 They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[264]

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

**KEY POINTS**

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

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

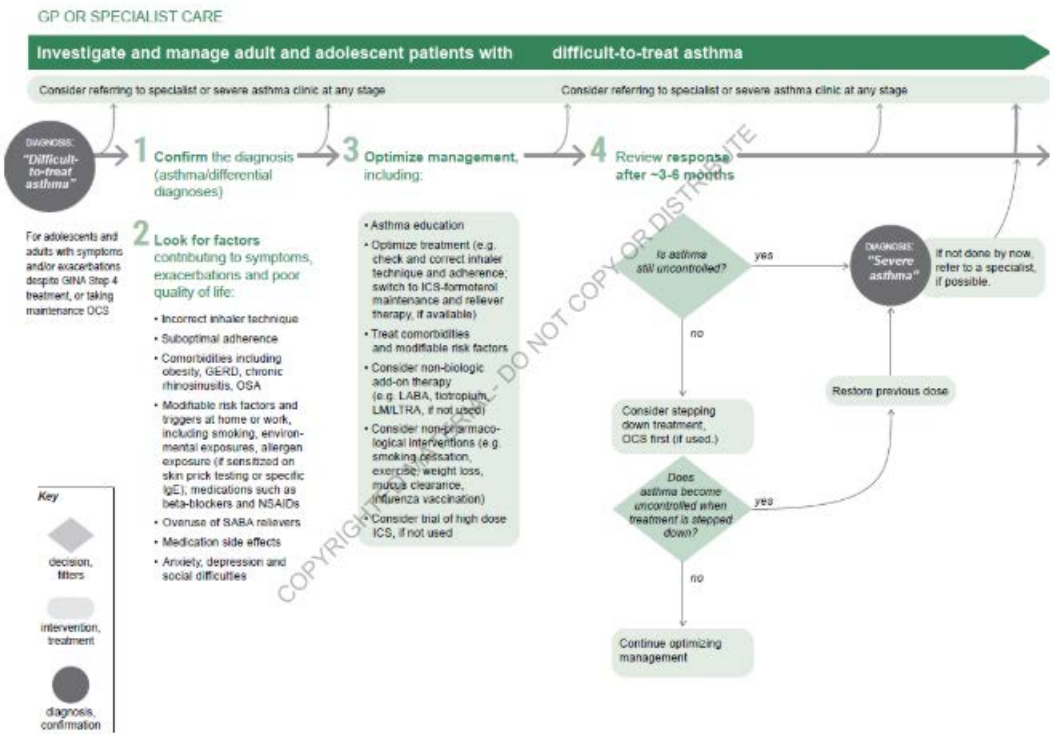
**How should these patients be assessed?**

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

**Management of severe asthma**

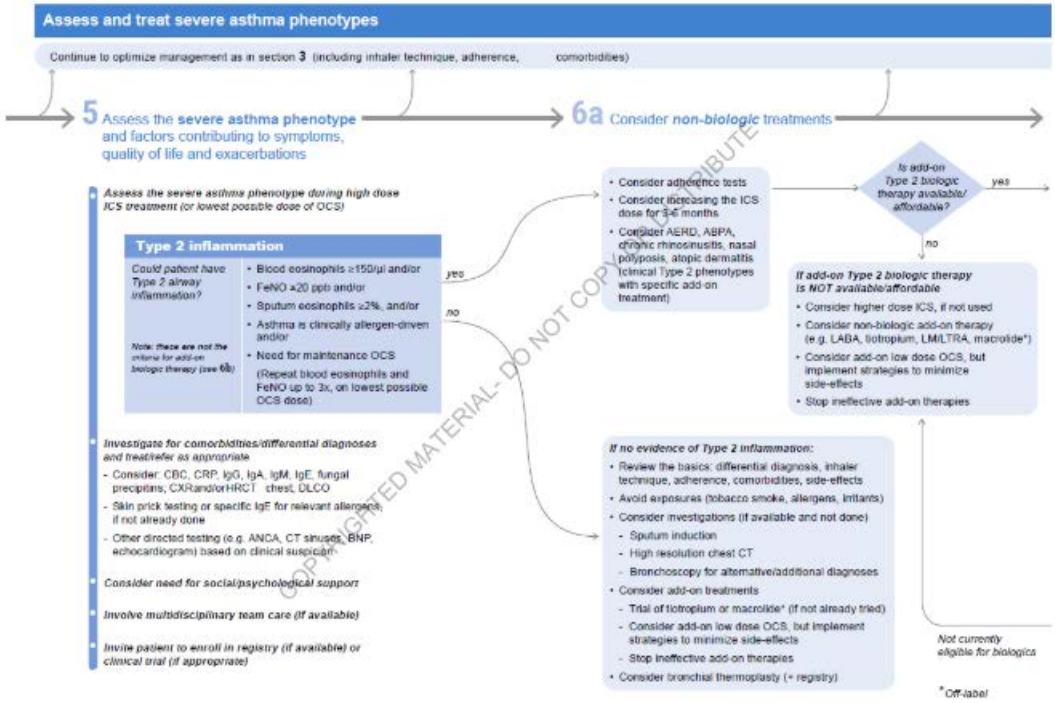
- Add-on treatments for severe asthma include tiotropium, LTRA and low dose macrolides, and biologic agents for severe allergic or severe Type 2 asthma. Maintenance OCS should be avoided if other options are available, because of its serious side-effects.
- Assess the response to any add-on treatment,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

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

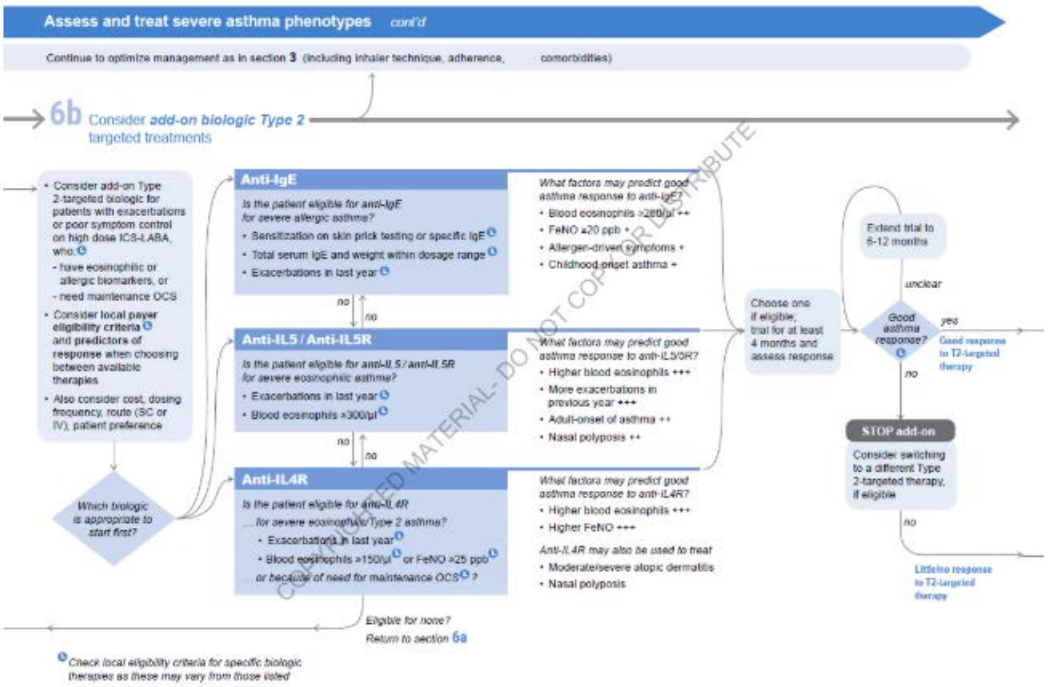




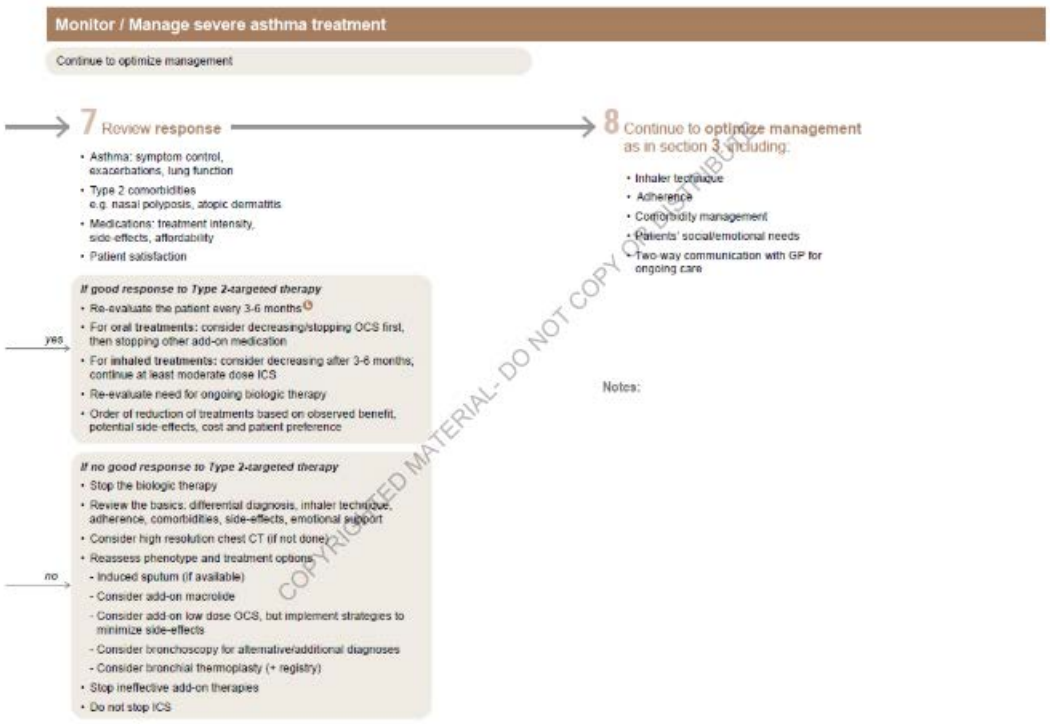

**Box 3-16B. Decision tree – assess and treat severe asthma phenotypes**



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




**Box 3-16D. Decision tree – monitor and manage severe asthma treatment**




Referenzen aus Leitlinien

Referenzen
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Backgroundinfos aus Leitlinien: Backgroundinfos aus Leitlinien: Backgroundinfos aus Leitlinien: Backgroundinfos aus Leitlinien: Backgroundinfos aus Leitlinien: Backgroundinfos aus Leitlinien: Backgroundinfos aus Leitlinien: Backgroundinfos aus Leitlinien:

**SIGN, 2019 [28].**

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

British guideline on the management of asthma

**Leitlinienorganisation/Fragestellung**

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

**Methodik**

Grundlage der Leitlinie

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

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

Loe/GoE:

### Key to evidence statements and recommendations

Levels of evidence

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

Grades of recommendation

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

| | |
|---|---|
| A | At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* |
| | 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. |

---

**Emfehlungen**

## 2.5 Pharmacological management

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

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

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

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

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

**Initial add-on**

- therapy A proportion of patients with asthma may not be adequately controlled with lowdose ICS alone. Before initiating a new drug therapy practitioners should recheck adherence (see section 5.4), inhaler technique and eliminate trigger factors. The duration of a trial of add-on therapy will depend on the desired outcome. For instance, preventing nocturnal awakening may require a relatively short trial of treatment (days or weeks), whereas preventing asthma attacks or decreasing steroid tablet use may require a longer trial of therapy (weeks or months). If there is no response to treatment the drug should be discontinued.

**Criteria for introduction of add-on therapy**

| | >12 years | 5–12 years | <5 years |
|---|---|---|---|
| No exact dose of ICS can be deemed the correct dose at which to add another therapy. The addition of other treatment options to ICS has been investigated at doses from 200–1,000 micrograms BDP in adults and up to 400 micrograms BDP in children.[462-465] Many patients will benefit more from add-on therapy than from increasing ICS above doses as low as 200 micrograms BDP/day. At doses of ICS above 800 micrograms BDP/day side effects become more frequent. An absolute threshold for introduction of add-on therapy in all patients cannot be defined. | 1++ | 1+ | |

**Inhaled long-acting β2 agonist**

| | >12 years | 5–12 years | <5 years |
|---|---|---|---|
| The addition of an inhaled long-acting $\beta_2$ agonist (LABA) to ICS alone improves lung function and symptoms, and decreases asthma attacks in adults and children.[462, 466-472] Long-acting inhaled $\beta_2$ agonists should not be used without ICS.[473] | 1++ | 1++ | |

Evidence to guide the choice of initial add-on therapy is stronger in adults than in children. On the basis of current evidence, LABA is the first choice initial add-on therapy in adults.

| | | | |
|---|---|---|---|
| In children, options for initial add-on therapy are limited to LABA and LTRA, with evidence to support both individually, but insufficient evidence to support use of one over the other *(see section 7.4.2)*.[472] LABA are not licensed for use in children under four years of age and evidence for use of LTRA in this age group is limited to studies comparing LTRA with ICS or placebo *(see section 7.2.7)*. | 1++ | 1++ | |

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

B **In children aged five and over, an inhaled long-acting $\beta_2$ agonist or a leukotriene receptor antagonist can be considered as initial add-on therapy.**

**Safety of long-acting β2 agonist**

Following a review in 2007 of LABA in the treatment of adults, adolescents, and children with asthma, the Medicines and Healthcare products Regulatory Agency (MHRA) further reviewed the use of LABA, specifically in children younger than 12 years of age and concluded that the benefits of these medicines used in conjunction with ICS in the control of asthma symptoms outweigh any apparent risks.[474]

✓ Long-acting inhaled $\beta_2$ agonists should only be started in patients who are already on inhaled corticosteroids, and the inhaled corticosteroid should be continued.

7.3.4 Combination inhaled corticosteroid/long-acting $\beta_2$ agonist inhalers

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

In efficacy studies, where there is generally good adherence, there is no difference in efficacy in giving ICS and a LABA in combination or in separate inhalers.[475]

In clinical practice it is generally considered that combination inhalers aid adherence and also have the advantage of guaranteeing that the LABA is not taken without the ICS.

✓ Combination inhalers are recommended to:

- guarantee that the long-acting $\beta_2$ agonist is not taken without inhaled corticosteroid
- improve inhaler adherence.

7.3.5 Single combination inhaler for maintenance and reliever therapy

The use of a single combination inhaler for maintenance and reliever therapy (MART) is an alternative approach to the introduction of a fixed-dose twice-daily combination inhaler which might suit some individuals. It relies on the rapid onset of reliever effect with formoterol and by including a dose of inhaled corticosteroid ensures that, as the need for a reliever increases, the dose of preventer medication is also increased. This underpins the self-management plan which must be provided with a MART regime. *See section 5.2.3* for a description of increasing inhaled corticosteroids at the onset of an attack. Maintenance and reliever therapy may also lower the overall dose of ICS needed to prevent asthma attacks.

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

A systematic review comparing a combined ICS/LABA inhaler as MART with ICS alone or with current best practice (ICS with or without LABA) showed that maintenance and reliever therapy can reduce the risk of asthma attacks requiring oral steroids in patients who are not well controlled on ICS alone and who have a history of asthma attacks.[476] The review reported more withdrawals due to adverse events in the maintenance and reliever therapy group (possibly because patients did not adjust well to the change in inhaler) compared with the current best practice group, but no significant difference between the groups in serious adverse events. All trials were funded by the manufacturer.

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

In a subsequent systematic review including 16 RCTs and 22,748 patients, a meta-analysis of five of the 16 studies concluded that, in patients aged 12 and over, use of MART was associated with a reduced risk of asthma attacks compared with standard ICS/LABA treatment including the same dose of ICS as the MART group (in five of the nine studies), or to standard ICS/LABA treatment including a higher dose of ICS than the MART group (in two of 16 studies). Among children aged 4–11, a subgroup analysis from a single RCT reported that MART was associated with a lower risk of asthma attacks compared with standard ICS/LABA treatment including the same dose of ICS as the MART group. There was no difference in impact on quality of life (QoL), asthma control, lung function and asthma medication use between MART and regular fixed-dose treatment regimens.[477] Fifteen of the 16 studies used a combination of budesonide and formoterol in a dry powder inhaler.

If this management option is introduced the total regular dose of daily ICS should not be decreased. Patients taking rescue doses of their combination inhaler once a day or more on a regular basis should have their treatment reviewed. Careful education of patients about the specific issues around this management strategy is required.

At present, maintenance and reliever therapy is only licensed for use with budesonide/formoterol or beclomethasone/formoterol. The summaries of product characteristics should be consulted for age-appropriate prescribing and maximum dosing regimens. Not all combination products are licensed for maintenance and reliever therapy. The appropriate combination inhaler should be prescribed by brand name.


**Consider the option of combined maintenance and reliever therapy in adult patients who have a history of asthma attacks on medium dose ICS or ICS/LABA.**

## Additional controller therapies

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

### Increased dose of inhaled corticosteroids

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

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

### Leukotriene receptor antagonists

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

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

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

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

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

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

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


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

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

  ***or***

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

*Anmerkung zu Empfehlungen: Stufenschema siehe Anhang*

# 4 Detaillierte Darstellung der Recherchestrategie

### Cochrane Library - Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2020) am 24.04.2020

| # | Suchfrage |
|---|---|
| 1 | [mh Asthma] |
| 2 | asthma*:ti |
| 3 | #1 OR #2 |
| 4 | #3 with Cochrane Library publication date from Apr 2015 to present, in Cochrane Reviews |

### Systematic Reviews in Medline (PubMed) am 24.04.2020

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

| | |
|---|---|
| | AND ((evidence[tiab]) AND based[tiab])))))) |
| 6 | (#5) AND ("2015/04/01"[PDAT] : "3000"[PDAT]) |
| 7 | (#6) NOT "The Cochrane database of systematic reviews"[Journal] |
| 8 | (#7) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Leitlinien in Medline (PubMed) am 24.04.2020**

| # | **Suchfrage** |
|---|---|
| 1 | asthma[majr] |
| 2 | asthma*[ti] |
| 3 | #1 OR #2 |
| 4 | (#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])* |
| 5 | (#4) AND ("2015/04/01"[PDAT] : "3000"[PDAT]) |
| 6 | (#5) NOT (retracted publication [pt] OR retraction of publication [pt]) |

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# Anhang

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

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

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

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

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

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

*Explanations*

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

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

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

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

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

***Explanations***

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

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

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

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

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

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

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

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

**TABLE 4** (Continued)

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

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

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

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

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

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

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

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

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

(Continues)

**TABLE 5** (Continued)

***Explanations***

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

b. Probable unimportant heterogeneity

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

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

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

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

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

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

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

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

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

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

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

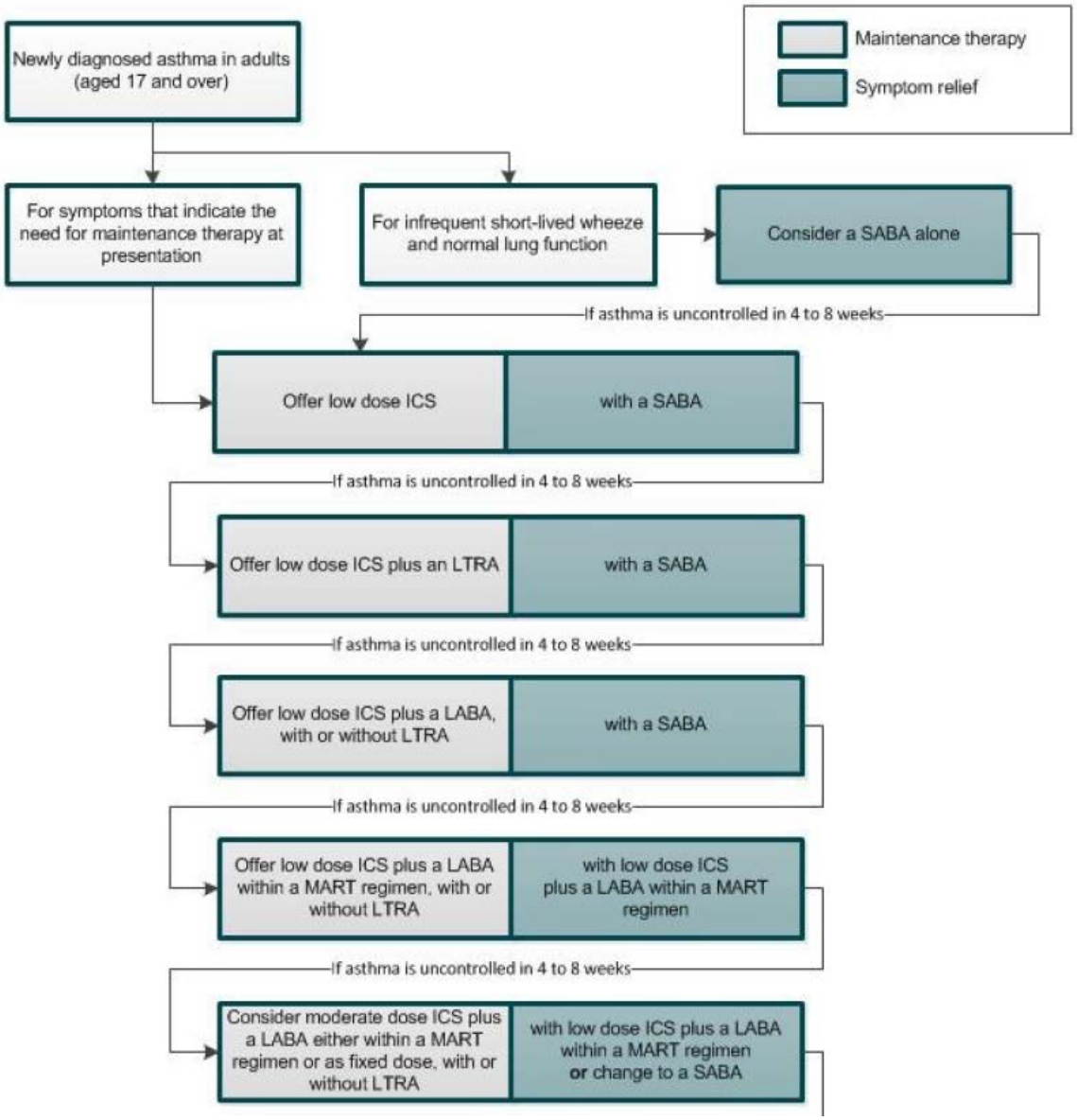
n. Very few numbers of events per arm

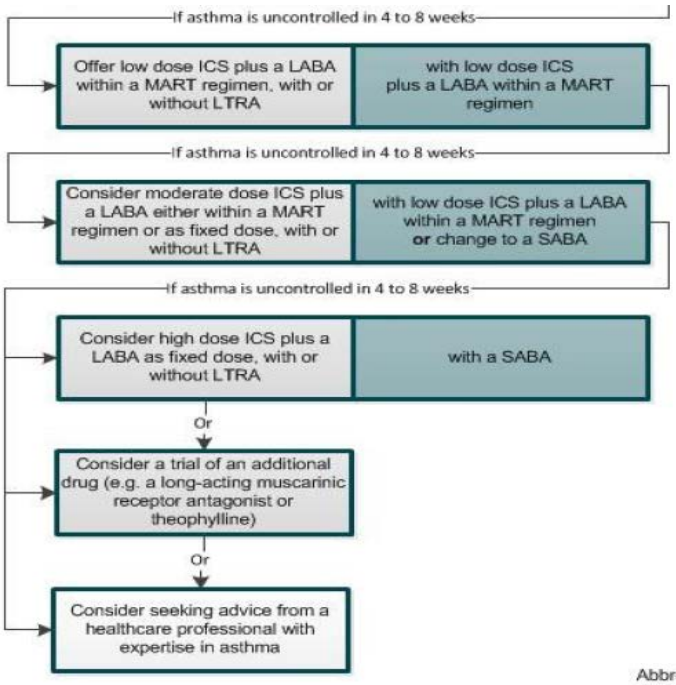
o. The minimal important difference for rescue medication use is −0.81 puffs/d.[35]

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

Asthma: diagnosis, monitoring and chronic asthma management.

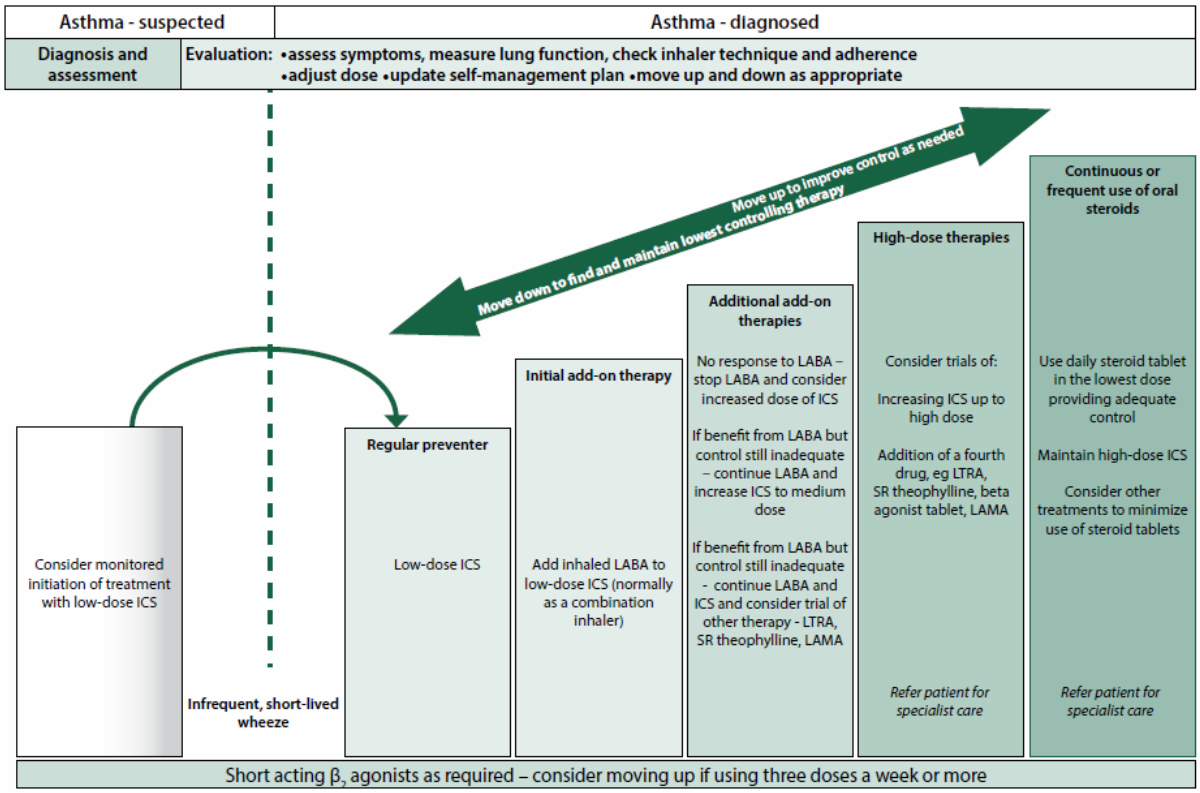
## Algorithm C: Pharmacological treatment of chronic asthma in adults aged 17 and over






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

**SIGN, 2016 [28]. British guideline on the management of asthma (2016)**



Gemeinsamer Bundesausschuss

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

**2020-B-177**

**Kontaktdaten**
Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 21.07.2020

Indikation gemäß Beratungsantrag
Erhaltungstherapie bei erwachsenen Patienten mit Asthma, die nicht adäquat durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten behandelt werden oder die bereits durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten plus einem langwirkenden Muskarin-Antagonisten behandelt werden

**Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei der „**Erhaltungstherapie bei erwachsenen Patienten mit Asthma, die nicht adäquat durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten behandelt werden oder die bereits durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten plus einem langwirkenden Muskarin-Antagonisten behandelt werden**“? Wie sieht die Versorgungspraxis in Deutschland aus?**

Die angefragte Indikation entspricht der Definition eines schweren Asthmas, vorausgesetzt, dass häufige Managementfehler wie nicht sachgemäße Anwendung der Inhalatoren oder fehlende Identifizierung externer Trigger, insbesondere inhalativer Allergene, ausgeschlossen sind. Darüber hinaus sind zahlreiche Differenzialdiagnosen, die ein „therapieresistentes“ Asthma vortäuschen können, in Betracht zu ziehen.
Unter dieser Voraussetzung besteht der Behandlungsstandard entsprechend der „Stufe 5“ im Stufenschema der Asthmatherapie in nationalen und internationalen Leitlinien (NVL Asthma, GINA) (1;2) zunächst in der Ausschöpfung von Dosisbreite und Kombinationsmöglichkeiten der inhalativen Therapie, was in der Praxis, aber auch in klinischen Studien nicht immer ausreichend Beachtung findet. Hierzu gehört die Verordnung einer Dreierkombination aus einem inhalativen Kortikosteroid (ICS) in Höchstdosis, einem langwirksamen Beta2-Agonisten (LABA) und einem langwirksamen Muscarin-Antagonisten (LAMA) über einen Zeitraum von mindestens drei Monaten. Empfehlungen zu den Dosierungen der ICS finden sich in der NVL (2), einziger bislang zugelassener LAMA ist Tiotropium. Erst bei Therapieversagen unter einer solchen Kombination wird der Einsatz von Biologika empfohlen (s. u.).

**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „**erwachsenen Patienten mit Asthma, die nicht adäquat durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten behandelt werden oder die bereits durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten plus einem langwirkenden Muskarin-Antagonisten behandelt werden**“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Bei schwerem Asthma mit dokumentiertem Versagen der regelrecht durchgeführten inhalativen Therapie bestehen folgende zugelassene Optionen, die möglichst zielgerichtet entsprechend dem vorherrschenden Phänotyp eingesetzt werden sollten:

**Kontaktdaten**
Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 21.07.2020

Indikation gemäß Beratungsantrag
Erhaltungstherapie bei erwachsenen Patienten mit Asthma, die nicht adäquat durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten behandelt werden oder die bereits durch eine Kombination aus einem inhalativen Kortikosteroid und einem langwirkenden Beta2-Agonisten plus einem langwirkenden Muskarin-Antagonisten behandelt werden

1. Bei eosinophilem Asthma mit nachgewiesener Bluteosinophilie: Ein Interleukin(IL)-5-Antagonist. Es stehen derzeit zwei Anti-IL-5-Antikörper und ein Anti-IL-5-Rezeptor-Antikörper zur Verfügung. Es besteht eine Assoziation zwischen Höhe der Bluteosinophilie und Effektivität dieser Therapie.

2. Bei nachgewiesener, anamnestisch relevanter Allergie gegen perenniale, inhalative Allergene: Anti-IgE-Antikörper (Omalizumab). Die Dosierung und Häufigkeit der Gabe von Omalizumab sind an die Höhe der Gesamt-IgE-Spiegel im Blut gebunden.

3. Ein Interleukin-4-Rezeptor-Antikörper (Dupilumab) ist bei schwerem Asthma seit kurzem ebenfalls zugelassen. Eine Zuordnung zu einem spezifischen Phänotyp wie unter 1. und 2. ist bei dieser Substanz bislang nicht definiert.

Begründung/Kommentar:
Es ergibt sich aus den vorausgegangenen Ausführungen, dass Asthmatherapie auf dieser Stufe nur von Ärzten mit Erfahrung in der Betreuung von Patienten mit schwerem Asthma durchgeführt werden sollte; es handelt sich dabei um eine Subgruppe von etwa 5–10 % aller Asthmatiker. Die Ausschöpfung von Dosierungen und Kombinationsmöglichkeiten der inhalativen Therapie vor Einsatz der Biologika ist wegen der langjährigen Erfahrung im Umgang mit dieser Therapie sinnvoll, die höhere Effektivität einer inhalativen Dreierkombination bei unkontrolliertem Asthma wurde in Phase-III-Studien belegt (3). Die Dosis-Wirkungs-Kurve der ICS verläuft relativ flach. Allerdings sollte bekannt werden, dass hochdosierte ICS einem Prednison-Äquivalent von 2–5 mg/d entsprechen können (4); die Möglichkeit einer Dosisreduktion sollte daher regelmäßig geprüft werden. Einigkeit besteht darin, dass systemische Glukokortikoide (OCS) in der Langzeittherapie wegen der damit verbundenen schweren Nebenwirkungen (anders als bei akuten Exazerbationen) auch auf dieser Stufe nur noch in Ausnahmefällen eingesetzt werden sollten. In der Praxis stellt die Reduktion und das schrittweise Absetzen einer bestehenden Langzeittherapie mit OCS allerdings immer noch einen der überzeugendsten Wirknachweise der Biologika dar. Dagegen entspricht nur ein Teil der Zulassungsstudien hinsichtlich der Ausschöpfung der inhalativen Therapie den o. g. Kriterien.

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