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: 2023-B-121-z Lumacaftor/Ivacaftor

Stand: Juni 2023

I. **Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA**
Lumacaftor/Ivacaftor **zur Behandlung der zystischen Fibrose (Alter 1 bis < 2 Jahre)**
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.	Ggf. Ernährungsbezogene Maßnahmen, Unterstützung der Atemfunktion, Physiotherapie (i. S. der Heilmittel-RL)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Änderung der Arzneimittel-Richtlinie, Anlage XII: Beschlüsse über die Nutzenbewertung von neuen Arzneimitteln nach § 35a SGB V - D-793/D-794/D-795/D-796/D-797 Ivacaftor (nAWG; Beschluss 4.8.2022) - D-773/D-774/D-775/D-776/D-777 Ivacaftor/Tezacaftor/Elexacaftor (nAWG; Beschluss 4.8.2022) - D-733 Lumacaftor/Ivacaftor (Neubewertung nach Fristablauf; Beschluss vom 18.02.2022) - D-690/D-688/D-686 Ivacaftor (nAWG; Beschluss 19.11.2021) - D-689/D-687/D-685 Ivacaftor/Tezacaftor/Elexacaftor (nAWG; Beschluss 19.11.2021) - D-623/D-624/D-619/D-605 Ivacaftor (nAWG; Beschluss 20.05.2021) - D-608/D-609 Tezacaftor/Ivacaftor (nAWG; Beschluss 20.05.2021) - D-586/587 Ivacaftor (nAWG; Beschluss 18.02.2021) - D-584/D-585 Ivacaftor/Tezacaftor/Elexacaftor (Beschluss 18.02.2021) - D-555 Ivacaftor (nAWG; Beschluss 17.12.2020) - D-552/D-553 Tezacaftor/Ivacaftor (Neubewertung (Überschreitung 50 Mio. €); Beschluss 17.12.2020) - D-500 Ivacaftor (nAWG; Beschluss am 04.06.2020) - D-476 bis D-481 Ivacaftor (nAWG; Beschluss am 20.02.2020) - D-431 Ivacaftor (nAWG; Beschluss am 20.02.2020) - D-432 Lumacaftor/Ivacaftor (Beschluss am 15.08.2019) - D-408 Tezacaftor/Ivacaftor (Beschluss vom 16.05.2019) - D-339 Lumacaftor/Ivacaftor (nAWG; Beschluss vom 02.08.2018) - D-204 Lumacaftor/Ivacaftor (Beschluss vom 02.06.2016)

	- D-200 Ivacaftor (nAWG; Beschluss vom 02.06.2016) - D-133 Ivacaftor (nAWG; Beschluss vom 19.02.2015) - D-034 Ivacaftor (Beschluss vom 07.02.2013)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Lumacaftor/ Ivacaftor R07AX30 Orkambi	<u>Neues Anwendungsgebiet laut positive opinion:</u> "Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in patients **aged 1 years and older** who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene"
CFTR-Modulatoren	
Ivacaftor R07AX02 Kalydeco	Kalydeco-Tabletten werden angewendet: • als Monotherapie zur Behandlung von Erwachsenen, Jugendlichen und Kindern **ab 6 Jahren** mit einem Körpergewicht von mindestens 25 kg mit zystischer Fibrose (CF, Mukoviszidose), die eine R117H-CFTR-Mutation oder eine der folgenden Gating-Mutationen (Klasse III) im Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R. • im Rahmen einer Kombinationsbehandlung mit Tezacaftor/Ivacaftor-Tabletten zur Behandlung von Erwachsenen, Jugendlichen und Kindern ab 6 Jahren mit zystischer Fibrose (CF), die homozygot für die F508del-Mutation sind oder heterozygot für die F508del-Mutation und eine der folgenden Mutationen im CFTR-Gen aufweisen: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10kbC→T.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
	• im Rahmen einer Kombinationsbehandlung mit Ivacaftor/Tezacaftor/Elexacaftor-Tabletten zur Behandlung von Erwachsenen, Jugendlichen und Kindern ab 6 Jahren mit zystischer Fibrose (CF), die mindestens eine F508del-Mutation im CFTR-Gen haben. *[Stand FI: 01/2022]* Kalydeco-Granulat wird angewendet zur Behandlung von Säuglingen **ab 4 Monaten**, Kleinkindern und Kindern mit einem Körpergewicht zwischen 5 kg und weniger als 25 kg mit zystischer Fibrose (CF, Mukoviszidose), die eine R117H-CFTR-Mutation oder eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R. *[Stand FI: 04/2022]*
Tezacaftor/ Ivacaftor R07AX31 Symkevi	Symkevi wird angewendet als Kombinationsbehandlung mit Ivacaftor-Tabletten zur Behandlung der zystischen Fibrose (CF) bei Patients **ab 6 Jahren**, die homozygot für die F508del-Mutation sind oder heterozygot für die F508del-Mutation und eine der folgenden Mutationen im CFTR-Gen (Cystic Fibrosis Transmembrane Conductance Regulator) aufweisen: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10kbC→T. *[Stand FI: 11/2020]*
Lumacaftor/ Ivacaftor/ Elexacaftor R07AX32 Kaftrio	Kaftrio wird angewendet als Kombinationsbehandlung mit Ivacaftor zur Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Patienten **ab 6 Jahren**, die mindestens eine F508del-Mutation im CFTR-Gen (Cystic Fibrosis Transmembrane Conductance Regulator) aufweisen. *[Stand FI: 01/2023]*
Antibiotika	
Ceftazidim J01DD02 Generisch	Ceftazidim wird angewendet bei Erwachsenen und Kindern inklusive Neugeborenen (**von Geburt an**) bei Infektionen die untenstehend aufgelistet sind: - Bronchopulmonale Infektionen bei zystischer Fibrose […] Bei der Wahl von Ceftazidim sollte sein antibakterielles Spektrum berücksichtigt werden, welches hauptsächlich auf aerobe Gramnegative Bakterien limitiert ist. Ceftazidim sollte gemeinsam mit anderen antibakteriellen Substanzen angewendet werden, wenn die mögliche Bandbreite der verursachenden Bakterien nicht vom Wirkspektrum von Ceftazidim abgedeckt wird. Offizielle Richtlinien zum angemessenen Gebrauch von antibakteriellen Arzneimitteln sollten berücksichtigt werden. [Stand FI Ceftazidim Kabi: 08/2015]

Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Fachinformation)
II. Zugelassene Arzneimittel im Anwendungsgebiet	
Aztreonam J01DF01 Cayston®	Aztreonam wird angewendet zur suppressiven Behandlung chronischer Lungeninfektionen durch Pseudomonas aeruginosa bei Patienten mit Mukoviszidose (zystischer Fibrose, CF) **ab einem Alter von 6 Jahren**. Offizielle Empfehlungen zur angemessenen Anwendung von Antibiotika sind zu berücksichtigen. [Stand FI: 04/2019]
Ciprofloxacin J01MA02 Generisch	Ciprofloxacin ist indiziert für die Behandlung der folgenden Infektionen. Vor Beginn der Behandlung müssen die vorliegenden Informationen zu Resistenzen gegenüber Ciprofloxacin besonders berücksichtigt werden. Offizielle Empfehlungen zum angemessenen Gebrauch von Antibiotika sollten berücksichtigt werden. Erwachsene: Untere Atemwegsinfektionen verursacht durch Gramnegative Bakterien: - Bronchopulmonale Infektionen bei zystischer Fibrose oder bei Bronchiektasien **Kinder und Jugendliche:** Durch Pseudomonas aeruginosa verursachte bronchopulmonale Infektionen bei zystischer Fibrose Die Behandlung sollte nur von einem in der Behandlung von zystischer Fibrose und/oder von schweren Infektionen bei Kindern und Jugendlichen erfahrenen Arzt initiiert werden. [Stand FI Ciprobay®: 01/2019]
Levofloxacin J01MA12 Generisch	Levofloxacin ist zur Behandlung von chronischen Infektionen der Lunge durch Pseudomonas aeruginosa bei **erwachsenen Patienten** mit zystischer Fibrose (cystic fibrosis [CF], Mukoviszidose) angezeigt. Offizielle Empfehlungen zur angemessenen Anwendung von Antibiotika sind zu berücksichtigen. [Stand FI Quinsair®: 02/2019]
Colistimethat J01XB01 Generisch	ColistiFlex ist bei **erwachsenen Patienten und Kindern** mit zystischer Fibrose zur Behandlung chronischer pulmonaler Infekte indiziert, die durch Pseudomonas aeruginosa verursacht warden. Die offiziellen Richtlinien zur sachgemäßen Anwendung von Antibiotika sind zu beachten. [Stand FI ColistiFlex®: 08/2017]
Meronem J01D H02 Meronem®	Meronem ist angezeigt zur Behandlung der folgenden Infektionen bei Erwachsenen und Kindern **ab einem Alter von 3 Monaten**: - Bronchopulmonale Infektionen bei zystischer Fibrose [...] Für den angemessenen Gebrauch von Antibiotika sollten die offiziellen Leitlinien beachtet werden. [Stand FI: 08/2019]
Tobramycin J01GB01 Generisch	Zur Behandlung chronischer Infektionen der Lunge mit Pseudomonas aeruginosa bei Patienten mit Mukoviszidose **ab einem Alter von 6 Jahren**. Bramitob ist für die inhalative Anwendung bestimmt und nicht für eine parenterale Anwendung geeignet. Die offiziellen Richtlinien zur sachgemäßen Anwendung von Antibiotika sind zu beachten. Die Therapie sollte von einem Arzt mit Erfahrung in der Behandlung von Mukoviszidose eingeleitet werden. [Stand FI Bramitob®: 03/2019]
Sekretolytische Therapie	

Wirkstoff ATC-Code Handelsname	**II.** **Zugelassene Arzneimittel im Anwendungsgebiet**
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Dornase alfa R05CB13 Pulmozyme®	Dornase alfa ist angezeigt zur Behandlung der cystischen Fibrose (Mukoviszidose) bei Patienten, die **älter als 5 Jahre** sind und deren forcierte Vitalkapazität (FVC) mehr als 40 % des Normalwertes beträgt. [Stand FI: 04/2017]
Mannitol R05CB16 Bronchitol®	Mannitol wird angewendet zur Behandlung der zystischen Fibrose (Mukoviszidose) bei Erwachsenen **ab 18 Jahren** zusätzlich zum besten Therapiestandard. [Stand FI: 04/2019]
Carbocistein R05CB03 Transbronchin® Kapseln	Zur begleitenden Behandlung bei akuten und chronischen bronchopulmonalen Erkrankungen, die mit einer Störung von Schleimbildung und Schleimtransport einhergehen. Aus FI 4.2. Dosierung nur für Erwachsene und Jugendliche **ab dem 13. Lebensjahr**. [Stand FI: 08/2006]

Quellen: AMIce-Datenbank, Fachinformationen Stand: 05/2023

Abteilung Fachberatung Medizin

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

Vorgang: 2023-B-121-z (Lumacaftor/Ivacaftor)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. Mai 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CF	Cystische Fibrose, Mukoviszidose
CFQ-R	Cystic Fibrosis Questionnaire Revised (CFQ-R)
FEV1	Forcierte Einsekundenkapazität
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LCI	lung clearance index
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
QoL	Quality of Life
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Kindern im Alter von 1 bis < 2 Jahren mit Zystischer Fibrose (CF)

Hinweise zur Synopse:

- *Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.*

- *Bei der Auswahl der Evidenz für diese Synopse wurde neben den üblichen Kriterien zusätzlich angewendet: Es müssen Kinder (bis 14. Lebensjahr) in den Studienkollektiven SR/CRs enthalten sein und/ oder es muss für Kleinkinder eine spezifische (altersbezogene) Subgruppenanalyse vorliegen.*

- *Übersichtsarbeiten zu Physiotherapie und Ernährungstherapie wurden nicht eingeschlossen.*

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Zystische Fibrose* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.ecosia.org/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 10.05.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 642 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. 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 Referenzen 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 14 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Skilton M et al., 2019 [8].
Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis.

Fragestellung
To evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with CF.

Population:
- children or adults with CF

Intervention/Komparator:
- CFTR potentiators to placebo or another intervention

Endpunkte:
- Survival, QoL, FEV1, adverse events, hospitalisation, nutrition, growth, etc.

Recherche/Suchzeitraum:
- The Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books.
- Also searched the reference lists of relevant articles, reviews and online clinical trial registries. Last search: 21 November 2018.

Qualitätsbewertung der Studien:
- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:
- five RCTs (447 participants with different mutations) lasting from 28 days to 48 weeks, all assessing the CFTR potentiator ivacaftor.

Charakteristika der Population:
- All 447 participants in the included trials had a confirmed diagnosis of CF. The F508del trial examined the effect of ivacaftor on people homozygous for the F508del mutation (class II mutation) (DISCOVER 2011). In the three G551D trials (class III mutation), participants were required to possess at least one G551D-CFTR allele (Accurso 2010; ENVISION 2013; STRIVE 2011). The R117H trial required participants to have at least one R117H-CFTR allele (KONDUCT 2015).
- Two trials recruited recruited participants aged 12 years and older (DISCOVER 2011; STRIVE 2011); participants in the F508del trial had a mean age of 25.5 years (DISCOVER 2011) and participants in the adult G551D trial had a mean age of 23.2 years (STRIVE 2011). The phase 2 G551D trial recruited participants aged 18 years and over and participants had a median 21 age of years (Accurso 2010). The paediatric phase 3 G551D trial enrolled participants aged 6 to 11 years of age and participants had a mean age of 8.9 years (ENVISION 2013). The R117H trial recruited those over 6 years of age and participants had a mean age of 31 years (KONDUCT 2015).

Qualität der Studien:

- The quality of the evidence was moderate to low, mainly due to risk of bias (incomplete outcome data and selective reporting) and imprecision of results, particularly where few individuals experienced adverse events. Trial design was generally well-documented. All trials were industry-sponsored and supported by other non-pharmaceutical funding bodies.

Studienergebnisse:

- *F508del (class II) (140 participants)*
  - One 16-week trial reported no deaths, or changes in quality of life (QoL) or lung function (either relative or absolute change in forced expiratory volume in one second (FEV1) (moderate-quality evidence). Pulmonary exacerbations and cough were the most reported adverse events in ivacaftor and placebo groups, but there was no difference between groups (low-quality evidence); there was also no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Number of days until the first exacerbation was not reported, but there was no difference between groups in how many participants developed pulmonary exacerbations. There was also no difference in weight. Sweat chloride concentration decreased, mean difference (MD) -2.90 mmol/L (95% confidence interval (CI) -5.60 to -0.20).

- **G551D (class III) (238 participants)**
  - The 28-day phase 2 trial (19 participants) and two 48-week phase 3 trials (adult trial (167 adults), paediatric trial (52 children)) reported no deaths. QoL scores (respiratory domain) were higher with ivacaftor in the adult trial at 24 weeks, MD 8.10 (95% CI 4.77 to 11.43) and 48 weeks, MD 8.60 (95% CI 5.27 to 11.93 (moderate-quality evidence). The adult trial reported a higher relative change in FEV1 with ivacaftor at 24 weeks, MD 16.90% (95% CI 13.60 to 20.20) and 48 weeks, MD 16.80% (95% CI 13.50 to 20.10); the paediatric trial reported this at 24 weeks, MD 17.4% (P < 0.0001)) (moderate-quality evidence). These trials demonstrated absolute improvements in FEV1 (% predicted) at 24 weeks, MD 10.80% (95% CI 8.91 to 12.69) and 48 weeks, MD 10.44% (95% CI 8.56 to 12.32). The phase 3 trials reported increased cough, odds ratio (OR) 0.57 (95% CI 0.33 to 1.00) and episodes of decreased pulmonary function, OR 0.29 (95% CI 0.10 to 0.82) in the placebo group; ivacaftor led to increased dizziness in adults, OR 10.55 (95% CI 1.32 to 84.47). There was no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Fewer participants taking ivacaftor developed serious pulmonary exacerbations; adults taking ivacaftor developed fewer exacerbations (serious or not), OR 0.54 (95% CI 0.29 to 1.01). A higher proportion of participants were exacerbation-free at 24 weeks with ivacaftor (moderate-quality evidence). Ivacaftor led to a greater absolute change from baseline in FEV1 (% predicted) at 24 weeks, MD 10.80% (95% CI 8.91 to 12.69) and 48 weeks, MD 10.44% (95% CI 8.56 to 12.32); weight also increased at 24 weeks, MD 2.37 kg (95% CI 1.68 to 3.06) and 48 weeks, MD 2.75 kg (95% CI 1.74 to 3.75). Sweat chloride concentration decreased at 24 weeks, MD -48.98 mmol/L (95% CI -52.07 to -45.89) and 48 weeks, MD -49.03 mmol/L (95% CI -52.11 to -45.94).

- **R117H (class IV) (69 participants)**

o One 24-week trial reported no deaths. QoL scores (respiratory domain) were higher with ivacaftor at 24 weeks, MD 8.40 (95% CI 2.17 to 14.63), but no relative changes in lung function were reported (moderate-quality evidence). Pulmonary exacerbations and cough were the most reported adverse events in both groups, but there was no difference between groups; there was no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Number of days until the first exacerbation was not reported, but there was no difference between groups in how many participants developed pulmonary exacerbations. No changes in absolute change in FEV1 or weight were reported. Sweat chloride concentration decreased, MD -24.00 mmol/L (CI 95% -24.69 to -23.31).

Fazit der Autoren

The F508del trial demonstrated no evidence to support the use of ivacaftor in those with the F508del mutation (DISCOVER 2011). The two G551D phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes at 24 and 48 weeks in children (over six years of age) and adults with cystic fibrosis (CF) and the G551D mutation (ENVISION 2013; STRIVE 2011). The R117H trial demonstrated an improvement in the respiratory domain of the CFQ-R but no improvement in respiratory function (KONDUCT 2015). These trials were judged to have a moderate risk of bias.

Smith S et al., 2018 [10].

Inhaled antibiotics for pulmonary exacerbations in cystic fibrosis.

Fragestellung

To determine if treatment of pulmonary exacerbations with inhaled antibiotics in people with cystic fibrosis improves their quality of life, reduces time off school or work and improves their long-term survival.

Methodik

Population:
- Children and adults with CF who are diagnosed with having a pulmonary exacerbation

Intervention/Komparator:
- any inhaled antibiotic

Endpunkte:
- QoL, Lung function (spirometry), Need for hospital admission, Need for additional antibiotics, Time to next pulmonary exacerbation, Weight, Adverse effects, etc.

Recherche/Suchzeitraum:
- Cochrane Cystic Fibrosis Group's Cystic Fibrosis Trials Register. Date of the last search: 03 October 2018.
- ClinicalTrials.gov, the Australia and New Zealand Clinical Trials Registry and WHO ICTRP for relevant trials. Date of last search: 09 October 2018.

Qualitätsbewertung der Studien:
- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien & Charakteristika der Population:

- Four trials with 167 participants are included in the review. Two trials (77 participants) compared inhaled antibiotics alone to intravenous antibiotics alone and two trials (90 participants) compared a combination of inhaled and intravenous antibiotics to intravenous antibiotics alone. In all trials the inhaled antibiotics were compared to the same antibiotics given intravenously. The numbers of participants in each trial ranged from 18 to 62.

Qualität der Studien:

- Risk of bias was difficult to assess in most trials, but for all trials we judged there to be a high risk from lack of blinding and an unclear risk with regards to randomisation. Results were not fully reported and only limited data were available for analysis.
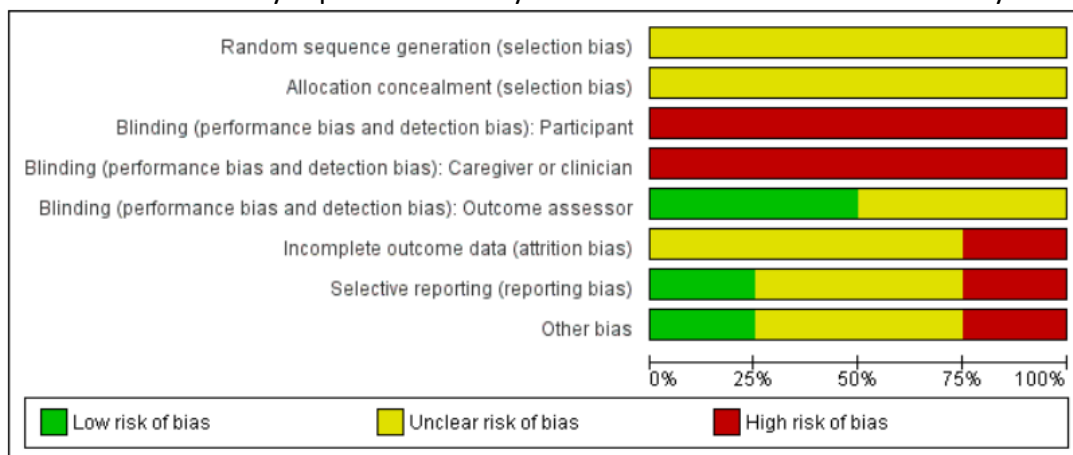
Studienergebnisse:

- Inhaled antibiotics alone versus intravenous antibiotics alone
  - Only one trial (n = 18) reported a perceived improvement in lifestyle (quality of life) in both groups (very low-quality of evidence).
  - Two trials measured lung function, but there was no difference reported between treatment groups (very low-quality evidence).
  - One trial (n = 18) reported no difference in the need for additional antibiotics and the second trial (n = 59) reported on the time to next exacerbation. In neither case was a difference between treatments identified (both very low-quality evidence).
  - The single trial (n = 18) measuring adverse events and sputum microbiology did not observe any in either treatment group for either outcome (very low-quality evidence).
- Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics alone
  - Two trials measured lung function, but found no difference between groups in forced expiratory volume in one second (one trial, n = 28, very low-quality evidence) or vital capacity (one trial, n = 62).
  - Neither trial reported on the need for additional antibiotics or the time to the next exacerbation; however, one trial (n = 28) reported on hospital admissions and found no difference between groups.
  - Two trials reported no difference between groups in adverse events (very low-quality evidence) and one trial (n = 62) reported no difference in the emergence of antibiotic-resistant organisms (very low-quality evidence).

Fazit der Autoren

There is little useful high-level evidence to judge the effectiveness of inhaled antibiotics for the treatment of pulmonary exacerbations in people with cystic fibrosis. The included trials were not sufficiently powered to achieve their goals. Hence, we are unable to demonstrate whether one treatment was superior to the other or not. Further research is needed to establish whether inhaled tobramycin may be used as an alternative to intravenous tobramycin for some pulmonary exacerbations.

Kommentare zum Review

- Sowohl Kinder als auch Erwachsene in den Studien. Keine separaten Analysen.

Frost F et al., 2021 [2].

Antibiotic therapy for chronic infection with Burkholderia cepacia complex in people with cystic fibrosis

Fragestellung

The objective of this review is to assess the effects of long-term oral and inhaled antibiotic therapy targeted against chronic BCC lung infections in people with CF. The primary objective is to assess the efficacy of treatments in terms of improvements in lung function and reductions in exacerbation rate. Secondary objectives include quantifying adverse events, mortality and changes in quality of life associated with treatment.

Methodik

Population:

- people with CF and chronic BCC infection

Intervention:

- Long-term (defined as a period of eight weeks or more) antibiotics (all agents, doses and regimens) via either the inhaled or oral route

Komparator:

- no treatment, placebo, another antibiotic agent, another mode of delivery, or another dose or regimen of the same antibiotic

Endpunkte:

- Primary outcomes
  1. Lung function a. forced expiratory volume in one second (FEV1) i. absolute change in volumes, % predicted or both ii. relative change in volumes, % predicted or both
  2. Pulmonary exacerbations a. time to next exacerbation b. hospitalisations c. exacerbation rate d. IV antibiotic use
  3. Adverse events a. mild: transient event, no treatment change, e.g. rash, nausea, diarrhoea

     b. moderate: treatment discontinued, e.g. nephrotoxicity, ototoxicity, hepatitis, visual impairment

     c. severe: causing hospitalisation or death
- Secondary outcomes

1. Mortality
2. QoL a. validated QoL score, e.g. CFQ-R Respiratory Symptom Score (RSS)
3. BCC culture a. sputum density of BCC
4. Changes in inflammatory markers a. sputum or bronchoalveolar lavage (BAL) samples b. serum or blood

Recherche/Suchzeitraum:

- Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched online trial registries and the reference lists of relevant articles and reviews.
- Date of last search: 12 April 2021.

Qualitätsbewertung der Studien:

- GRADE, Cochrane RoB

Ergebnisse

Anzahl eingeschlossener Studien:

- N=1

Charakteristika der Population/Studien:

- (100 participants) which lasted 52 weeks comparing continuous inhaled aztreonam lysine (AZLI) and placebo in a double-blind RCT for 24 weeks, followed by a 24-week open-label extension and a four-week follow-up period. The average participant age was 26.3 years, 61% were male and average lung function was 56.5% predicted.

Characteristics of included studies *[ordered by study ID]*

Tullis 2014

Study characteristics	
Methods	RCT
	Conducted in 35 centres (USA: 34; Canada:1 (Feb 2010 - Sept 2011)
Participants	100 participants (48 given AZLI treatment; 52 given placebo)
	Eligible participants ≥ 6 years of age had documented CF and chronic infection with *Burkholderia* spp.
	61 participants were male
Interventions	24 weeks of continuous treatment with 75 mg inhaled AZLI (3 times a day) or placebo

Tullis 2014 *(Continued)*	
	Followed by a 24-week extension period of open-label AZLI treatment for all participants (weeks 24 - 48); and a 4-week follow-up period (weeks 48 - 52)
Outcomes	Primary outcome was change in lung function (FEV_1) at 24 weeks
	Secondary outcomes included: number of respiratory exacerbations requiring IV, oral or inhaled antibiotics (or both); number of respiratory hospitalisations; AUC_{ave} through week 24 for CF Questionnaire-Revised (CFQ-R) Respiratory Symptoms scores; time to respiratory exacerbation requiring IV, oral or inhaled antibiotics (or both); and adverse events
Notes	The study was funded by Gilead Sciences

Qualität der Studien:

- Overall quality of evidence was considered to be moderate across all outcomes, which means further research is likely to have an important impact on results.
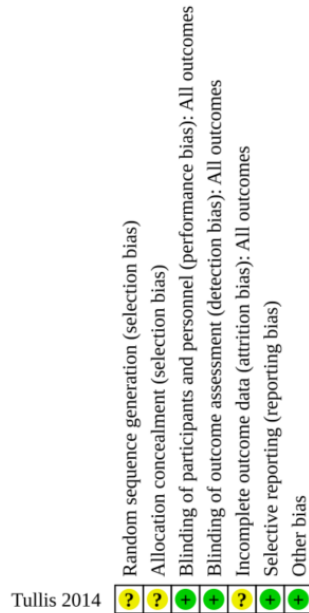
Studienergebnisse:

- The only study included in this review found inhaled aztreonam had no beneficial effect on lung function or rates of chest infections in people with cystic fibrosis and Burkholderia cepacia complex infection. There was no difference between groups in relation to the average time to the next exacerbation or the number of people hospitalised for an exacerbation. Overall adverse events were similar between groups and with regards to other outcomes assessed, there was no difference between treatment groups for mortality, quality of life or sputum density. More research is needed to establish if other inhaled antibiotics may be useful.

Summary of findings 1. Summary of findings - AZLI compared with placebo for chronic *Burkholderia cepacia* complex infection in people with CF

AZLI compared with placebo for chronic *Burkholderia cepacia* complex infection in people with CF

Patient or population: adults and children with CF

Settings: CF treatment centres across North America

Intervention: AZLI for inhalation 75 mg three times a day via nebuliser for 24 weeks

Comparison: placebo, three times a day via nebuliser for 24 weeks

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Placebo	**AZLI**				
Relative change in FEV_1% predicted	The mean change in FEV_1 (% predicted) in the control group was **-0.75%**	The mean change in FEV_1 (% predicted) in the intervention group was **0.91%** higher (3.15% lower to 4.97% higher)	NA	99 (1 study)	⊕⊕⊕⊖ **Moderate[a]**	
Days to next exacerbation	See comment		NA	100 (1 study)	⊕⊕⊕⊖ **Moderate[a]**	Median days to next exacerbation in the control group was **75** days. Median days to next exacerbation in the intervention group was **24** days lower.
Participants hospitalised for respiratory exacerbation	400 per 1000	352 per 1000 (212 to 580)	**RR 0.88** (95% CI 0.53 to 1.45)	100 (1 study)	⊕⊕⊕⊖ **Moderate[a]**	
Any AEs	904 per 1000	976 per 1000 (886 to 1076)	**RR 1.08** (95% CI 0.98 to 1.19)	100 (1 study)	⊕⊕⊕⊖ **Moderate[a]**	Wheeze was more frequent in the AZLI group compared to placebo but groups were otherwise well matched.
Mortality	There were **0** deaths in the placebo group	There were **2** deaths in the intervention arm	**RR 5.41** (95% CI 0.27 to 109.87)	100 (1 study)	⊕⊕⊕⊖ **Moderate[a]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AE: adverse event; **AZLI**: aztreonam lysine for inhalation; **CF**: cystic fibrosis; **CI**: confidence interval; **FEV_1**: forced expiratory volume in one second; **RR**: risk ratio.

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

a Downgraded once due to imprecision of results (small sample size and subsequent wide CIs)

Anmerkung/Fazit der Autoren

We found insufficient evidence from the literature to determine an effective strategy for antibiotic therapy for treating chronic BCC infection.

Kommentar zum Review

Anteil von Kindern an allen Studienteilnehmenden nicht dargestellt. Keine Subgruppenanalysen

Yang C, Montgomery M, 2021 [14].

Dornase alfa for cystic fibrosis (Review)

Fragestellung

To determine whether the use of dornase alfa in cystic fibrosis is associated with improved mortality and morbidity compared to placebo or other medications that improve airway clearance, and to identify any adverse events associated with its use.

Methodik

Population:

- Children and adults, of any age, with CF diagnosed clinically and by sweat or genetic testing. Participants with all stages of lung disease were included.

Intervention:

- Dornase alfa administered at any dose, using any nebuliser, at any frequency and for any duration

Komparator:

- other medications that are adjuncts to airway clearance (typically hyperosmotic agents such as hypertonic saline or mannitol)

Endpunkte:

- Primary outcomes
  1. Changes in lung function from baseline a. forced expiratory volume at one second (FEV1) b. forced vital capacity (FVC) c. lung clearance index (LCI) d. forced expiratory volume at 0.5 seconds (FEV0.5)
  2. Change from baseline in quality of life (QoL)
  3. Mean number of exacerbations
- Secondary outcomes
  1. Number of deaths
  2. Number of days treatment with intravenous (IV) antibiotics
  3. Number of days treatment with oral antibiotics
  4. Number of days in hospital due to respiratory exacerbations
  5. Change in weight from baseline
  6. Number of adverse events such as alteration in voice, haemoptysis, bronchospasm
  7. Cost (including indirect costs of therapy)

Recherche/Suchzeitraum:

- Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises references identified from comprehensive electronic database searches, handsearching relevant journals and abstracts from conferences
- 12 October 2020

Qualitätsbewertung der Studien:

- Cochrane tool for this as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Ergebnisse

Anzahl eingeschlossener Studien:

- N=19

Charakteristika der Population/Studien:

Three papers analysed the healthcare costs of using dornase alfa (Menzin 1996; Oster 1995; von der Schulenburg 1995) using the data from the included Fuchs trial (Fuchs 1994). Three trials were available in abstract form only (Adde 2004; Castile 2009; Dodd 2000); but the remaining included trials were published as full papers.

15 trials (n = 2447) compared dornase alfa to placebo or no dornase alfa treatment (Amin 2011; Castile 2009; Dodd 2000; Frederiksen 2006; Fuchs 1994; Laube 1996; McCoy 1996; Paul 2004; Quan 2001; Ramsey 1993; Ranasinha 1993; Robinson 2000; Robinson 2005; Shah 1995a; Wilmott 1996). One trial (n = 48) compared daily dornase alfa to hypertonic saline and to alternate day dornase alfa (Suri 2001), and two trials (n = 32) compared dornase alfa to hypertonic saline (Adde 2004; Ballmann 2002). The remaining trial (n = 38) compared dry powder mannitol to dornase alfa and to a combination of both drugs (Minasian 2010).

Dornase alfa versus placebo or no dornase alfa treatment

There were 15 trials (n = 2447) included in this comparison (Amin 2011; Castile 2009; Dodd 2000; Frederiksen 2006; Fuchs 1994; Laube 1996; McCoy 1996; Paul 2004; Quan 2001; Ramsey 1993; Ranasinha 1993; Robinson 2000; Robinson 2005; Shah 1995a; Wilmott 1996).

- Trial design

Most of these trials were of parallel design, but we included four trials of cross-over design (Amin 2011; Castile 2009; Dodd 2000; Robinson 2000). Amin used two four-week treatment periods with a four-week washout period (Amin 2011); Castile used sixmonth treatment periods with no washout although only data for the first period was available (Castile 2009); Dodd had two-week treatment periods with a seven-day washout period (Dodd 2000); and Robinson used seven-day treatment periods with a two-week washout (Robinson 2000). The duration of the trials varied from six days (Laube 1996) to three years (Paul 2004) (Table 1). Duration of treatment was less than or equal to one month in eight trials (Amin 2011; Dodd 2000; Laube 1996; Ramsey 1993; Ranasinha 1993; Robinson 2000; Shah 1995a; Wilmott 1996), three months in one trial (McCoy 1996), six months in two trials (Castile 2009; Fuchs 1994), one year in two trials (Frederiksen 2006; Robinson 2005), two years in one trial (Quan 2001) and three years in one trial (Paul 2004).

The size of trials varied from 19 participants (Amin 2011) to 968 participants (Fuchs 1994).

- Participants

Four trials included adults only (Dodd 2000; Laube 1996; Ranasinha 1993; Robinson 2000). Four trials included children only; one trial enrolled children aged six to 10 years (Quan 2001), two trials enrolled participants aged six to 18 years (Amin 2011; Robinson 2005) and the remaining trial recruited infants with a mean (SD) age of 42 (32) weeks (Castile 2009). Seven trials included mixed adult and paediatric populations. One trial included participants aged one year and over (Frederiksen 2006), four trials included participants aged five years or older (Fuchs 1994; Paul 2004; Shah 1995a; Wilmott 1996), one trial included participants aged seven years or older (McCoy 1996) and a further trial included participants aged eight years or older (Ramsey 1993).

All trials except for one included participants with stable lung disease; only Wilmott looked at the effects of dornase alfa during treatment for a respiratory exacerbation (Wilmott 1996).

Severity of lung disease varied across the trials. Two trials recruited only participants with severe lung disease (FVC less than 40% predicted) (McCoy 1996; Shah 1995a). Five trials studied participants who had mild to moderate disease (FVC greater than 35% to 40% predicted) (Fuchs 1994; Quan 2001; Ramsey 1993; Ranasinha 1993; Wilmott 1996). One trial looked at participants with moderate disease (FVC between 35% and 75% predicted) (Laube 1996). Three trials included participants with mild lung disease, defined as FVC greater than or equal to 85% in one trial (Robinson 2005), or FEV1 greater than 80% in two trials (Amin 2011; Paul 2004). Three trials did not report information on severity of disease (Castile 2009; Dodd 2000; Frederiksen 2006). The participants in the Castile trial were all infants, so this information would not be available and the abstract simply stated that the participants were all clinically well.

- Interventions

The dose and frequency of dornase alfa received by participants varied. Six trials used 2.5 mg dornase alfa twice daily in the treatment group (Laube 1996; Paul 2004; Ranasinha 1993; Robinson 2000; Shah 1995a; Wilmott 1996). Seven trials used used 2.5 mg dornase alfa once daily (Amin 2011; Castile 2009; Dodd 2000; Frederiksen 2006; McCoy 1996; Quan 2001; Robinson 2005). Ramsey gave three different doses of dornase alfa as a twice-daily regimen: 0.6 mg; 2.5 mg; and 10 mg (Ramsey 1993). Fuchs administered a dose of 2.5 mg dornase alfa either once or twice daily (Fuchs 1994).

In two trials the placebo used was normal saline solution (Dodd 2000; Robinson 2005), six trials stated that the placebo used was excipient alone (Fuchs 1994; Laube 1996; Ranasinha 1993; Shah 1995a; Wilmott 1996; Robinson 2000) and five trials stated that a placebo was used but did not give a formal definition (Amin 2011; Castile 2009; McCoy 1996; Quan 2001; Ramsey 1993).

- Outcomes

All trials assessed lung function parameters (FEV1 % predicted, FVC % predicted) with one trial examining FEV0.5 in infants (Castile 2009). Three trials assessed QoL; however, only one trial used a validated measure (CFQ-R) (Amin 2011). None of the trials reported respiratory exacerbations expressed as mean number per period of follow up. Adverse events and deaths were reported in nine trials (Amin 2011; Castile 2009; Fuchs 1994; McCoy 1996; Quan 2001; Ramsey 1993; Ranasinha 1993; Shah 1995a; Wilmott 1996). One trial reported on the use of IV antibiotics and the days in hospital (McCoy 1996), one trial reported the number of days of antibiotics but did not specify the route of administration (Castile 2009) and one trial reported on weight (Quan 2001).

Qualität der Studien:

The quality of evidence from the trials comparing dornase alfa to placebo or no treatment was moderate to high for lung function results, but only one trial reported any changes in quality of life so the evidence for this outcome is limited.

Also, there were few trials comparing different treatment schedules of dornase alfa (e.g. once a day versus twice a day) or comparing dornase alfa to other medications which help with clearing secretions, so current evidence from these trials is limited and of low quality.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Adde 2004	+	?	−	?	+	+
Amin 2011	+	+	+	?	+	+
Ballmann 2002	?	?	−	?	+	+
Castile 2009	?	?	+	−	?	?
Dodd 2000	?	?	+	?	+	−
Frederiksen 2006	?	?	?	?	+	+
Fuchs 1994	?	?	+	+	?	+
Laube 1996	?	?	+	+	+	+
McCoy 1996	?	?	+	+	?	+
Minasian 2010	+	?	−	+	+	+
Paul 2004	?	?	+	+	+	+
Quan 2001	+	+	+	+	?	+
Ramsey 1993	?	?	+	+	?	+
Ranasinha 1993	+	+	+	?	+	+
Robinson 2000	?	?	+	+	+	+
Robinson 2005	?	?	+	+	+	+
Shah 1995a	?	?	+	+	+	+
Suri 2001	+	+	−	+	+	+
Wilmott 1996	?	?	+	+	?	?

Studienergebnisse:

Dornase alfa compared to placebo or no treatment

We found that dornase alfa probably improves lung function within one month when compared to a placebo or no treatment and this improvement was also seen in longer trials lasting from six months to two years (eight trials; 1708 participants). There were also fewer

pulmonary exacerbations (flare up of lung inflammation) in these longer trials. One trial found that the cost savings from dornase alfa offset 18% to 38% of the medication costs.

Dornase alfa - daily versus alternate day One trial (43 children) found no differences between treatment schedules for lung function, quality of life or pulmonary exacerbations. Dornase alfa compared to other medications that improve airway clearance

The results from trials comparing dornase alfa to hypertonic saline or mannitol were mixed. One trial (43 children) showed a greater improvement in lung function with dornase alfa compared to hypertonic saline and one trial (23 participants) reported no difference in lung function between dornase alfa and mannitol or dornase alfa and dornase alfa plus mannitol. In one trial (23 participants) quality of life scores were better with dornase alfa alone than with dornase alfa plus mannitol; other drug comparisons found no difference between treatments for quality of life. No trials in any comparison of treatments reported any difference between groups in the number of pulmonary exacerbations.

Overall, no serious side effects were reported, with only rash and a change in voice seen more frequently in those people taking dornase alfa. However, it is not definitively clear from the current evidence if dornase alfa is better than other medications such as hypertonic saline or mannitol.

SUMMARY OF FINDINGS

Summary of findings 1. Dornase alfa versus placebo or no dornase alfa treatment

Dornase alfa compared with placebo or no dornase alfa treatment for cystic fibrosis

Patient or population: Adults and children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa

Comparison: Placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no dornase alfa treatment	Dornase alfa				
Relative mean percentage change in FEV$_1$ (% predicted) at 3 months	The relative mean percentage change in FEV$_1$ (% predicted) was **2.10**	The relative mean percentage change in FEV$_1$ (% predicted) was **7.30 higher** (4.04 higher to 10.56 higher)	NA	320 (1 study)[1]	⊕⊕⊕⊝ moderate[2]	
Relative mean percentage change in FEV$_1$ (% predicted) at 6 months	The relative mean percentage change in FEV$_1$ (% predicted) was **0.00**	The relative mean percentage change in FEV$_1$ (% predicted) was **5.80 higher** (3.99 higher to 7.61 higher)	NA	647 (1 study)[1]	⊕⊕⊕⊕ high[3]	Result presented from once-daily dornase alfa group. Significant benefit for dornase alfa also present in twice-daily dornase alfa group
Relative mean percentage change in FVC (% predicted) at 3 months	The relative mean percentage change in FVC (% predicted) was **7.30**	The relative mean percentage change in FVC (% predicted) was **5.10 higher** (1.23 higher to 8.97 higher)	NA	318 (1 study)[4]	⊕⊕⊕⊝ moderate[2]	

Outcome	Assumed risk	Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Relative mean percentage change in FVC (% predicted) at 6 months	See comment	See comment	MD 3.80 (2.62 to 4.98)	647 (1 study)[1]	⊕⊕⊕⊕ high[3]	Mean difference between groups only presented. Result presented from once-daily dornase alfa group. Significant benefit for dornase alfa also present in twice-daily dornase alfa group
Change in quality of life - CFQ-R respiratory at 1 month	See comment	See comment	MD 0.84 (-10.74 to 12.42)	19 (1 cross-over study)[5]	⊕⊕⊖⊖ low[6,7]	Positive MD indicates an advantage for dornase alfa daily. Participants received both interventions in cross-over design.
Change in quality of life - CFQ-R respiratory (parent) at 1 month	See comment	See comment	MD 9.78 (-2.58 to 22.14)	19 (1 cross-over study)[5]	⊕⊕⊖⊖ low[6,7]	Positive MD indicates an advantage for dornase alfa daily. Participants received both interventions in cross-over design.
Number of people experiencing exacerbations at up to 2 years	252 per 1000	196 per 1000 (156 to 242)	RR 0.78 (0.62 to 0.96)	1157 (3 studies)[8]	⊕⊕⊕⊖ moderate[9]	RR <1 indicates an advantage for dornase alfa.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Assumed and corresponding risk not calculated for quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study
CI: confidence interval; **RR:** risk ratio **MD:** mean difference

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

1. Additionally four trials included in analysis at one month showed a significant advantage to dornase alfa over placebo or no dornase alfa treatment (Laube 1996; Ramsey 1993; Ranasinha 1993; Shah 1995a). Three studies not included in pooled analysis showed no difference between groups in relative FEV$_1$(L) (Robinson 2000) and relative FEV$_1$ (% predicted) (Wilmott 1996) or absolute FEV$_1$ (% predicted) (Amin 2011) at one month. At one year, one study showed a significant advantage to dornase alfa over placebo or no dornase alfa treatment (Frederiksen 2006) and one study showed no difference between treatments (Robinson 2005). At one year, one study showed a significant advantage to dornase alfa over placebo or no dornase alfa treatment (Quan 2001) and at three years, one study showed no significant difference between treatments (Paul 2004).
2. Downgraded due to indirectness: participants in McCoy 1996 had severe lung disease (FVC below 40%).
3. No evidence of imprecision, inconsistency, indirectness, publication bias or serious risk of bias.

4. Additionally four trials included in analysis at one month (Laube 1996; Ramsey 1993; Ranasinha 1993; Shah 1995a) showed a significant advantage to dornase alfa over placebo or no dornase alfa treatment. One study not included in pooled analysis showed a significant advantage in relative FVC (L) to dornase alfa over placebo or no dornase alfa treatment (Robinson 2000) and one study showed no significant different in absolute FVC (% predicted) between groups (Amin 2011) at one month. No significant difference was found between groups at one year (Robinson 2005) and at two years (Quan 2001).

5. Additionally, four studies reported quality of life data which could not be included in pooled analysis. Wilmott 1996 showed no difference between groups in CFQ-R. Ramsey reported that the frequency and magnitude of improvement across all quality of life questions was greater among participants receiving dornase alfa (Ramsey 1993). Ranasinha reported significant improvements in overall well-being and significant improvements in general well-being, cough frequency and chest congestion (Ranasinha 1993) and Fuchs reported significant improvements in well-being score and dyspnoea score on dornase alfa compared to placebo (Fuchs 1994).

6. Downgraded once for lack of applicability: Amin included children only so results are not applicable to adults (Amin 2011).

7. Downgraded once for imprecision: wide confidence intervals around the effect size due to limited sample size of the trial.

8. Additionally, one study reported an age-adjusted RR of having more than one respiratory exacerbation, but these data were not included in the pooled analysis (McCoy 1996). No significant difference was found between dornase alfa and control.

9. Downgraded once as data from one cross-over trial was analysed as parallel data (Amin 2011), which is a conservative approach.

Summary of findings 2. Dornase alfa daily versus alternate days

Dornase alfa daily compared with dornase alfa on alternate days for cystic fibrosis

Patient or population: Children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa daily

Comparison: Dornase alfa alternate days

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dornase alfa alternate days	Dornase alfa daily				
Mean relative percentage change in FEV_1 (L) at 3 months	See comment	See comment	MD 2.00 (-5.00 to 9.00)	43 (1 cross-over study)	⊕⊕⊙⊙ low[1,2]	Positive MD indicates an advantage for dornase alfa daily. Participants received both interventions in cross-over design.
Mean relative percentage in FVC (L) at 3 months	See comment	See comment	MD 0.03 (-0.06 to 0.12)	43 (1 cross-over study)	⊕⊕⊙⊙ low[1,2]	Positive MD indicates an advantage for dornase alfa daily.

Outcomes	Assumed risk	Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	Quality of evidence (GRADE)	Comments
						Participants received both interventions in cross-over design.
Mean relative percentage in quality of life score at 3 months	See comment	See comment	MD 0.01 (-0.02 to 0.04)	43 (1 cross-over study)	⊕⊕⊖⊖ low[1,2]	Positive MD indicates an advantage for dornase alfa daily. Participants received both interventions in cross-over design.
Number of pulmonary exacerbations at 3 months	17 exacerbations	18 exacerbations	NA (see comment)	43 (1 cross-over study)	⊕⊕⊖⊖ low[1,2]	No difference was found in the number of pulmonary exacerbations (no statistical comparison made)

*Assumed and corresponding risk not calculated lung function and quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study.
CI: confidence interval; **MD**: mean difference

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

1. Downgraded once for lack of applicability: Suri included children only so results are not applicable to adults (Suri 2001).
2. Downgraded once for high risk of bias due to lack of blinding.

Summary of findings 3. Dornase alfa versus hypertonic saline

Dornase alfa compared with hypertonic saline for cystic fibrosis

Patient or population: Children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa (once daily)

Comparison: Hypertonic saline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Hypertonic Saline	Dornase alfa				
Mean relative percentage in FEV$_1$ (L) at 3 months	See comment	See comment	MD 8.00 (2.00 to 14.00)	up to 43[1,2] (1 cross-over study) (see comment)	⊕⊕⊖⊖ low[3,4]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Mean relative percentage in FVC (L) at 3 months	See comment	See comment	MD 0.08, (-0.02 to 0.18)	up to 43[1,2] (1 cross-over study)	⊕⊕⊖⊖ low[3,4]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Mean relative percentage in quality of life score at 3 months	See comment	See comment	MD 0.03, (-0.01 to 0.07)	up to 43[1,2] (1 cross-over study)	⊕⊕⊖⊖ low[3,4]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Number of pulmonary exacerbations at 3 months	15 exacerbations	17 exacerbations	NA (see comment)	up to 43[1,2] (1 cross-over study)	⊕⊕⊖⊖ low[3,4]	No difference was found in the number of pulmonary exacerbations (no statistical comparison made)

*Assumed and corresponding risk not calculated lung function and quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study.
CI: confidence interval; **MD**: mean difference

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

1. In the cross-over trial, 43 participants completed the dornase alfa arm and 40 completed the hypertonic saline arm (Suri 2001).
2. Two additional cross-over trials compared dornase alfa and hypertonic saline, no significant differences were found between the treatments for % change in FEV$_1$ and other primary outcomes of the review were not recorded in these trials (Adde 2004; Ballmann 2002).
3. Downgraded once for lack of applicability: Suri included children only so results are not applicable to adults (Suri 2001).
4. Downgraded once for high risk of bias due to lack of blinding.

Summary of findings 4. Dornase alfa versus mannitol

Dornase alfa compared with mannitol for cystic fibrosis

Patient or population: Children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa

Comparison: Mannitol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Partici-pants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Mannitol	Dornase Alfa				
Mean absolute change in FEV1 (L) at 3 months	See comment	See comment	MD 0.02 (-0.11 to 0.16)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ low[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Mean absolute change in FVC (L) at 3 months	See comment	See comment	MD -0.02, (-0.23 to 0.19)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ low[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Change in quality of life - CFQ-R at 3 months	See comment	See comment	MD 10.61 (0.27 to 20.95)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ low[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Number of people experiencing ex-acerbations - at 3 months	130 per 1000	143 per 1000 (33 to 631)	RR 1.10 (0.25 to 4.84)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ low[2,3]	RR <1 indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.

*Assumed and corresponding risk not calculated for lung function and quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study.
CFQ-R: Cystic Fibrosis Questionnaire - Revised; **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

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

1. In the cross-over trial, 21 participants completed the dornase alfa arm and 23 participants completed the mannitol arm (Minasian 2010).
2. Downgraded once for lack of applicability: Minasian included children only so results are not applicable to adults (Minasian 2010).
3. Downgraded once for high risk of bias due to lack of blinding.

Summary of findings 5. Dornase alfa versus dornase alfa and mannitol

Dornase alfa compared with dornase alfa and mannitol for cystic fibrosis

Patient or population: Children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa

Comparison: Dornase alfa and Mannitol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Partici-pants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dornase alfa and mannitol	Dornase alfa				
Mean absolute change in FEV$_1$ (L) at 3 months	See comment	See comment	MD 0.10 (-0.06 to 0.25)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ low[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Mean absolute change in FVC (L) at 3 months	See comment	See comment	MD 0.13 (-0.11 to 0.37)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ low[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.

Change in quality of life - CFQ-R at 3 months	See comment	See comment	MD 10.61 (0.27 to 20.95)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ low[2,3]	Positive MD indicates an advantage for dornase al-fa. Participants received both interventions in cross-over design.
Number of people experiencing exac-erbations at 3 months	261 per 1000	143 per 1000 (41 to 501)	RR 0.55 (0.16 to 1.92)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ low[2,3]	RR <1 indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.

*Assumed and corresponding risk not calculated lung function and quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study.
CI: confidence interval; **MD**: mean difference; **RR**: risk ratio

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

1. In the crossover trial, 21 participants completed the dornase alfa arm and 23 participants completed the dornase alfa plus mannitol arm (Minasian 2010).
2. Downgraded once for lack of applicability: Minasian included children only so results are not applicable to adults (Minasian 2010).
3. Downgraded once for high risk of bias due to lack of blinding.

Anmerkung/Fazit der Autoren

There is evidence to show that, compared with placebo, therapy with dornase alfa may improve lung function in people with cystic fibrosis in trials lasting from one month to two years. There was a decrease in pulmonary exacerbations in trials of six months or longer, probably due to treatment. Voice alteration and rash appear to be the only adverse events reported with increased frequency in randomised controlled trials. There is not enough evidence to firmly conclude if dornase alfa is superior to other hyperosmolar agents in improving lung function.

Hinweise:

Keine Auswertung für (Klein-)Kinder

Smith S, Rowbotham NJ, 2022 [9].

Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis

Fragestellung

To evaluate the effects of long-term inhaled antibiotic therapy in people with cystic fibrosis on clinical outcomes (lung function, frequency of exacerbations and nutrition), quality of life and adverse events (including drug-sensitivity reactions and survival).

Methodik

Population:
- People with CF diagnosed by clinical features associated with an abnormal sweat electrolyte test or mutations of the CFTR gene or both. All ages and all levels of severity of respiratory disease were included.

Intervention:
- Any inhaled antibiotic (all doses and methods of inhalation) with activity against P aeruginosa given for at least three months

Komparator:
- inhaled placebo or no placebo, i.e. usual treatment (where this did not include any oral or intravenous antibiotic therapy during the trial), or another inhaled anti-

pseudomonal antibiotic. Trials in which an antibiotic was tested at two or more doses are also eligible.

Endpunkte:

- Primary outcomes
  1. Lung function (measured in litres (L) or per cent (%) predicted) a. forced expiratory volume in one second (FEV1) b. forced vital capacity (FVC)
  2. Exacerbation of respiratory infection (defined as any deterioration in clinical condition resulting in treatment with oral or intravenous antibiotics, either at home or in hospital) a. hospital admissions b. days in hospital c. courses of intravenous antibiotics d. pulmonary exacerbations i. frequency ii. time to first exacerbation
- Secondary outcomes
  1. Nutrition a. height b. weight
  2. QoL
  3. Survival
  4. Antibiotic resistance in P aeruginosa or other organisms
  5. Adverse events a. renal impairment - serum creatinine increase b. auditory impairment - impaired audiometry c. sensitivity reactions - bronchospasm d. other (post hoc change)

Recherche/Suchzeitraum:

- Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - Pediatric Pulmonology and the Journal of Cystic Fibrosis. Unpublished work is identified by searching through the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference, the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference
- 28 June 2022

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017)

Ergebnisse

Anzahl eingeschlossener Studien:

- N=18

Charakteristika der Population/Studien:

- Inhaled anti-pseudomonal antibiotic compared to placebo or usual treatment

An inhaled anti-pseudomonal antibiotic was compared to placebo or usual treatment in 11 of the 18 included trials (1130 participants) (Chuchalin 2007; Day 1988; Hodson 1981; Jensen 1987; Kun 1984; MacLusky 1989; Murphy 2004; Nathanson 1985; Ramsey 1999; Stead 1987; Wiesemann 1998). Two trials were published only as abstracts in conference proceedings (Day 1988; Nathanson 1985). There was large variation between trials in terms of design, intervention and outcome measures. One trial compared an inhaled antibiotic to both placebo and another inhaled antibiotic and is therefore included in two comparisons in this review (Stead 1987).

Searches of the Group's CF Trials Register identified 32 citations that report data from a single trial which was first fully published in 1999 (Ramsey 1999). This trial is widely known as the 'TOBI' trial from the trade name of the preservative-free formulation of tobramycin used in the trial (Ramsey 1999). Another report of this trial is published in full and provides information on the effect of tobramycin treatment on the isolation of drug-resistant organisms (Burns 1999). A third report of this trial is on the effect of tobramycin on hospitalisation and home intravenous antibiotic use; it is only an abstract and results can not be analysed (Birnbaum 1998).

- Trial design

Seven out of 11 trials were described as double-blinded (Chuchalin 2007; Day 1988; Hodson 1981; Jensen 1987; Nathanson 1985; Ramsey 1999; Wiesemann 1998), three trials were described as single-blinded (Kun 1984; MacLusky 1989; Stead 1987). One trial was not blinded (Murphy 2004).

A cross-over design was used in five trials with 92 participants (8% of the total participants for this comparison) (Day 1988; Hodson 1981; Kun 1984; Nathanson 1985; Stead 1987). In one of these trials, the first period could be analysed as a parallel design trial for the first year (Kun 1984). None of the five cross-over trials examined for carry-over or period effects. The remaining six trials were of parallel design (Chuchalin 2007; Jensen 1987; MacLusky 1989; Murphy 2004; Ramsey 1999; Wiesemann 1998).

Duration of treatment ranged from a minimum of three months (Jensen 1987; Nathanson 1985) to the longest which had a mean treatment duration of 33 months (MacLusky 1989). Treatment lasted three months in two trials (Jensen 1987; Nathanson 1985), four months in one trial (Stead 1987), six months in four trials (Chuchalin 2007; Day 1988; Hodson 1981; Ramsey 1999), 12 months in two trials (Kun 1984; Wiesemann 1998), 56 weeks in one trial (Murphy 2004) and there was a mean treatment duration of 33 months in one trial (MacLusky 1989).

Four of the trials were multicentre, these were carried out in: Hungary, Poland and Russia (Chuchalin 2007); USA and Canada (Murphy 2004); USA (Ramsey 1999); and Germany (Wiesemann 1998). Two were single-centre trials carried out in Australia (Kun 1984) and Canada (MacLusky 1989). The remaining five trials did not state whether they were single-centre or multicentre or in which country they were carried out (Day 1988; Hodson 1981; Jensen 1987; Nathanson 1985; Stead 1987).

The sample size for each trial varied from seven randomised participants (Nathanson 1985) to 520 randomised participants (Ramsey 1999), with a total of 1130 participants enroled across all included trials.

- Participants

Participants were both children and adults, with the youngest being five years of age (Day 1988) and the eldest being 45 years old (Chuchalin 2007), although an accurate age distribution is difficult to determine from the reports and is not available for the largest trial (Ramsey 1999). The numbers of males and females was equally distributed in seven of the trials where 50% to 55% of the participants were male (Chuchalin 2007; Day 1988; Hodson 1981; Jensen 1987; MacLusky 1989; Murphy 2004; Ramsey 1999). Two of the trials were weighted towards males with 67% male participants in the Stead trial (Stead 1987) and 60% male participants in the Wiesemann trial (Wiesemann 1998). The numbers of male and female participants was not stated in either the Kun trial or the Nathanson trial (Kun 1984; Nathanson 1985).

Six out of 11 trials stated criteria for the diagnosis of CF (Chuchalin 2007; Hodson 1981; MacLusky 1989; Murphy 2004; Ramsey 1999; Stead 1987); however since participants

were recruited from CF centres we accepted all 11 trials. It is unlikely that an important number of participants without CF were included.

There is also a wide range of disease severity as measured by baseline FEV1, with some participants having an FEV1 lower than 30% predicted and some over 100% predicted. However, it is not possible to know the numbers in categories of 'no', 'mild', 'moderate' or 'severe' impairment of lung function. Evidence of P aeruginosa in sputum culture was an inclusion requirement in all trials except one, in which P aeruginosa was present in eight out of 33 participants (Kun 1984).

The pattern of respiratory disease in CF tends to be of progressive deterioration over years and with episodes of acute deterioration and some recovery. Due to these short-term fluctuations in severity, the timing of entry of participants into a trial in relation to exacerbations may determine outcome. In two trials, participants were recruited immediately after a course of anti-pseudomonal intravenous antibiotics (Day 1988; Jensen 1987). Three trials stated that participants were recruited at least two weeks after a course of intravenous antibiotics in an attempt to ensure a stable state (Hodson 1981; Ramsey 1999; Stead 1987). One trial excluded participants if they had had an exacerbation in the previous month (Chuchalin 2007). This aspect of participant selection was not stated in the remaining five trials (Kun 1984; MacLusky 1989; Murphy 2004; Stead 1987; Wiesemann 1998).

- Interventions

A unique feature of two trials was the intermittent use of nebulised tobramycin, i.e. cycles of tobramycin 300 mg twice daily for four weeks, followed by four weeks off treatment for a trial duration of six months (Ramsey 1999) and 56 weeks (Murphy 2004).

The dose of drug delivered to the lung depends on a number of factors including the method of aerosol generation and delivery, the volume of solution in the nebuliser and the method of inhalation (Newman 1985). Four trials reported details of the nebuliser and pump system (Chuchalin 2007; Kun 1984; Murphy 2004; Ramsey 1999). Another four trials stated which nebuliser the participants used (Jensen 1987; MacLusky 1989; Stead 1987; Wiesemann 1998). Five of the eight trials which reported using jet nebulisers stated the volume of solution they used, which varied from 1 mL to 5 mL (Jensen 1987; MacLusky 1989; Ramsey 1999; Stead 1987; Wiesemann 1998). Three trials did not provide any details of aerosol delivery (Day 1988; Hodson 1981; Nathanson 1985).

In three of the seven double-blinded trials, the placebo was normal saline, and it is possible that in these trials the taste of the antibiotic solution was not completely masked (Day 1988; Jensen 1987; Nathanson 1985). In the remaining four double-blinded trials, investigators uses varying saline concentrations and the addition of other chemicals (lactose or quinine or preservatives) to match drug and placebo solutions (Chuchalin 2007; Hodson 1981; Ramsey 1999; Wiesemann 1998). Of the four trials which did not use a double-blind design, Kun and Murphy used usual treatment as control (Kun 1984; Murphy 2004), MacLusky used normal saline (MacLusky 1989) and Stead used 3.5% sodium chloride solution (hypertonic saline) as a placebo (Stead 1987), but since then hypertonic saline has been shown to have a therapeutic effect in CF (Wark 2009).

- The trials used the following individual antibiotics.

Colistin

Two trials with 54 participants compared colistin to placebo, using a dose of one million units twice daily for three months (Jensen 1987) and for six months (Day 1988).

Tobramycin

Five trials with 998 participants compared tobramycin to placebo or usual treatment for between six and 33 months (Chuchalin 2007; MacLusky 1989; Murphy 2004; Ramsey

1999; Wiesemann 1998); 52% of participants were in one high-quality trial (Ramsey 1999). Tobramycin was used in varying doses; two trials used 80 mg (MacLusky 1989; Wiesemann 1998) and three trials used 300 mg (Chuchalin 2007; Murphy 2004; Ramsey 1999). The frequency of dosing also varied with four trials using twice-daily nebulisation (Chuchalin 2007; Murphy 2004; Ramsey 1999; Wiesemann 1998) and one trial using three-times daily nebulisation (MacLusky 1989).

Gentamicin

Two cross-over trials (n = 40) compared gentamicin as a single agent; one trial used 20 mg twice daily for 12 months (Kun 1984) and the second used 80 mg three times daily for three months (Nathanson 1985).

Ceftazidime

Only one trial with 18 participants used ceftazidime in the third arm of a three-way cross-over trial without a washout period; the dose was 1.0 g twice daily (Stead 1987).

Gentamicin and carbenicillin

Two cross-over trials with 38 participants tested a combination of gentamicin 80 mg with carbenicillin 1.0 g twice daily (Hodson 1981; Stead 1987).

Aztreonam lysine (AZLI)

No trial investigated the use of AZLI compared to placebo.

Qualität der Studien:

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Assael 2013	+	+	–	?	+	+	?
Bilton 2020	?	?	–	?	+	+	+
Chuchalin 2007	?	?	+	?	+	?	?
Day 1988	?	?	?	?	–	–	?
Elborn 2015	+	+	–	+	+	+	+
Flume 2016b	?	?	?	+	?	+	?
Hodson 1981	?	?	?	?	?	?	?
Jensen 1987	?	?	?	?	+	–	–
Konstan 2010b	?	?	–	–	+	+	?
Kun 1984	?	–	–	+	+	+	–
MacLusky 1989	–	+	–	+	+	+	
Murphy 2004	?	?	–	–	+	–	–
Nathanson 1985	?	?	?	?	–	?	?
Nikolaizik 2008	?	?	–	–	?	–	?
Ramsey 1999	?	?	+	?	+	–	?
Schuster 2013	?	?	–	+	+	+	?
Stead 1987	+	?	?	?	+	+	?

Stead 1987	+	?	?	?	+	+	?
Wiesemann 1998	+	–	+	?	+	–	

Summary of findings 1. Summary of findings: anti-pseudomonal antibiotics versus placebo

Anti-pseudomonal antibiotics compared with placebo for long-term therapy in CF

Patient population: adults and children with CF and *P aeruginosa*

Settings: outpatients

Intervention: inhaled anti-pseudomonal antibiotics

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Placebo	**Inhaled anti-pseudomonal antibiotics**				
FEV$_1$ (% predicted) Follow-up: at 3 months and up to 36 months	4 trials found a significant improvement in FEV$_1$ with inhaled antibiotics compared to placebo, although no data were available for 3 of these. 1 trial reported that the rate of decline in FEV$_1$ favoured antibiotics. The remaining 6 trials showed no significant difference between inhaled antibiotics and placebo.		NA	1130 (11)	⊕⊕⊝⊝ low[a]	The included trials all measured FEV$_1$ but in different ways and for different lengths of time. It was not possible to combine the trials in a meta-analysis.
FVC (% predicted) Follow-up: at 3 months and up to 36 months	5 of the 10 trials found significant changes in FVC at the end of the trial period, favouring inhaled antibiotics when compared to placebo. 1 trial found no significant difference in absolute values of FVC % predicted between inhaled antibiotics and control but found that mean change in FVC % predicted was significantly different (favouring antibiotics). 1 trial found a combination of gentamycin and carbenicillin versus placebo to be significantly different and favouring antibiotics yet ceftazidime versus placebo was not significantly different. 3 trials found no significant difference between antibiotics and placebo with regard to FVC % predicted.		NA	1097 (10)	⊕⊕⊝⊝ low[a]	FVC was measured differently across the trials.
Pulmonary exacerbations: frequency of one or more hospital admissions Follow-up: over 3 months and up to 12 months	397 per 1000	262 per 1000 (187 to 369 per 1000)	RR 0.66 (0.47 to 0.93)	946 (3)	⊕⊕⊝⊝ low[a]	
Quality of life: lost school or working days Follow-up: over 3 months and up to 12 months	The mean number of lost school or working days in the control group was 10 days.	The mean number of lost school or working days in the inhaled antibiotic group was 5.3 days lower (8.59 lower to 2.01 lower).	NA	245 (1)	⊕⊕⊝⊝ low[b,c]	
Survival: number of deaths Follow-up: over 3 months and up to 12 months	17 per 1000	3 per 1000 (1 to 19 per 1000)	RR 0.17 (0.03 to 1.09)	767 (2)	⊕⊕⊝⊝ low[b,c]	
Antibiotic resistance: frequency of tobramycin-resistant *P aeruginosa*	105 per 1000	205 per 1000 (90 to 464 per 1000)	RR 1.95 (0.86 to 4.42)	672 (2)	⊕⊕⊕⊝ moderate[b]	

Follow-up: at end of trial (12 months)					
Adverse events Follow-up: at the end of the trial (84 days to 33 months)	There were no significant differences between inhaled antibiotics and placebo for auditory impairment, pneumothorax, haemoptysis. Tinnitus and voice alteration were significantly more common in the inhaled antibiotics groups.	NA	1014 (6)	⊕◯◯◯ very low[a,c]	Rate of auditory impairment reported in 5 trials for 996 participants. Rate of pneumothorax reported in 3 trials for 558 participants. Rate of haemoptysis reported in 1 trial for 520 participants. Rate of tinnitus reported in 1 trial for 520 participants. Rate of voice alteration reported in 2 trials for 701 participants.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CF: cystic fibrosis; **CI**: confidence interval; **FEV$_1$**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **P aeruginosa**: Pseudomonas aeruginosa; **RR**: risk ratio.

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.

[a]Downgraded twice due to most trials included in the comparison being at unclear or high risk of bias. 3 trials were at high or unclear risk of bias across all domains. All the 11 trials were at high or unclear risk of bias for randomisation or allocation concealment (or both) and also blinding of participants or outcome assessors (or both).
[b]Downgraded once because of unclear risk of bias across some domains (randomisation or allocation concealment (or both) and blinding of participants or outcome assessment (or both)) of the included trials.
[c]Downgraded once due to imprecision due to low event rates.

Summary of findings 2. Summary of findings: colistimethate dry powder for inhalation (Colobreathe®) versus tobramycin for inhalation solution

Colistimethate dry powder (Colobreathe®) compared with TIS for long-term therapy in CF

Patient population: children and adults with CF and P aeruginosa infection

Settings: outpatients

Intervention: colistimethate dry powder for inhalation (1 1.6625 MU capsule twice daily for 24 weeks)

Comparison: TIS (3 cycles of 28 days of TIS (300 mg/5 mL) twice daily followed by a 28-day off period)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk **TIS**	**Corresponding risk** **Colistimethate dry powder for inhalation (Colobreathe®)**				
FEV$_1$ (% predicted): mean change from baseline Follow-up: 24 weeks	Adjusted mean difference between the groups (ITT population LOCF) for the change in FEV$_1$ % predicted, MD -0.98% (95% CI -2.74% to 0.86%). There was no significant difference between the 2 groups for this outcome.		NA	374 (1)	⊕⊕◯◯ low[a,b]	The data were not normally distributed and were analysed using log-transformation analysis. We have reported the results directly from the paper.
FVC (% predicted): mean change from baseline Follow-up: 24 weeks	There was no significant difference between groups for FVC % predicted in the ITT population (LOCF), MD 0.01 L (95% CI -0.09 to 0.10).		NA	374 (1)	⊕⊕◯◯ low[a,b]	The data were not normally distributed and were analysed using log-transformation analysis. We have reported the results directly from the paper.
Pulmonary exacerbations: number of pulmonary exacerbations Follow-up: 24 weeks	**262 per 1000**	**312 per 1000** (225 to 430 per 1000)	**RR 1.19** (0.86 to 1.64)	374 (1)	⊕⊕⊕◯ moderate[a]	

Quality of life: adjusted mean change in CFQ-R score at the end of treatment Follow-up: 24 weeks	The adjusted mean changes at the end of the trial favoured the Colobreathe® group in terms of treatment burden (P = 0.091). This difference was significant at Week 4 (P < 0.001).		NA	374 (1)	⊕⊕⊖⊖ low[a],[c]	The trial was not powered to detect differences in overall quality of life. Results reported directly from paper.
Survival: number of deaths Follow-up: over 3 months and up to 12 months	10 per 1000	2 per 1000 (0 to 43 per 1000)	RR 0.21 (0.01 to 4.32)	374 (1)	⊕⊕⊖⊖ low[a],[d]	
Antibiotic resistance: change in mean MIC_{50} and MIC_{90} at the end of the trial Follow-up: 24 weeks	The mean MIC_{50} (breakpoint of ≥ 8 mg/L) changed in the TIS group by 0.5 compared to 0.0 in the Colobreathe® group. The mean MIC_{90} (breakpoint of ≥ 8 mg/L) changed in the both groups by 4.0.		NA	374 (1)	⊕⊕⊖⊖ low[a],[c]	
Adverse events: number of treatment related adverse events Follow-up: 24 weeks	466 per 1000	820 per 1000 (699 to 969 per 1000)	RR 1.76 (1.50 to 2.08)	379 (1)	⊕⊕⊖⊖ low[a],[d]	Treatment-related adverse events were significantly lower in the TIS group than the Colobreathe® group P < 0.0001.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CF: cystic fibrosis; CI: confidence interval; FEV_1: forced expiratory volume at 1 second; FVC: forced vital capacity; ITT: intention-to-treat; LOCF: last observation carried forward; MIC: minimum inhibitory concentration; *P aeruginosa*: *Pseudomonas aeruginosa*; RR: risk ratio; TIS: tobramycin for inhalation solution.

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.

[a]Downgraded once due to an unclear or high risk of bias across 4 out of the 7 domains, particularly randomisation, allocation concealment and participant blinding.
[b]Downgraded once due to LOCF analysis increasing risk of bias.
[c]Downgraded once for imprecision; the trial was underpowered to detect differences in overall quality of life.
[d]Downgraded once for imprecision due to low event rates.

Summary of findings 3. Summary of findings: inhaled TOBI® (IV preparation) versus tobramycin for inhalation solution

Inhaled TOBI® (IV preparation) compared with TIS for long-term therapy in CF						

Patient population: adults and children with CF and *P aeruginosa*

Settings: outpatients

Intervention: inhaled tobramycin (TOBI®) (IV preparation) continuous twice-daily 80 mg

Comparison: TIS intermittent (4-weekly on-off cycles) twice-daily 300 mg/5 mL

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	TIS intermittent	**Inhaled tobramycin (IV preparation) continuous**				
FEV_1 (% predicted): change from baseline Follow-up: the end of the first treatment phase (12 weeks)	The change from baseline in FEV_1 % predicted was on average 1.07% less in the TIS group than in the inhaled tobramycin (IV preparation) group, values ranged from 11.20% less to 9.06% higher.		NA	32 (1)	⊕◯◯◯ very low[a,b]	Trial investigators provided individual participant data for lung function and we have analysed the first-period data ourselves using the generic inverse variance method in RevMan.
FVC (% predicted): change from baseline Follow-up: the end of the first treatment phase (12 weeks)	The change from baseline in FVC % predicted was on average 0.01% more in the TIS group than in the inhaled tobramycin (IV preparation) group, values ranged from 9.48% less to 9.50% higher.		NA	32 (1)	⊕◯◯◯ very low[a,b]	Trial investigators provided individual participant data for lung function and we have analysed the first-period data ourselves using the generic inverse variance method in RevMan.
Pulmonary exacerbations Follow-up: NA	Outcome not reported.				NA	
Quality of life Follow-up: NA	Outcome not reported.				NA	
Survival Follow-up: NA	Outcome not reported.				NA	
Antibiotic resistance Follow-up: NA	Outcome not reported.				NA	
Adverse events Follow-up: NA	Outcome not reported.				NA	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CF: cystic fibrosis; **CI**: confidence interval; FEV_1: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **IV**: intravenous; **NA**: not applicable; *P aeruginosa*: *Pseudomonas aeruginosa*; **TIS**: tobramycin for inhalation solution.

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.

[a]Downgraded twice due to risk of bias being unclear or high across all the domains. The trial was at risk due to lack of blinding of participants or outcome measurement. This was because of the interventions being significantly different making it impossible to blind. Some outcomes (sputum bacteriology and oxygen saturation) were listed in the methods but not reported in the results.
[b]Downgraded once due to imprecision. The sample size was small as only the first arm of a cross-over trial was used.

Summary of findings 4.   Summary of findings: tobramycin for inhalation powder versus tobramycin for inhalation solution

TIP compared with TIS for long-term therapy in CF

Patient population: children and adults with CF and *P aeruginosa*

Settings: outpatients

Intervention: TIP twice-daily 4 capsules (total of 112 mg) (3 cycles (28 days on-drug, 28 days off-drug))

Comparison: TIS twice-daily 300 mg/5 mL

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS	TIP				
FEV$_1$ (% predicted): relative change from baseline Follow-up: 24 weeks	The MD between the 2 groups was 1.10 (95% CI -2.33 to 4.53) favouring TIS, but not significantly.		NA	517 (1)	⊕⊕⊕⊝ **moderate**[a]	TIP was found to be non-inferior to TIS.
FVC Follow-up: NA	Outcome not reported.				NA	
Pulmonary exacerbations: number of participants experiencing pulmonary exacerbation Follow-up: 24 weeks	301 per 1000	337 per 1000 (259 to 436 per 1000)	RR 1.12 (0.86 to 1.45)	517 (1)	⊕⊕⊕⊝ **moderate**[a]	
Quality of life	Outcome not reported.				NA	

Follow-up: NA				
Survival: number of deaths Follow-up: 24 weeks	Not calculable as there were no deaths in the TIS group. There were 3 deaths in the TIP group.	**RR4.76** (0.25 to 91.62)	517 (1)	⊕⊕⊖⊖ **low**[a,b]	
Antibiotic resistance: mean change from baseline in *P aeruginosa* sputum density Follow-up: 24 weeks	Mucoid and non-mucoid *P aeruginosa* sputum densities showed a decrease from baseline in both groups at all time points. Mean change was -1.6 versus -0.92 $\log_{10}$ CFU/g for mucoid phenotype and -1.77 versus -0.73 $\log_{10}$ CFU/g for non-mucoid phenotype.	NA	517 (1)	⊕⊕⊕⊖ **moderate**[a]	
Adverse events: number of any adverse event reported Follow-up: 24 weeks	842 per 1000	901 per 1000 (842 to 968 per 1000)	**RR 1.07** (1.00 to 1.15)	517 (1)	⊕⊕⊕⊖ **moderate**[a]	A range of adverse events were reported but the only adverse events which were significantly different between the 2 groups were *favouring TIS* • cough: RR 1.56 (95% CI 1.23 to 1.96) • hoarseness: 3.56 (95% CI 1.71 to 7.43).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CF: cystic fibrosis; **CFU**: colony forming units; **CI**: confidence interval; **FEV$_1$**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **NA**: not applicable; **P aeruginosa**: *Pseudomonas aeruginosa*; **RR**: risk ratio; **TIP**: tobramycin inhalation powder **TIS**: tobramycin for inhalation solution.

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.

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[a]Downgraded once due to risk of bias within the trial. This was an open-label trial and so was at high risk of bias for blinding and had an unclear risk for randomisation and allocation concealment.
[b]Downgraded once for imprecision due to low event rates.

Summary of findings 5. Summary of findings: aztreonam lysine for inhalation versus tobramycin for inhalation solution

AZLI compared with TIS for long-term therapy in CF						

Patient population: children and adults with CF and *P aeruginosa*

Settings: outpatients

Intervention: AZLI 75 mg 3 times daily

Comparison: TIS 300 mg twice-daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS	AZLI				
FEV$_1$ (% predicted): mean relative change from baseline averaged across 3 cycles Follow-up: 24 weeks	The MD between groups was -3.40 (95% CI -6.63 to -0.17), favouring AZLI.		NA	268 (1)	⊕⊕⊕⊖ moderate[a]	
FVC Follow-up: NA	Outcome not reported.				NA	
Pulmonary exacerbations: need for additional antibiotics	576 per 1000	380 per 1000 (294 to 495 per 1000)	RR 0.66 (0.51 to 0.86)	268 (1)	⊕⊕⊕⊖ moderate[a]	

Follow-up: 24 weeks						
Quality of life: mean change from baseline in CFQ-R respiratory symptom scale averaged across 3 cycles Follow-up: 24 weeks	The mean (SD) change in CFQ-R score was 2.2 (17.7) in the TIS group.	The mean change in CFQ-R score in the AZLI group was 4.10 points higher (0.06 points lower to 8.26 points higher).	NA	268 (1)	⊕⊕⊕⊝ **moderate**[a]	
Survival Follow-up: 24 weeks	See comments.			268 (1)	⊕⊕⊝⊝ **low**[a,b]	2 participants died during the trial, but neither were related to treatment and the treatment group was not specified.
Antibiotic resistance: change from baseline in *P aeruginosa* CFU/g of sputum at week 24 Follow-up: 24 weeks	The mean (SD) change in log_{10} CFU/g was -0.32 (1.87) in the TIS group.	The mean change in log_{10} CFU/g in the AZLI group was 0.23 lower (0.76 lower to 0.3 log_{10} CFU/g higher).	NA	268 (1)	⊕⊕⊕⊝ **moderate**[a]	
Adverse events: number of treatment-related adverse events Follow-up: 24 weeks	129 per 1000	228 per 1000 (133 to 392 per 1000)	**RR 1.77** (1.03 to 3.04)	268 (1)	⊕⊕⊕⊝ **moderate**[a]	Whilst treatment-related events were significantly more likely in the AZLI-treated group P < 0.04), the difference in serious adverse events (also more likely in the AZLI group) did not quite reach significance. No significant difference was reported for any other reported adverse event.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AZLI: aztreonam lysine for inhalation; **CFQ-R**: cystic fibrosis questionnaire - revised; **CF**: cystic fibrosis; **CFU**: colony forming units; **CI**: confidence interval; **FEV₁**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **NA**: not applicable; *P aeruginosa*: *Pseudomonas aeruginosa*; **RR**: risk ratio; **SD**: standard deviation; **TIS**: tobramycin for inhalation solution.

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 estimate of effect.

[a]Downgraded once due to risk of bias within the trial. The trial was open-label with the treatments given at a different frequency and so obvious to participants. There was also an unclear risk attributed to blinding of outcome assessment.
[b]Downgraded once due to imprecision from low event rates.

Summary of findings 6. Summary of findings: amikacin liposome inhalation suspension (ALIS) versus tobramycin for inhalation solution

ALIS compared with TIS for long-term therapy in CF

Patient or population: children and adults with CF and *P aeruginosa*

Settings: outpatients

Intervention: ALIS 590 mg once daily with eFlow® nebuliser

Comparison: TIS 300 mg twice daily via PARI LC® PLUS nebuliser

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS	ALIS				
FEV$_1$: LS mean FEV$_1$ (L) Follow-up: 168 days	The difference in LS mean FEV$_1$ (L) adjusted for treatment and randomisation strata, at the end of treatment was MD −1.31% (95% CI, −4.95 to 2.34; P = 0.48).		NA	262 (1)	⊕⊕⊕⊝ **moderate**[a]	This analysis was carried out on the per-protocol data. The lower CI was above -5% indicating non-inferiority of ALIS to TIS.
FVC Follow-up: NA	Outcome not reported.			NA		
Pulmonary exacerbations: frequency of pulmonary exacerbations Follow-up: 168 days	There were more participants in the ALIS group experiencing an exacerbation than in the TIS group (63.5% in the ALIS group compared to 51.4% in the TIS group, P = 0.02).		NA	294 (1)	⊕⊕⊕⊝ **moderate**[a]	The study also reported on hospitalisations and found that there was no difference, RR 0.82 (95% CI 0.50 to 1.33). Time to first exacerbation was also shorter in the ALIS group, HR 1.51 (95% CI 1.07 to 2.13) P = 0.03.
Quality of life: change in CFQ-R domain scores (mean CFQ-R score) Follow-up: 168 days	There was no difference in change in CFQ-R scores between groups at the end of the study across any domain.		NA	294 (1)	⊕⊕⊕⊝ **moderate**[a]	
Survival Follow-up: NA	Outcome not reported.			NA	No deaths were reported in either group for the duration of the study (Bilton 2020).
Antibiotic resistance: change from baseline in *P aeruginosa* CFU/g of sputum density Follow-up: 168 days	LS mean difference was no different between groups at the end of the study P = 0.13		NA	259 (1)	⊕⊕⊕⊝ **moderate**[a]	The authors also report that mean *P aeruginosa* sputum densities were below baseline level at day 168 in both the ALIS group and the TIS group (Bilton 2020).
Adverse events: number of participants experiencing any TEAE Follow-up: 168 days	788 per 1000	1000 per 1000 (638 to 1000 per 1000)	RR 1.47 (0.81 to 2.66)	294 (1)	⊕⊕⊕⊝ **moderate**[a]	There were no differences between groups by severity of TEAE.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ALIS: amikacin liposome inhalation solution; **CFU** colony forming units; **CF**: cystic fibrosis; **CFQ-R**: cystic fibrosis questionnaire - revised; **CI**: confidence interval; **FEV$_1$**: forced expiratory volume at 1 second; **HR**: hazard ratio; **LS**: least squares; **MD**: mean difference; **NA**: not applicable; *P aeruginosa*: *Pseudomonas aeruginosa*; **RR**: risk ratio; **TEAE**: treatment-related adverse event; **TIS**: tobramycin for inhalation solution.

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.

¹Downgraded once due to risk of bias within the trial being unclear or high across all domains, largely due to the trial being open label with unclear process for generation of sequence and allocation concealment.

Summary of findings 7. Summary of findings: levofloxacin for inhalation solution versus tobramycin for inhalation solution

LIS compared with TIS for long-term therapy in CF

Patient population: adults and children aged over 12 with CF and *P aeruginosa*

Settings: outpatients

Intervention: LIS (Aeroquin™, MP376, APT-1026) 240 mg (2.4 mL of 100 mg per mL solution) twice daily

Comparison: TIS 300 mg/5 mL twice daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	TIS	**LIS**				
FEV₁ (% predicted): relative mean change from baseline Follow-up: 6 months	The mean (SD) change in % predicted FEV₁ was -1.5 (14.8) in the TIS group.	The mean change in % predicted FEV₁ in the LIS group was 0.30 higher (3.02 lower to 3.62 higher).	NA	282 (1)	⊕⊕⊕⊕ **high**	
FVC(% predicted): relative mean change from baseline Follow-up: 6 months	The mean (SD) change in FVC % predicted was -1.3 (12.8) in the TIS group.	The mean change in FVC % predicted in the LIS group was 0.60 higher (2.23 lower to 3.43 higher).	NA	282 (1)	⊕⊕⊕⊕ **high**	
Pulmonary exacerbations:	280 per 1000	173 per 1000 (112 to 274 per 1000)	RR 0.62 (0.40 to 0.98)	282 (1)	⊕⊕⊕⊕ **high**	

number of hospitalisations due to respiratory exacerbations Follow-up: 6 months					
Quality of life: change from baseline in CFQ-R Follow-up: 6 months	The trial reported that scores in the respiratory domain of the CFQ-R were similar in the 2 groups at baseline, increased in the LIS group and decreased in the TIS group at day 28 and were similar again by the end of the trial.		NA	282 (1)	⊕⊕⊙⊙ **low**[a,b]	No data could be entered into analysis.
Survival Follow-up: NA	Outcome not reported.				NA	
Antibiotic resistance: mean change in *P aeruginosa* sputum density (log$_{10}$ CFU/g) Follow-up: 6 months	The mean (SD) sputum density in the TIS group was -0.25 (1.76) log$_{10}$ CFU/g.	The mean sputum density in the LIS group was 0.12 higher (0.31 log$_{10}$ CFU/g lower to 0.55 log$_{10}$ CFU/g higher).	NA	282 (1)	⊕⊕⊕⊕ **high**	
Adverse events: number of treatment-related adverse events Follow-up: 6 months	Significantly fewer participants in the LIS group reported epistaxis, RR 0.2 (95% CI 0.04 to 1.00), general malaise, RR 0.1 (95% CI 0.01 to 0.83) and increased blood glucose, RR 0.28 (95% CI 0.08 to 0.94). Significantly more participants in the LIS group reported dysgeusia, RR 46.25 (95% CI 2.88 to 742). No other differences were noted.		NA	282 (1)	⊕⊕⊕⊕ **high**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CF: cystic fibrosis; **CFU**: colony forming units; **CI**: confidence interval; **FEV$_1$**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **LIS**: levofloxacin for inhalation solution; **NA**: not applicable; *P aeruginosa*: *Pseudomonas aeruginosa*; **RR**: risk ratio; **TIS**: tobramycin for inhalation solution.

[a]Downgraded once due to indirectness. Quality of life was measured by the CFQ-R score but no data were provided, just a summary. It is unclear which participants were included in this outcome.
[b]Downgraded once due to publication bias as the results were not presented in full for this outcome.

Summary of findings 8.   Summary of findings: continuous cycles alternating aztreonam lysine for inhalation with tobramycin for inhalation solution versus continuous cycles alternating placebo with tobramycin for inhalation solution

Continuous AZLI/TIS compared with continuous placebo/TIS (i.e. intermittent TIS) for long-term therapy in CF

Patient population: children and adults with CF and *P aeruginosa*

Settings: outpatients

Intervention: continuous alternating cycles of AZLI (75 mg (diluted in 0.17% NaCL) 3 times-daily) and TIS (300 mg/5 mL twice-daily)

Comparison: alternating cycles of placebo (lactose monohydrate and sodium chloride reconstituted with the same diluent used for AZLI 3 times daily) and TIS (300 mg/5 mL twice-daily)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	TIS/placebo	**AZLI/TIS**				
FEV$_1$ (% predicted): mean change from baseline (average values across the end of the 3 treatment cycles) Follow-up: 6 months (24 weeks)	The change from baseline in FEV$_1$ % predicted was on average 1.33% more in the AZLI/TIS group than in the in the TIS/placebo group, values ranged from 0.51% lower to 3.17% higher.		NA	90 (1)	⊕⊕⊝⊝ low[a],[b]	
FVC	Outcome not reported.			NA		

Outcome	Assumed risk* (Placebo)	Corresponding risk* (Intervention)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Follow-up: NA						
Pulmonary exacerbations: rate of PDEs per participant year Follow-up: 24 weeks	489 per 1000	347 per 1000 (210 to 577 per 1000)	RR 0.71 (0.43 to 1.18)	90 (1)	⊕⊕⊖⊖ low[a,b]	The rate of PDEs was lower in the AZLI/TIS group (1.31 PDEs per participant year) than in the placebo/TIS group (1.76 PDEs per participant year). The difference between the groups was not reported to be significant (P = 0.25, RR 0.74 (95% CI 0.45 to 1.24)).
Quality of life: CFQ-R respiratory symptom scores averaged from weeks 4, 12 and 20 Follow-up: 24 weeks	Scores improved by a mean (SE) 1.00 (1.74) in the AZLI/tobramycin group, they worsened by a mean (SE) -2.06 (1.63) in the placebo/TIS group. The difference between the groups was not found to be significant, MD 3.06 (95% CI -1.61 to 7.73).		NA	90 (1)	⊕⊕⊖⊖ low[a,b]	
Survival Follow-up: NA	Outcome not reported.				NA	
Antibiotic resistance: mean change from baseline in *P aeruginosa* sputum density (CFU/g) Follow-up: 24 weeks	Adjusted mean changes from baseline sputum *P aeruginosa* density after each course of AZLI/placebo or TIS during the comparative phase were small (0.36 to -0.55 $\log_{10}$ CFU/g) and differences between treatment groups were not statistically significant.		NA	87 (1)	⊕⊕⊖⊖ low[a,b]	Results reported narratively from the paper.
Adverse events: any adverse event in the comparative phase Follow-up: 24 weeks	978 per 1000	949 per 1000 (880 to 1000)	RR 0.97 (0.90 to 1.05)	88 (1)	⊕⊕⊖⊖ low[a,b]	A range of adverse events were reported but the only adverse events which were significantly different between the 2 groups were: *favouring continuous treatment* • dyspnoea: RR 0.59 (95% CI 0.35 to 1.01); • decrease in exercise tolerance: RR 0.27 (95% CI 0.08 to 0.90); • decreased appetite: RR 0.34 (95% CI 0.14 to 0.85) *favouring intermittent treatment* • nasal congestion: RR 3.01 (95% CI 1.04 to 8.74).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AZLI: inhaled aztreonam lysine; **CF**: cystic fibrosis; **CFQ-R**: cystic fibrosis questionnaire - revised; **CFU**: colony forming units; **CI**: confidence interval; **FEV₁**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **NA**: not applicable; **PDE**: protocol-defined exacerbation; *P aeruginosa*: *Pseudomonas aeruginosa*; **RR**: risk ratio; **SE**: standard error; **TIS**: tobramycin for inhalation solution.

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.

[a]Downgraded once due to risk of bias being unclear across 5 of the domains around randomisation, allocation concealment, blinding of participants and incomplete outcome data.
[b]Downgraded once due to imprecision as trial enrolment was limited and the trial was underpowered.

Anmerkung/Fazit der Autoren

Long-term treatment with inhaled anti-pseudomonal antibiotics probably improves lung function and reduces exacerbation rates, but pooled estimates of the level of benefit were very limited. The best evidence available is for inhaled tobramycin. More evidence from trials measuring similar outcomes in the same way is needed to determine a better

measure of benefit. Longer-term trials are needed to look at the effect of inhaled antibiotics on quality of life, survival and nutritional outcomes.

Kommentare zum Review

Anteil der Kinder in der Gesamtpopulation nicht dargestellt. Keine Subgruppenanalysen für Kinder

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Southern KW, Murphy J, Sinha IP, Nevitt SJ, 2020 [11].

Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del) (Review)

Fragestellung

To evaluate the effects of CFTR correctors (with or without potentiators) on clinically important benefits and harms in pwCF of any age with class II CFTR mutations (most commonly F508del).

Methodik

Population:

- children or adults with CF, as confirmed either by the presence of two disease-causing variants (at least one class II variant), or by a combination of positive sweat test and recognised clinical features of CF
- participants with any level of disease severity

Intervention:

- A CFTR corrector is defined as a drug which aims to increase the amount of CFTR expressed at the epithelial cell apical membrane, by reducing or preventing degradation of CFTR by normal intracellular mechanisms. The main variant targeted by this approach is F508del. As this review focuses on small molecule therapies that correct the intracellular trafficking defect of variants, such as F508del, interventions that target DNA correction (e.g. antisense technology) are not included.

Komparator:

- placebo or another intervention

Endpunkte:

- Primary outcomes
  1. Survival
  2. Quality of life (QoL) (measured using validated quantitative scales or scores (e.g. Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner 2009)) a. total QoL score b. different sub-domains which may be reported
  3. Physiological measures of lung function (L or per cent (%) predicted for age, sex and height) a. forced expiratory flow rate at one second (FEV1) (relative change from baseline)
  b. FEV1 absolute values (and change from baseline) c. forced vital capacity (FVC) (absolute values and change from baseline)
  d. lung clearance index (LCI) (post hoc change) e. other relevant physiological measures of lung function

- Secondary outcomes
  1. Adverse effects
     a. graded by review authors as mild (therapy does not need to be discontinued)
     b. graded by review authors as moderate (therapy is discontinued, and the adverse effect ceases)
     c. graded by review authors as severe (life-threatening or debilitating, or which persists even after treatment is discontinued)
     d. other adverse effects of therapy (of any severity) that are not classifiable according to these categories
  2. Hospitalisation a. number of days b. number of episodes c. time to next hospitalisation
  3. School or work attendance (i.e. number of days missed) 4. Extra courses of antibiotics (measured as time to the next course of antibiotics and the total number of courses of antibiotics) a. oral b. intravenous c. inhaled
  5. Sweat chloride (change from baseline) as a measure of CFTR function
  6. Radiological measures of lung disease (assessed using any scoring system) a. chest radiograph scores b. computerised tomogram (CT) score

Recherche/Suchzeitraum:

- The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the handsearching of two journals - Pediatric Pulmonology and the Journal of Cystic Fibrosis. Unpublished work was identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference

Qualitätsbewertung der Studien:

- 4 October 2020

Ergebnisse

Anzahl eingeschlossener Studien:

- N=15

Charakteristika der Population/Studien:

The 19 included studies ranged from Phase 1 to Phase 3 RCTs, and all employed a parallel study design (Boyle 2014; Clancy 2012; Davies 2018a; Davies 2018b; Donaldson 2014; Donaldson 2017; Donaldson 2018; Horsley 2017; Heijerman 2019; Keating 2018; McCarty 2002; Middleton 2019; PROGRESS 2017; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002). The PROGRESS study was an extension study of the TRAFFIC and TRANSPORT studies included in the review (TRAFFIC 2015; TRANSPORT 2015), but with participants in the control group from the initial trials randomised to receive the active treatment at one of two doses (PROGRESS 2017).

A total of 2959 randomised participants were included in this review (participants in the PROGRESS study have only been counted in their original studies and not in this extension study). Study sample sizes ranged from 12 participants (Davies 2018a) to 563 participants (TRANSPORT 2015). One study was composed of three cohorts cohort 1 (n = 62), cohort 2 (n = 109) and cohort 3 (n = 15); any reference to this study is to participants randomised

to cohort 1 only, since data for the placebo participants from cohorts 2 and 3 were pooled, undoing the effects of randomisation and rendering them ineligible for inclusion in this review (Boyle 2014). In the Phase 2 study of tezacaftor-ivacaftor, only data from the heterozygous population are included (n = 18), as the placebo groups in the homozygous arms of the trial were pooled (Donaldson 2018).

The duration of the included studies ranged from a single day (Phase 1 single-dose testing) (McCarty 2002) to 24 weeks (Middleton 2019; Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015) with an extension of two of these studies of 96 weeks (PROGRESS 2017).

Two studies were undertaken at single centres (Rubenstein 1998; Zeitlin 2002), but the remaining studies were conducted at multiple centres, ranging from four (McCarty 2002) to 191 sites (PROGRESS 2017). Five studies were conducted in the USA only (Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002), two in the UK only (Davies 2018a; Davies 2018b), four in North America and Europe (Clancy 2012; Donaldson 2018; Heijerman 2019; Ratjen 2017; Taylor-Cousar 2017), one in Europe and Australia (Horsley 2017) and the remainder across North America, Europe and Australia (Boyle 2014; Keating 2018; Middleton 2019; PROGRESS 2017; TRAFFIC 2015; TRANSPORT 2015).

Full texts were available for 17 studies (Boyle 2014; Clancy 2012; Davies 2018a; Davies 2018b; Donaldson 2017; Donaldson 2018; Heijerman 2019; Keating 2018; McCarty 2002; Middleton 2019; PROGRESS 2017; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002); for one study as two conference abstracts (Horsley 2017) and for one further study as two conference abstracts and an online summary on Clinicaltrials.gov (Donaldson 2014).

One Phase 2 study of triple combination therapy indicated there had been a corresponding Phase 1 study, but it was conducted in "healthy volunteers"; the paper does not state if this means people who do not have CF or people who do have CF but are in a good state of health (Keating 2018). The publication does not include any data for the Phase 1 study, although a continuation into a Phase 2 study implies that the safety profile was considered acceptable during the study period. It was not explicitly stated whether any adverse events or safety concerns were observed in the Phase 1 study, nor does it state the dose tested or whether elexacaftor was tested in triple combination or as an individual agent for the purposes of the Phase 1 study (Keating 2018).

- Participants

  One study recruited pwCF with one F508del variant (the other variant was classified as residual function (ivacaftor responsive)) (Donaldson 2018). Three studies recruited a number of pwCF with two F508del variant copies and a number of pwCF with one F508del copy and a minimal function (MF) (non-ivacaftor responsive) variant (Davies 2018a; Davies 2018b; Keating 2018). One study recruited adults with F508del/MF genotypes (Middleton 2019). The remaining 15 studies recruited participants who had F508del/F508del genotypes.

  One study recruited children between the ages of 6 to 11 years (Ratjen 2017), five studies recruited adolescents and adults (PROGRESS 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015) and the remaining 13 studies recruited only adults.

- Interventions

  The included studies examined the effects of 4-phenylbutyrate (4PBA) (Rubenstein 1998; Zeitlin 2002), 8-cyclopentyl-1, 3dipropylxanthine (CPX) (McCarty 2002), N6022 (Donaldson 2014), cavosonstat (N91115) (Donaldson 2017), lumacaftor monotherapy (Boyle 2014; Clancy 2012), FDL169 monotherapy (Horsley 2017), lumacaftor-ivacaftor dual combination therapy (Boyle 2014; PROGRESS 2017; Ratjen 2017; TRAFFIC 2015;

TRANSPORT 2015), tezacaftor-ivacaftor dual combination therapy (Donaldson 2018; Taylor-Cousar 2017), VX-659-tezacaftor-ivacaftor triple combination therapy (Davies 2018a; Davies 2018b) and elexacaftortezacaftor-ivacaftor triple combination therapy (Heijerman 2019; Keating 2018; Middleton 2019).
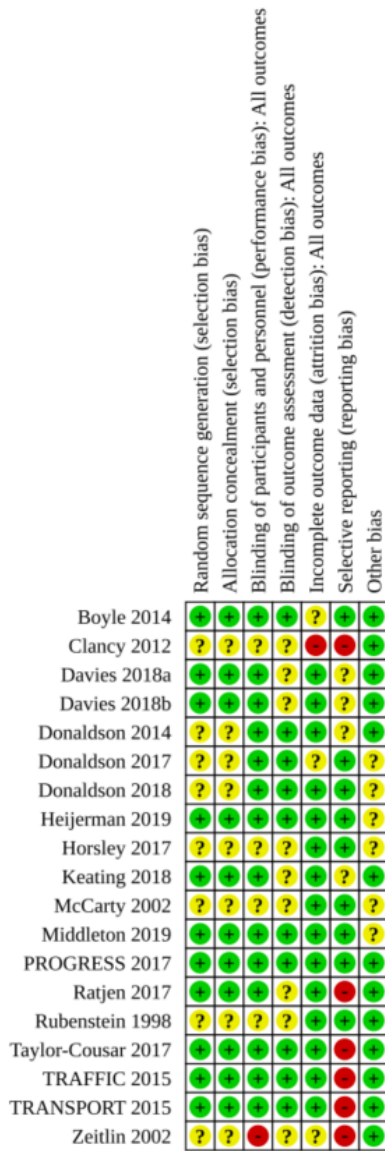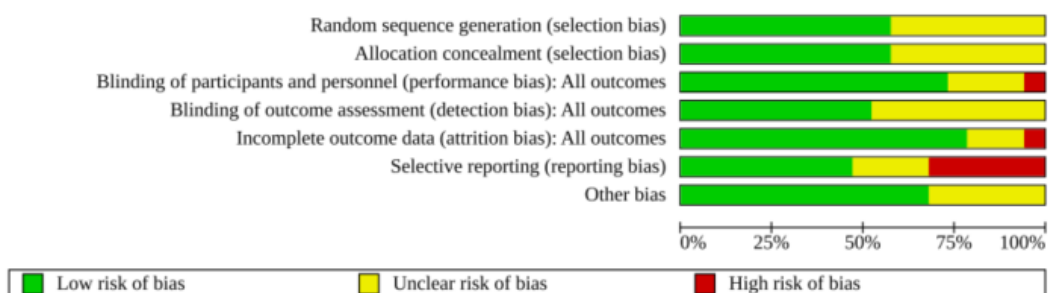
Qualität der Studien:

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Studienergebnisse:

We assessed eight monotherapy RCTs (344 participants) (4PBA, CPX, lumacaſtor, cavosonstat and FDL169), six dual-therapy RCTs (1840 participants) (lumacaſtor-ivacaſtor or tezacaſtor-ivacaſtor) and five triple-therapy RCTs (775 participants) (elexacaſtor-tezacaſtor-ivacaſtor or VX-659-tezacaſtor-ivacaſtor); below we report only the data from elexacaſtortezacaſtor-ivacaſtor combination which proceeded to Phase 3 trials. In 14 RCTs participants had F508del/F508del genotypes, in three RCTs F508del/minimal function (MF) genotypes and in two RCTs both genotypes.

- Monotherapy

Investigators reported no deaths or clinically-relevant improvements in quality of life (QoL). There was insufficient evidence to determine any important effects on lung function.

No placebo-controlled monotherapy RCT demonstrated differences in mild, moderate or severe adverse effects (AEs); the clinical relevance of these events is difficult to assess with their variety and small number of participants (all F508del/F508del).

- Dual therapy

Investigators reported no deaths (moderate- to high-quality evidence). QoL scores (respiratory domain) favoured both lumacaſtor-ivacaſtor and tezacaſtor-ivacaſtor therapy compared to placebo at all time points. At six months lumacaſtor 600 mg or 400 mg (both once daily) plus ivacaſtor improved Cystic Fibrosis Questionnaire (CFQ) scores slightly compared with placebo (mean difference (MD) 2.62 points (95% confidence interval (CI) 0.64 to 4.59); 1061 participants; high-quality evidence). A similar effect was observed for twice-daily lumacaſtor (200 mg) plus ivacaſtor (250 mg), but with low-quality evidence (MD 2.50 points (95% CI 0.10 to 5.10)). The mean increase in CFQ scores with twice-daily tezacaſtor (100 mg) and ivacaſtor (150 mg) was approximately five points (95% CI 3.20 to 7.00; 504 participants; moderatequality evidence). At six months, the relative change in forced expiratory volume in one second (FEV1) % predicted improved with combination therapies compared to placebo by: 5.21% with once-daily lumacaſtor-ivacaſtor (95% CI 3.61% to 6.80%; 504 participants; high-quality evidence); 2.40% with twice-daily lumacaſtor-ivacaſtor (95% CI 0.40% to 4.40%; 204 participants; low-quality evidence); and 6.80% with tezacaſtor-ivacaſtor (95% CI 5.30 to 8.30%; 520 participants; moderate-quality evidence).

More pwCF reported early transient breathlessness with lumacaſtor-ivacaſtor, odds ratio 2.05 (99% CI 1.10 to 3.83; 739 participants; highquality evidence). Over 120 weeks (initial study period and follow-up) systolic blood pressure rose by 5.1 mmHg and diastolic blood pressure by 4.1 mmHg with twice-daily 400 mg lumacaſtor-ivacaſtor (80 participants; high-quality evidence). The tezacaſtor-ivacaſtor RCTs did not report these adverse effects.

Pulmonary exacerbation rates decreased in pwCF receiving additional therapies to ivacaſtor compared to placebo: lumacaſtor 600 mg hazard ratio (HR) 0.70 (95% CI 0.57 to 0.87; 739 participants); lumacaſtor 400 mg, HR 0.61 (95% CI 0.49 to 0.76; 740 participants); and tezacaſtor, HR 0.64 (95% CI, 0.46 to 0.89; 506 participants) (moderate-quality evidence).

- Triple therapy

Three RCTs of elexacaſtor to tezacaſtor-ivacaſtor in pwCF (aged 12 years and older with either one or two F508del variants) reported no deaths (high-quality evidence). All other evidence was graded as moderate quality. In 403 participants with F508del/minimal function (MF) elexacaſtor-tezacaſtor-ivacaſtor improved QoL respiratory scores (MD 20.2 points (95% CI 16.2 to 24.2)) and absolute change in FEV1

(MD 14.3% predicted (95% CI 12.7 to 15.8)) compared to placebo at 24 weeks. At four weeks in 107 F508del/F508del participants, elexacaftortezacaftor-ivacaftor improved QoL respiratory scores (17.4 points (95% CI 11.9 to 22.9)) and absolute change in FEV1 (MD 10.0% predicted (95% CI 7.5 to 12.5)) compared to tezacaftor-ivacaftor. There was probably little or no difference in the number or severity of AEs between elexacaftor-tezacaftor-ivacaftor and placebo or control (moderate-quality evidence). In 403 F508del/F508del participants, there was a longer time to protocol-defined pulmonary exacerbation with elexacaftor-tezacaftor-ivacaftor over 24 weeks (moderate-quality evidence).

Summary of findings 1.   Summary of findings - monotherapy: lumacaftor compared to placebo for cystic fibrosis

Lumacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of partici-pants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Placebo	**Lumacaftor**				
Survival Follow-up: 14 to 28 days	No deaths reported.	No deaths reported.	NA	147 (2 studies)	⊕⊕⊙⊙ low[a]	
Quality of life - total score Follow-up: 14 to 28 days	Outcome not reported.				NA	A higher score indi-cates a better out-come.
Quality of life - CFQ-R respiratory domain: absolute change from baseline Follow-up: 14 to 28 days	There was a significant decrease in the CFQ-R respiratory domain in the 50 mg lumacaftor group compared to place-bo. No differences were found in the other dose groups (25 mg, 100 mg, 200 mg) compared to placebo.		NA	85 (1 study)	⊕⊕⊙⊙ low[a]	A higher score indi-cates a better out-come.
FEV$_1$ % predicted: relative change from baseline Follow-up: 14 to 28 days	Outcome not reported.				NA	
FEV$_1$ % predicted: absolute change from baseline Follow-up: 14 to 28 days	The mean change from baseline was 1.7% pre-dicted.	The mean change from base-line was 1.90% predicted lower (4.13 lower to 0.33 higher).	NA	61 (1 study)	⊕⊕⊕⊙ moderate[b]	

Adverse events Follow-up: 14 to 28 days	There were no significant differences between groups in terms of participants experiencing any specific adverse event. In 1 of the studies, 1 participant from each of the lumacaftor arms - 1 participant in each of the discontinued the study drug due to respiratory adverse effects. No participants discontinued from the placebo group.	NA	115 (2 studies)	⊕⊖⊖⊖ very low[a,b,c]	
Time to first pulmonary exacerbation Follow-up: 14 to 28 days	Outcome not reported (see comment).			NA	Time to first pulmonary exacerbation was not reported. There was no significant difference between groups in the number of participants experiencing pulmonary exacerbations.

*The basis for the **assumed risk** is the mean placebo group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval, **EQ-5D-3L**: 5-Dimension-3 Level, **FEV$_1$**: forced expiratory volume at one second; **MD**: mean difference.

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

a Downgraded twice due to risk of bias: in one study, data were selectively reported and often presentation of data did not allow for inclusion in analysis. There are also incomplete outcome data in the study with participants unaccounted for in analysis.
b Downgraded once due to indirectness: design of the study means that monotherapy treatment was measured for only 14 days before a combination therapy phase was started.
c Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide.

Summary of findings 2. Summary of findings - monotherapy: cavosonstat compared to placebo for cystic fibrosis

Cavosonstat compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: cavosonstat 200 mg

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Placebo	Cavosonstat				
Survival Follow-up: 28 days	No deaths reported.	No deaths reported.	NA	26 (1 study)	⊕○○○ **very low**[a,b,c]	
Quality of life: total score Follow-up: NA	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life: CFQ-R respiratory domain: absolute change from baseline Follow-up: 28 days	The mean absolute change from baseline in CFQ-R respiratory domain was -4.6 points in the placebo group.	The mean absolute change from baseline in CFQ-R respiratory domain was 3.80 higher (11.30 lower to 18.90 higher) in the Cavosonstat group than the placebo group.	NA	26 (1 study)	⊕○○○ **very low**[a,c,d]	A higher score indicates a better outcome.
FEV₁ % predicted: relative change from baseline Follow-up: NA	Outcome not reported.				NA	
FEV₁ % predicted: absolute change from baseline Follow-up: 28 days	There were no treatment-related changes in FEV₁ (% predicted) compared to placebo.		NA	26 (1 study)	⊕○○○ **very low**[a,b,c]	A graphical figure of change from baseline in FEV₁ (% predicted) is provided but numerical data cannot be extracted to include in analysis due to overlapping lines.
Adverse events: occurring in at least 10% of cavosonstat treated participants	There was no significant difference between groups in terms of cough, pulmonary exacerbation, chest discomfort and fatigue.		NA	26 (1 study)	⊕○○○ **very low**[a,b,c,e]	

Follow-up: 28 days		
Time to first pulmonary exacerbation Follow-up: NA	Outcome not reported.	NA

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CII) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **FEV$_1$**: forced expiratory volume in 1 second; **NA**: not applicable.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

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a Downgraded once due to potential risk of bias: unclear details related to methodological design and some unbalanced baseline characteristics.

b Downgraded once due to indirectness: adults only were recruited into the study, therefore, results are not applicable to children.

c Downgraded once due to imprecision: a single study with a small sample size.

d Downgraded once due to imprecision: wide CIs around the result.

e Downgraded once due to imprecision: very wide CIs around results (due to small event numbers).

Summary of findings 3. Summary of findings - dual therapy: lumacaftor plus ivacaftor (once daily) compared with placebo for cystic fibrosis (short term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (600 mg once daily or 400 mg once daily) plus ivacaftor (250 mg twice daily)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Placebo	**Lumacaftor plus ivacaftor**				
Survival	No deaths reported.	No deaths reported.	NA	1108	⊕⊕⊕⊕ **high**	

Follow-up: 6 months				(2 studies)		
Quality of life - (EuroQol) EQ-5D-3L Index Score (total score): absolute change from base-line Follow-up: 6 months	The mean absolute change from baseline ranged from 0.0006 to 0.0017 points.	The mean absolute change from base-line was 0.00 points higher (0.01 lower to 0.01 higher).	NA	1061 (2 studies)	⊕⊕⊕⊝ **moderate[a]**	A higher score in-dicates a better outcome.
Quality of life - CFQ-R respiratory domain: absolute change from base-line Follow-up: 6 months	The mean absolute change from baseline ranged from 1.1 to 2.81 points.	The mean absolute change from base-line was 2.62 points higher (0.64 higher to 4.59).	NA	1076 (2 studies)	⊕⊕⊕⊝ **moderate[a]**	A higher score in-dicates a better outcome. There was al-so a significant difference be-tween groups at 28 days, MD 3.70 points (95% CI 1.81 to 5.58).
FEV_1 % predict-ed: relative change from baseline Follow-up: 6 months	The mean relative change from baseline ranged from -0.34% to 0%.	The mean relative change from base-line was 5.21% higher (3.61% higher to 6.80% higher).	NA	1072 (2 studies)	⊕⊕⊕⊕ **high**	
FEV_1 % predicted: absolute change from baseline Follow-up: 6 months	The mean absolute change from baseline ranged from -0.44 to -0.15% predicted.	The mean absolute change from base-line was 3.07% predicted higher (2.17 higher to 3.97 higher).	NA	1072 (2 studies)	⊕⊕⊕⊝ **moderate[a]**	There was al-so a significant difference be-tween groups at 28 days, MD 2.37% predicted (95% CI 1.52 to 3.22).
Adverse events Follow-up: 6 months	Cough was significantly more common in the placebo group com-pared to the lumacaftor-ivacaftor group. Dyspnoea was significantly more common in the lumacaftor-ivacaftor group compared to the placebo group.		NA	1108 (2 studies)	⊕⊕⊕⊕ **high**	

	There were no significant differences between groups in terms of number of participants experiencing adverse events, serious adverse events or other adverse events. Long-term open-label follow-up data of the 2 studies showed a significant increase in early transient shortness of breath. In participants allocated a 400 mg twice-daily dose, there was a significant rise in blood pressure.				
Time to first pulmonary exacerbation Follow-up: 6 months	Time to first pulmonary exacerbation was significantly longer in both in the lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily and the lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily groups	NA	1108 (2 studies)	⊕⊕⊕⊖ **moderate**[a]	Presentation of data did not allow an analysis of the lumacaftor doses pooled.

*The basis for the **assumed risk** is the mean placebo group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **EQ-5D-3L**: 5-Dimension-3 Level; **EuroQol**: Euro Quality of Life Scale; **FEV$_1$**: forced expiratory volume at one second; **MD**: mean difference.

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

a Downgraded once due to risk of bias from selective reporting: data contributing to analyses were extrapolated from published graphs or estimated. We have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update and this judgement will be reconsidered.

Summary of findings 4.   Summary of findings - dual therapy: lumacaftor plus ivacaftor (twice daily) compared with placebo for cystic fibrosis (short term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Survival Follow-up: 24 weeks	No deaths reported.	No deaths reported.	NA	204 (1 study)	⊕⊕⊕⊖ **moderate**[a]	
Quality of life - total score Follow-up: 24 weeks	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life - CFQ-R respiratory domain: absolute change from baseline Follow-up: 24 weeks	See comment.	The mean change in the CFQ-R respiratory domain was 2.50 points higher in the lumacaftor-ivacaftor group compared to the placebo group, ranging from 0.10 lower to 5.10 higher.	NA	204 (1 study)	⊕⊕⊖⊖ **low**[a,b]	A higher score indicates a better outcome. Data were analysed via a MMRM. Results provided by this model can be interpreted as treatment effect averaged from each study visit until week 24.
FEV$_1$ % predicted: relative change from baseline Follow-up: 24 weeks	Outcome not reported.				NA	Relative change from baseline in FEV$_1$ was listed in the methods of the study but no numerical results were presented. if numerical data becomes available at a later date, it will be included in an update of this review.
FEV$_1$ % predicted: absolute change from baseline Follow-up: 24 weeks	See comment.	The mean change in FEV$_1$ % predicted was 2.40 higher in the lumacaftor-ivacaftor group compared to the placebo group, ranging from 0.40 higher to 4.40 higher.	NA	204 (1 study)	⊕⊕⊖⊖ **low**[a,b]	Data were analysed via a MMRM. Results provided by this model can be interpreted as treatment effect averaged from each study visit until week 24.
Adverse events Follow-up: 24 weeks	There was no significant difference between the groups in terms of productive cough, nasal congestion, oropharyngeal pain, upper abdominal pain, rhinorrhoea, increased sputum, cough, pyrexia, headache, upper respiratory		NA	204 (1 study)	⊕⊕⊖⊖ **low**[b,c]	

	tract infection, abdominal pain, nausea, vomiting, fatigue and respiratory events (such as wheezing, dyspnoea, asthma and chest discomfort).			
Time to first pulmonary exacerbation Follow-up: 24 weeks	Outcome not reported.	NA		Time to first pulmonary exacerbation was listed in the methods of the study but no numerical results were presented. If numerical data become available at a later date, they will be included in an update of this review.

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **FEV$_1$**: forced expiratory volume at 1 second; **MMRM**: mixed model for repeated measures; **NA**: not applicable.

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

a Downgraded once due to indirectness: children aged 6 - 11 years were recruited in this study, therefore, results are not applicable to other age groups.
b Downgraded once due to risk of bias from selective reporting: limited data available which is adjusted for all visits. Further graphical data were available in the publication but could not be accurately extracted. We have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update and this judgement will be reconsidered
c Downgraded once due to imprecision; few events occurred therefore CIs for occurrence of specific events are very wide.

Summary of findings 5.   Summary of findings - dual therapy: lumacaftor plus ivacaftor compared with placebo for cystic fibrosis (immediate term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (200 mg) plus ivacaftor (150 mg or 250 mg twice daily)[a]

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants	Quality of the evidence	Comments

	Assumed risk	Corresponding risk		(studies)	(GRADE)	
	Placebo	Lumacaftor plus ivacaftor[a]				
Survival Follow-up: 21 days[1]	No deaths reported.	No deaths reported.	NA	62 (1 study)	⊕⊕⊕⊖ **moderate**[b]	
Quality of life: total score Follow-up: 21 days[1]	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life: respiratory domain Follow-up: 21 days[1]	Outcome not reported.				NA	A higher score indicates a better outcome.
FEV$_1$ % predicted: relative change from baseline Follow-up: 21 days[1]	Outcome not reported.				NA	
FEV$_1$ % predicted: absolute change from baseline Follow-up: 21 days[1]	The mean change from baseline was 0.3.	The mean change from baseline was 1.57% predicted higher (-2.13 lower to 5.27 higher).	NA	59 (1 study)	⊕⊕⊕⊖ **moderate**[b]	
Adverse events Follow-up: 21 days[1]	There were no significant differences between groups in terms of participants experiencing: cough, oropharyngeal pain, nasal congestion, dizziness, a prolonged prothrombin time, and upper respiratory tract infection.		NA	61 (1 study)	⊕⊕⊖⊖ **low**[b,c]	
Time to first pulmonary exacerbation Follow-up: 21 days[1]	Outcome not reported (see comment).				NA	Time to first pulmonary exacerbation was not reported. There was no significant difference between groups in the number of participants experiencing pulmonary exacerbations.

*The basis for the **assumed risk** is the mean placebo group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FEV₁**: forced expiratory volume at 1 second.

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

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a The design of the study was 14 days of lumacaftor monotherapy (200 mg once daily) then a dose of ivacaftor (150 mg or 250 mg once daily) was added on for 7 days of combination therapy. Results presented in this table are from the combination treatment period only.
b Downgraded once due to indirectness: design of the study means that combination treatment was measured for only 7 days and prior lumacaftor monotherapy phase (see footnote 1) may have influenced results of the combination phase.
c Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide.

Summary of findings 6.   Summary of findings - dual therapy: tezacaftor plus ivacaftor compared with placebo or ivacaftor alone for cystic fibrosis

Tezacaftor plus ivacaftor compared with placebo or ivacaftor alone for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: tezacaftor (100 mg daily) plus ivacaftor (150 mg twice daily)

Comparison: placebo (i.e. tezacaftor placebo) or ivacaftor (150 mg twice daily)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Placebo or ivacaftor alone	**Tezacaftor plus ivacaftor**				
Survival Follow-up: up to 24 weeks	No deaths reported.	No deaths reported.	NA	522 (2 studies)	⊕⊕⊕⊝ moderate[a,b]	
Quality of life: total score	Outcome not reported.				NA	A higher score indicates a better outcome.

Follow-up: NA

Quality of life: CFQ-R respiratory domain: absolute change from baseline Follow-up: up to 24 weeks	See comment.	The mean absolute change from baseline in CFQ-R respiratory domain score in the tezacaftor-ivacaftor group was 5.10 points higher (3.20 higher to 7.00 higher) than the placebo group (result from 1 study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊝ moderate[a,b]	A higher score indicates a better outcome Difference in absolute change from baseline calculated by least-squares regression, hence assumed risk not presented. The mean absolute change from baseline in CFQ-R respiratory domain score in the tezacaftor plus ivacaftor group was also significantly higher than the placebo group at 4 weeks: MD 5.10 (95% CI 2.99 to 7.21) The second study (n = 18) showed that the treatment effect of tezacaftor-ivacaftor versus placebo was 6.81 points of CFQ-R respiratory domain (P = 0.2451) up to day 28.
FEV_1 % predicted: relative change from baseline Follow-up: up to 24 weeks	See comment.	The mean relative change from baseline in FEV_1 % predicted in the tezacaftor-ivacaftor group was 6.80% higher (5.30% higher to 8.30% higher) than the placebo group (result from 1 study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊝ moderate[a,b]	Difference in relative change from baseline calculated by least-squares regression, hence assumed risk not presented. The second study (n = 18) showed no significant difference between groups in mean relative change from baseline in FEV_1 % predicted MD 3.72 (95% CI -7.77 to 15.21).
FEV_1 % predicted: absolute change from baseline Follow-up: up to 24 weeks	See comment	The mean absolute change from baseline in FEV_1 % predicted in the tezacaftor plus ivacaftor group was 4.00 % predicted higher (3.10 higher to 4.90 higher) than the placebo group (result from one study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊝ moderate[a,b]	Difference in absolute change from baseline calculated by least-squares regression, hence assumed risk not presented. The mean absolute change from baseline in FEV_1 % predicted in the tezacaftor-ivacaftor group was also significantly higher than the placebo group at 4 weeks, MD 3.59 (95% CI 2.40 to 4.78), 2 studies, n = 528, I^2 =0%.
Adverse events: most commonly occurring events (occurring in at least 10% of participants) Follow-up: up to 24 weeks	The most commonly occurring adverse events in both groups were cough and pulmonary exacerbation. There were no significant differences between groups (99% confidence intervals) in the number of participants experiencing cough, pulmonary exacerbation, headache, nasal congestion or nasopharyngitis, increased sputum, haemoptysis, pyrexia, oropharyngeal pain, nausea or fatigue.		NA	527 (2 studies)	⊕⊕⊕⊝ moderate[a,b]	
Time to first pulmonary exacerbation Follow-up: up to 24 weeks	The hazard ratio for pulmonary exacerbation in the tezacaftor plus–ivacaftor group, as compared with the placebo group was 0.64 (95% CI 0.46 to 0.89).		NA	504 (1 study)	⊕⊕⊕⊝ moderate[a,b]	A hazard ratio below 1 favours the tezacaftor-ivacaftor group.

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **MD**: mean difference; **NA**: not applicable.

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

Downgraded once due to indirectness: 1 study recruited individuals over the age of 12 (Taylor-Cousar 2017) and 1 study recruited individuals over the age of 18 with one F508del mutation and one G551D mutation (Donaldson 2018). Therefore, results are not applicable to children under the age of 12 and some results are not applicable to individuals omozygous for F508del.
One study has some unclear details related to methodological design and had unbalanced treatment group sizes and baseline characteristics (Donaldson 2018). However, this study contributed a small proportion of the evidence of this comparison (n = 18, 3% of evidence) compared to the second study in the comparison (n = 509, 97% of evidence, verall low risk of bias) (Taylor-Cousar 2017). Therefore, no downgrading is made due to potential risks of bias in the smaller study.

Summary of findings 7. Summary of findings - triple therapy: VX-659-tezacaftor-ivacaftor/VX-561 compared to control for cystic fibrosis

VX-659 plus tezacaftor plus ivacaftor or VX-561 compared with control for cystic fibrosis

Patient or population: adults with cystic fibrosis and either F508del/MF or F508del/F508del genotype

Settings: outpatients

Intervention: VX-659 (80 mg once daily, 120 mg twice daily, 240 mg once daily or 400 mg once daily) plus tezacaftor 100 mg once per day plus ivacaftor 150 mg twice daily or VX-561 150 mg once daily

Comparison: F508del/MF participants: triple placebo; F508del/F508del participants: placebo tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Triple placebo or placebo-tezacaftor-ivacaftor	VX-659 plus tezacaftor plus ivacaftor or VX-561				
Survival Follow-up: 2 to 4 weeks	No deaths reported.	No deaths reported.	NA	129 (2 studies)	⊕⊕⊕⊕ **high**	
Quality of life: total score Follow-up: NA	Outcome not reported.				NA	
Quality of life: CFQ-R respiratory domain: absolute change from baseline Follow-up: up to 4 weeks	See comment.	A significant improvement was seen in the VX-659 plus tezacaftor plus ivacaftor 80 mg group, MD 10.00 (95% CI 0.29 to 19.71) (F508del/MF genotype); in the VX-659 plus tezacaftor plus ivacaftor 400 mg group, MD 18.10 (95% CI 10.85 to 25.35) (F508del/F508del genotype); and in the VX-561 group, MD 20.30 (95% CI 70.5 to 33.55) (F508del/MF genotype) compared to the controls. No such differences were seen in the other dose groups.	NA	129 (2 studies)	⊕⊕⊕⊖ **moderate**[a]	A higher score indicates a better outcome. Data were analysed via a MMRM, hence assumed risk not presented. Results provided by this model can be interpreted as treatment effect averaged from week 2 and week 4.
FEV$_1$ (% predicted): relative change from baseline Follow-up: up to 4 weeks	See comment.	Significant improvements were seen in the relative change from baseline in FEV$_1$ % predicted across all dose levels and genotypes when compared to placebo.	NA	117 (1 study)	⊕⊕⊕⊖ **moderate**[a]	Data were analysed via a MMRM, hence assumed risk not presented. Results provided by this model can be interpreted as treatment effect averaged from week 2 and week 4.

FEV$_1$ (% predicted): absolute change from baseline Follow-up: 2 weeks	One study found a significant improvement in the absolute change from baseline in FEV$_1$ % predicted at the dose of 120 mg twice daily versus placebo, MD 10.00 % predicted (95% CI 3.04 to 16.96).	NA	12 (1 study)	⊕⊕⊕⊝ moderate[a]	A second study (n = 117) found a significant improvement in the absolute change in FEV$_1$ (L) at all dose levels and genotypes for the interventions compared to control.
Adverse events Follow-up: 2 to 4 weeks	There was no significant difference in the number of participants experiencing at least 1 adverse event between the intervention and placebo groups at any dose or for any genotype. There was also no statistical difference versus placebo relating to the severity of adverse events across all doses and genotype groups.	NA	129 (2 studies)	⊕⊕⊕⊝ moderate[a]	
Time to first pulmonary exacerbation	Outcome not reported.			NA	1 study (n = 117) did report that there was no difference in the number of courses of antibiotics required or the number of pulmonary exacerbations between groups at all dose levels and genotypes for the interventions compared to control.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **FEV$_1$**: forced expiratory volume at 1 second; **MD**: mean difference; **MF**: minimal function; **MMRM**: mixed model for repeated measures; **NA**: not applicable.

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

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a Downgraded once due to indirectness or lack of applicability: data do not include children under the age of 12 and those with more severe disease. Also short-term data only.

Summary of findings 8. Summary of findings - triple therapy: elexacaftor-tezacaftor-ivacaftor/VX-561 compared to control for cystic fibrosis

Elexacaftor plus tezacaftor plus ivacaftor or VX-561 compared with placebo for cystic fibrosis

Patient or population: adults with cystic fibrosis and either F508del/MF or F508del/F508del genotype

Settings: outpatients

Intervention: elexacaftor (50 mg once daily, 100 mg once daily or 200 mg once daily) plus tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily or VX-561 150 mg once daily

Comparison: F508del/MF participants: triple placebo; F508del/F508del participants: placebo tezacaftor 100 mg once daily plus ivacaftor 150 mg twice daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Triple placebo or placebo tezacaftor plus ivacaftor	**Elexacaftor plus tezacaftor plus ivacaftor or VX-561**				
Survival Follow-up: 4 weeks to 24 weeks	No deaths reported.	No deaths reported.	NA	603 (3 studies)	⊕⊕⊕⊕ **high**	
Quality of life: total score Follow-up: NA	Outcome not reported.				NA	
Quality of life: CFQ-R respiratory domain absolute change from baseline Follow-up: 4 weeks to 24 weeks	A significant improvement in the elexacaftor plus tezacaftor plus ivacaftor or VX-561 groups in the CFQ-R respiratory domain was observed compared to control versus placebo across all dose levels and both genotypes		NA	599 (3 studies)	⊕⊕⊕⊖ **moderate**[a]	A higher score indicates a better outcome.
FEV_1 (% predicted): relative change from baseline Follow-up: 4 weeks to 24 weeks	A significant improvement in the relative change from baseline in FEV_1 % predicted in the elexacaftor plus tezacaftor plus ivacaftor groups was observed across all dose levels and genotypes when compared to control groups .		NA	603 (3 studies)	⊕⊕⊕⊖ **moderate**[a]	
FEV_1 (% predicted): absolute change from baseline Follow-up: NA	A significant improvement in the absolute change from baseline in FEV_1 % predicted in the elexacaftor plus tezacaftor plus ivacaftor groups compared to control groups was observed in 2 studies including participants with F508del/MF genotype and F508del/F508del genotype.		NA	510 (2 studies)	NA	1 study (n = 123) reported a significant improvement in the absolute change from baseline in FEV_1 (L) favouring the intervention across all dose levels and genotypes for the interventions compared to control.
Adverse events Follow-up: 4 weeks to 24 weeks	There was no significant difference in the number of participants experiencing at least 1 adverse event between the intervention and placebo groups at any dose or for any genotype. There was also no statistical difference versus placebo relating to the severity of adverse events across all doses and genotype groups.		NA	603 (3 studies)	⊕⊕⊕⊖ **moderate**[a]	
Time to first pulmonary exacerbation Follow-up: 24 weeks	A longer time to pulmonary exacerbation (protocol-defined) was seen in participants in the intervention group compared to participants in the placebo group (F508del/MF genotype).		NA	403 participants (1 study)	⊕⊕⊕⊖ **moderate**[a]	Combined data at 1 month from 2 studies (n = 230) reported a lower number of pulmonary exacerbations (either physician-defined or not clear how they were defined) in the intervention groups across all dose levels for the F508del/F508del genotype.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **MD**: mean difference; **MF**: minimal function: **NA**: not applicable.

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

a Downgraded once due to indirectness or lack of applicability: Data do not include children under the age of 12 and those with more severe disease.

Anmerkung/Fazit der Autoren

There is insufficient evidence that corrector monotherapy has clinically important effects in pwCF with F508del/F508del.

Both dual therapies (lumacaftor-ivacaftor, tezacaftor-ivacaftor) result in similar improvements in QoL and respiratory function with lower pulmonary exacerbation rates. Lumacaftor-ivacaftor was associated with an increase in early transient shortness of breath and longer-term increases in blood pressure (not observed for tezacaftor-ivacaftor). Tezacaftor-ivacaftor has a better safety profile, although data are lacking in children under 12 years. In this population, lumacaftor-ivacaftor had an important impact on respiratory function with no apparent immediate safety concerns; but this should be balanced against the blood pressure increase and shortness of breath seen in longer-term adult data when considering lumacaftor-ivacaftor.

There is high-quality evidence of clinical efficacy with probably little or no difference in AEs for triple (elexacaftor-tezacaftor-ivacaftor) therapy in pwCF with one or two F508del variants aged 12 years or older. Further RCTs are required in children (under 12 years) and those with more severe respiratory function.

Kommentare zum Review

Anteil von Kindern ist nicht berichtet. Keine Subgruppenauswertungen für Kinder

3.2 Systematische Reviews

Hamdan AHY et al., 2023 [4].

Cystic Fibrosis Transmembrane Conductance Regulator Protein Modulators in Children and Adolescents with Different CF Genotypes - Systematic Review and Meta-Analysis

Fragestellung

To determine the efficacy of the first triple CFTR protein modulators in children and adolescents with cystic fibrosis.

Methodik

Population:

- children more than 6 years of age and adolescents who were diagnosed with CF of all genotypes: including mutations leading to instability of the RNA, defect in the biogenesis of CFTR, folding and trafficking defects, as well as splicing defects

Intervention:

- first generation (Ivacaftor, Tezacaftor or in combination) and triple CFTR protein modulators (Elexacaftor, Tezacaftor, and Ivacaftor)

Komparator:

- placebo or standard of care

Endpunkte:

- lung function test, body mass index, sweat chloride test, quality of life, and safety profile

Recherche/Suchzeitraum:

- PubMed/Medline, Clinical trials.gov, Google Scholar, Scopus, Embase, and Europe PMC
- from origin to July 28, 2021

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias (ROB 2) assessment

Ergebnisse

Anzahl eingeschlossener Studien:

- N=10

Charakteristika der Population/Studien:

- A total of 1915 individuals were included for analysis of which 522 were male in the experimental group, and 4226 in the control group, while 540,427 were female in each group, respectively. A number of patients from North America who received the CFTR protein modulators were 345 out of 679, from Europe was 404 out of 759, and from Australia 100 out of 198. In the paediatric population aged more than 6 years and less than 18, 207 out of 810 took the modulators, while the number in the adolescent population was 602 out of 810.
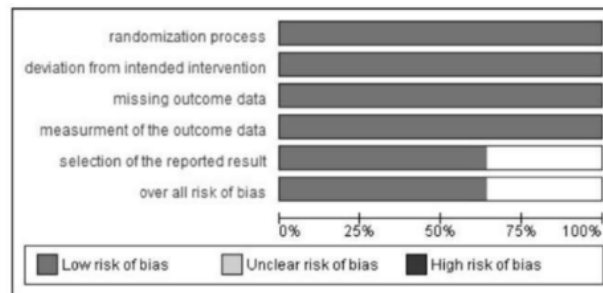
Qualität der Studien:
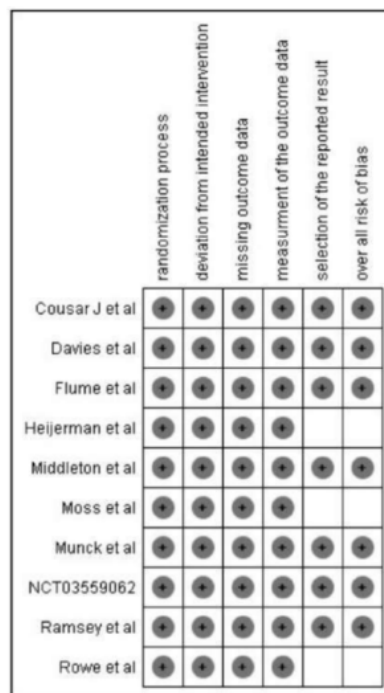

Fig. (2). Risk of bias assessment.

Fig. (3). Risk of Bias assessment.

Studienergebnisse:

- Absolute Change in Predicted FEV1 from Baseline A significant improvement was demonstrated in the predicative FEV1 triple therapy (MD 11.80; 95% CI 8.47 to 15.12; p value < 0.00001) [10, 19].

  Combination therapy of Tezacaftor and Ivacaftor demonstrated no significant improvement in pFEV1 (MD= 1.72, 95% CI= -0.95-4.39, p value= 0.21) [23, 25, 26]. Sensitivity analysis excluding Cousar et al. decreased heterogeneity (19%) but revealed no significant difference between the treatment and control group (MD 0.35; 95% CI -0.56 to 1.26; p value= 0.45). Treatment with Ivacaftor is shown to be more beneficial compared to placebo in the improvement of pFEV1 (MD 3.51; 95% CI 0.34-6.68; p value= 0.03; I2 = 97%) [17, 18, 20, 23, 24]. The Ivacaftor group by Ramsey; Davies and Moss et al. showed no significant change through 24 weeks (MD 6.29; 95% CI -2.04 to 14.62; p value= 0.14). Similar findings were reported by Flume et al. at week 16 (MD 1.70; 95% CI -0.60 to 4.00; p value= 0.15), and Rowe et al. at week 4 and 8 (MD 0.00; 95% CI -1.00 to 1.00; p value= 1.00) (Fig. 11 A-C).
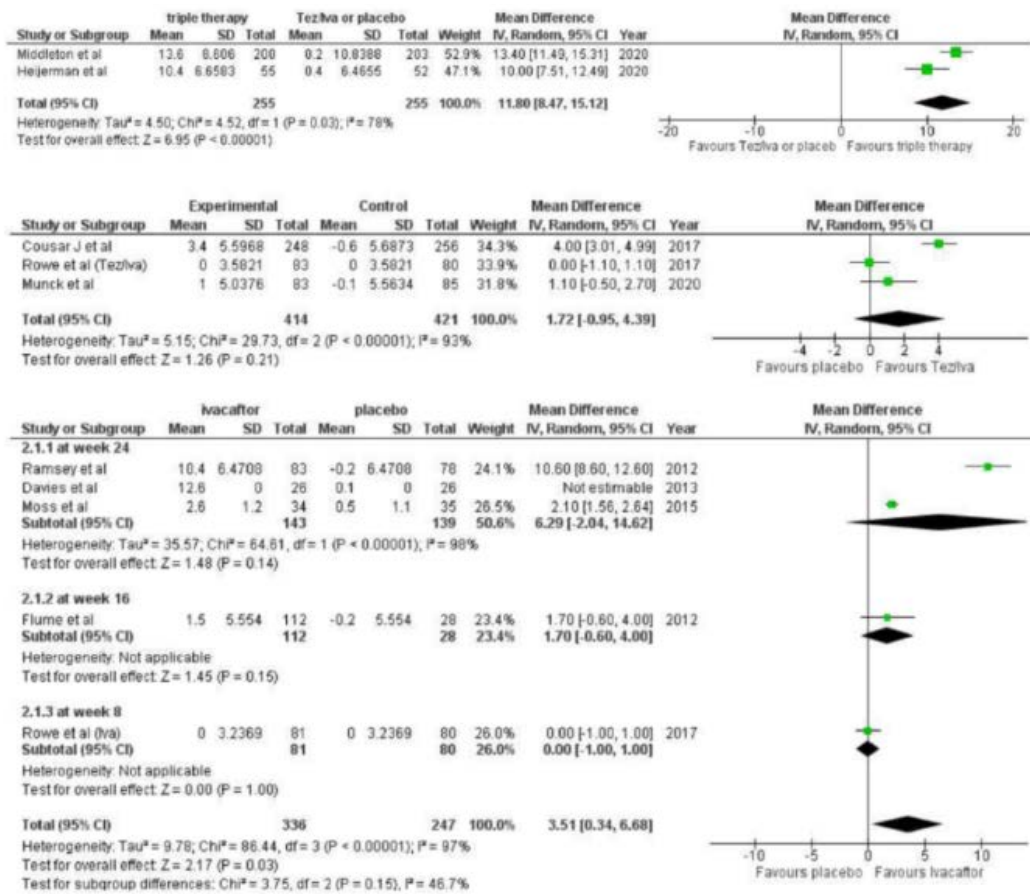
Fig. (11). Forest plot: Absolute change in predictive FEV1 from baseline outcome. **(A)** Triple therapy, **(B)** Tez/IVA combination therapy *vs.* control, **(C)** Ivacaftor single therapy. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

- Absolute Change in Sweat Chloride Test from Baseline

No significant improvement in CFTR function was observed for triple therapy in comparison to placebo or Tez/Iva therapy (MD -12.57; 95% CI -94.46 to -69.32, p value= 0.76). No difference in CFTR channel was observed between the Tez/Iva and the control group (MD=4.33,95%CI=-10.43_1.78, p value<0.00001). Cousar et al. at and NCT03559062 through week 24 revealed nonsignificant decline in sweat chloride test (MD -5.14; 95% CI=-15.03 to 4.76; p value < 0.00001). Significant improvement was observed in the Ivacaftor group (MD -18.37; 95% CI -35.76 to -0.99; p value= 0.04). However, while no change has been seen for Flume et al. at week 16 (MD 0.00; 95% CI -2.70 to 2.70; p value= 1.00) and Rowe et al. at week 4 and 8 (MD 0.00, 95% CI -11.20 to 11.20, p value= 1.00), a significant reduction in sweat chloride test through 24 weeks by Ramsey; Davies and Moss et al. was seen in Ivacaftor therapy (MD -35.89; 95% CI -59.31 to -12.47; p value= 0.003) (Fig. 12 A-C) [10, 17-20, 24-26].
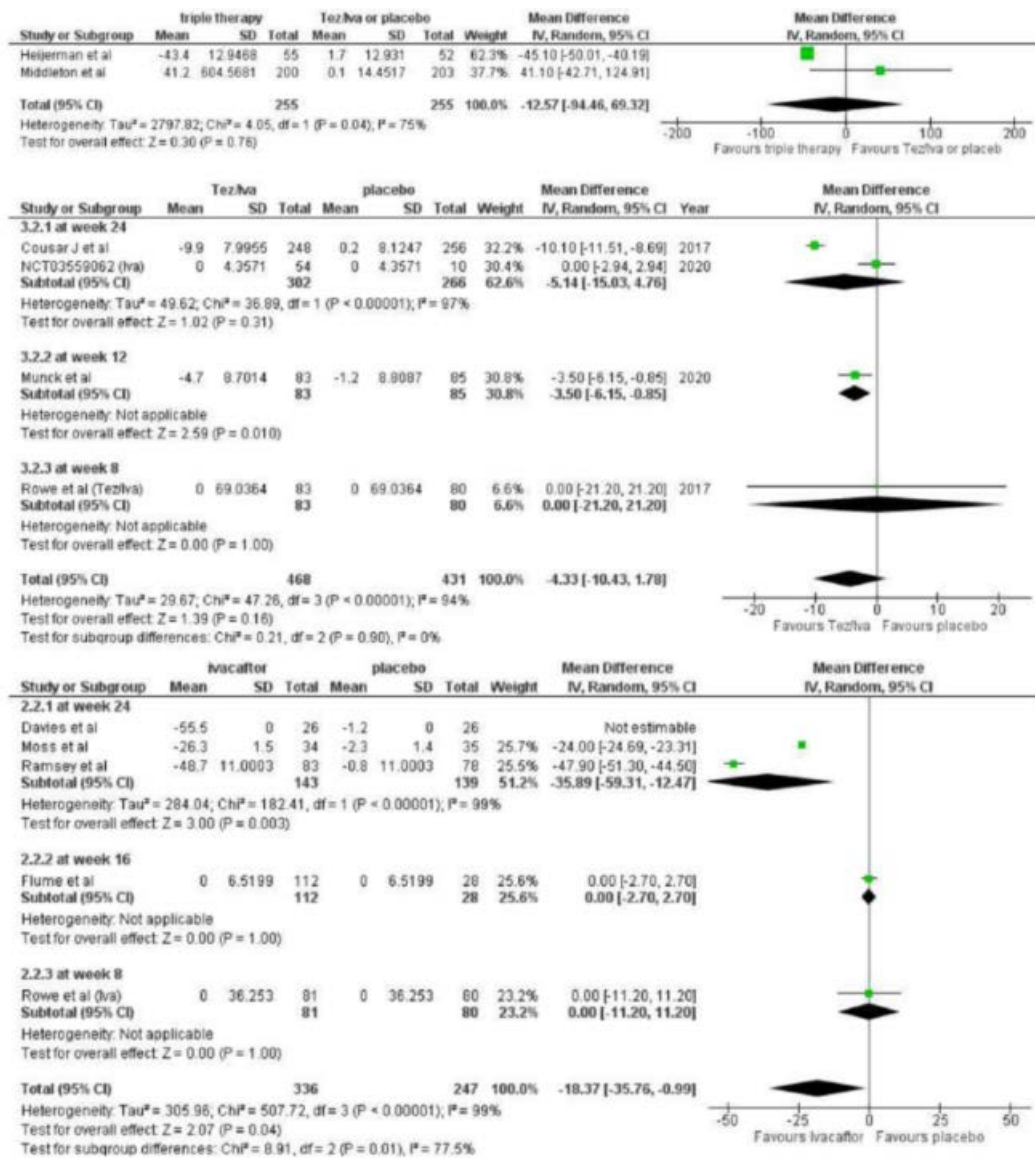
Panel A — Triple therapy

Study or Subgroup	triple therapy Mean	SD	Total	Tez/Iva or placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Heijerman et al	-43.4	12.9468	55	1.7	12.931	52	62.3%	-45.10 [-50.01, -40.19]
Middleton et al	41.2	604.5681	200	0.1	14.4517	203	37.7%	41.10 [-42.71, 124.91]
Total (95% CI)			255			255	100.0%	-12.57 [-94.46, 69.32]

Heterogeneity: Tau² = 2797.82; Chi² = 4.05, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 0.30 (P = 0.76)
Favours triple therapy / Favours Tez/Iva or placebo

Panel B — Tez/Iva

Study or Subgroup	Tez/Iva Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
3.2.1 at week 24									
Cousar J et al	-9.9	7.9955	248	0.2	8.1247	256	32.2%	-10.10 [-11.51, -8.69]	2017
NCT03559062 (Iva)	0	4.3571	54	0	4.3571	10	30.4%	0.00 [-2.94, 2.94]	2020
Subtotal (95% CI)			302			266	62.6%	-5.14 [-15.03, 4.76]	
3.2.2 at week 12									
Munck et al	-4.7	8.7014	83	-1.2	8.8087	85	30.8%	-3.50 [-6.15, -0.85]	2020
Subtotal (95% CI)			83			85	30.8%	-3.50 [-6.15, -0.85]	
3.2.3 at week 8									
Rowe et al (Tez/Iva)	0	69.0364	83	0	69.0364	80	6.6%	0.00 [-21.20, 21.20]	2017
Subtotal (95% CI)			83			80	6.6%	0.00 [-21.20, 21.20]	
Total (95% CI)			468			431	100.0%	-4.33 [-10.43, 1.78]	

Subtotal 3.2.1 Heterogeneity: Tau² = 49.62; Chi² = 36.89, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.02 (P = 0.31)
Subtotal 3.2.2 Heterogeneity: Not applicable
Test for overall effect: Z = 2.59 (P = 0.010)
Subtotal 3.2.3 Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Total Heterogeneity: Tau² = 29.67; Chi² = 47.26, df = 3 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.39 (P = 0.16)
Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%
Favours Tez/Iva / Favours placebo

Panel C — Ivacaftor

Study or Subgroup	Ivacaftor Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 at week 24								
Davies et al	-55.5	0	26	-1.2	0	26		Not estimable
Moss et al	-26.3	1.5	34	-2.3	1.4	35	25.7%	-24.00 [-24.69, -23.31]
Ramsey et al	-48.7	11.0003	83	-0.8	11.0003	78	25.5%	-47.90 [-51.30, -44.50]
Subtotal (95% CI)			143			139	51.2%	-35.89 [-59.31, -12.47]
2.2.2 at week 16								
Flume et al	0	6.5199	112	0	6.5199	28	25.6%	0.00 [-2.70, 2.70]
Subtotal (95% CI)			112			28	25.6%	0.00 [-2.70, 2.70]
2.2.3 at week 8								
Rowe et al (Iva)	0	36.253	81	0	36.253	80	23.2%	0.00 [-11.20, 11.20]
Subtotal (95% CI)			81			80	23.2%	0.00 [-11.20, 11.20]
Total (95% CI)			336			247	100.0%	-18.37 [-35.76, -0.99]

Subtotal 2.2.1 Heterogeneity: Tau² = 284.04; Chi² = 182.41, df = 1 (P < 0.00001); I² = 99%
Test for overall effect: Z = 3.00 (P = 0.003)
Subtotal 2.2.2 Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Subtotal 2.2.3 Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Total Heterogeneity: Tau² = 305.96; Chi² = 507.72, df = 3 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Chi² = 8.91, df = 2 (P = 0.01), I² = 77.5%
Favours Ivacaftor / Favours placebo

Fig. (12). Forest plot: Absolute change in sweat chloride test from the baseline outcome. (A) Triple therapy, (B) Tez/IVA combination therapy *vs.* control, (C) Ivacaftor single therapy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

- Absolute Change in CF-QR from Baseline Triple therapy showed significant improvement in CFQR score (MD 16.90; 95% CI 12.73-21.06, p value < 0.00001; I2 = 0%) in four weeks, as compared to the standard of care (SOC) or placebo [19]. For CF-QR score, the analysis favoured placebo as compared to the combination therapy with Tez/Iva (MD 1.82; 95% CI-0.92-4.56; p value= 0.19) (Taylor-Cousar et al. 2019; Rowe et al. 2005; Munck et al. 2020, Suthersan et al., 2021) [23, 25, 26]. Sensitivity analysis based on the number of weeks of treatment did not change the results (Figs. 13A and B).

- Absolute Change in BMI from Baseline There was a non-notifiable body weight change in participants who received Tez/Iva therapy in comparison to placebo from baseline (MD 0.03, 95% CI -0.09 to 0.14; p value= 0.66) (25,26) (Fig. 14).
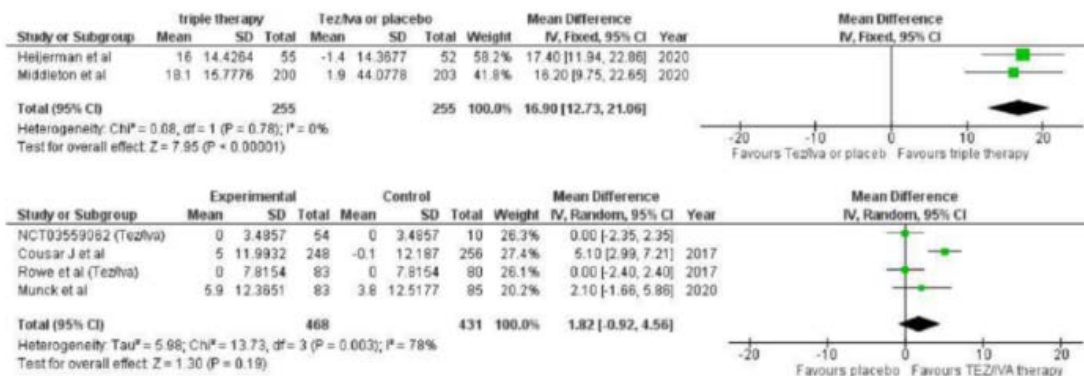
Fig. (13). Forest plot: Absolute change in CF_QR from the baseline. (A) Triple therapy, (B) Tez/IVA combination therapy *vs.* control. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).
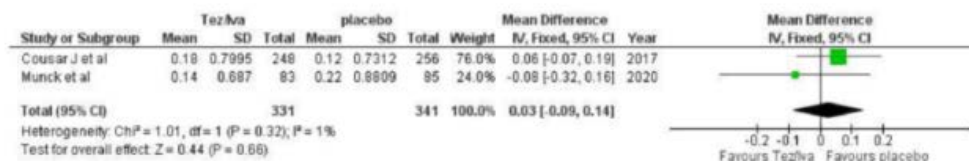

Fig. (14). Forest plot: Absolute change in BMI from the baseline- TEZ/IVA combination therapy *vs.* control. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

- Adverse Events The occurrence of any adverse event with triple therapy and combination of Tez/Iva was no different from those receiving placebo or standard of care (odds ratio (OR) 0.66; 95% CI 0.40-1.10, p value= 0.11 and OR 0.71; 95% CI 0.48-1.05; p value= 0.08) [10, 19]. However, results show that placebo yielded significantly less adverse events than therapy with Ivacaftor alone (OR 0.55; 95% CI 0.36-0.85; p value= 0.006). The most common adverse events were respiratory, such as cough and pulmonary exacerbations. Cough was reported in 16.8% of the patients and pulmonary exacerbations in 21.8% [19]. Similarly, cough was reported in 15% of the patients and pulmonary exacerbations in 2% [10]. Elevated aminotransferase levels and rash were commonly associated with adverse effects in people on CFTR protein modulator therapy. The triple therapy was associated with only mild to moderate elevation of aminotransferases that did not lead to any discontinuation of therapy. Middle-ton reported rash as an adverse event in 22% of patients in the triple therapy group and 6.5% in the placebo group. Similarly, Heijerman reported rash in 1% of the patients in triple therapy as compared to Tez/Iva with no rash. Two patients discontinued treatment due to adverse effects in the study conducted by Middleton, whereas Heijerman reported no treatment discontinuation due to adverse effects (Figs. 15 A-C).
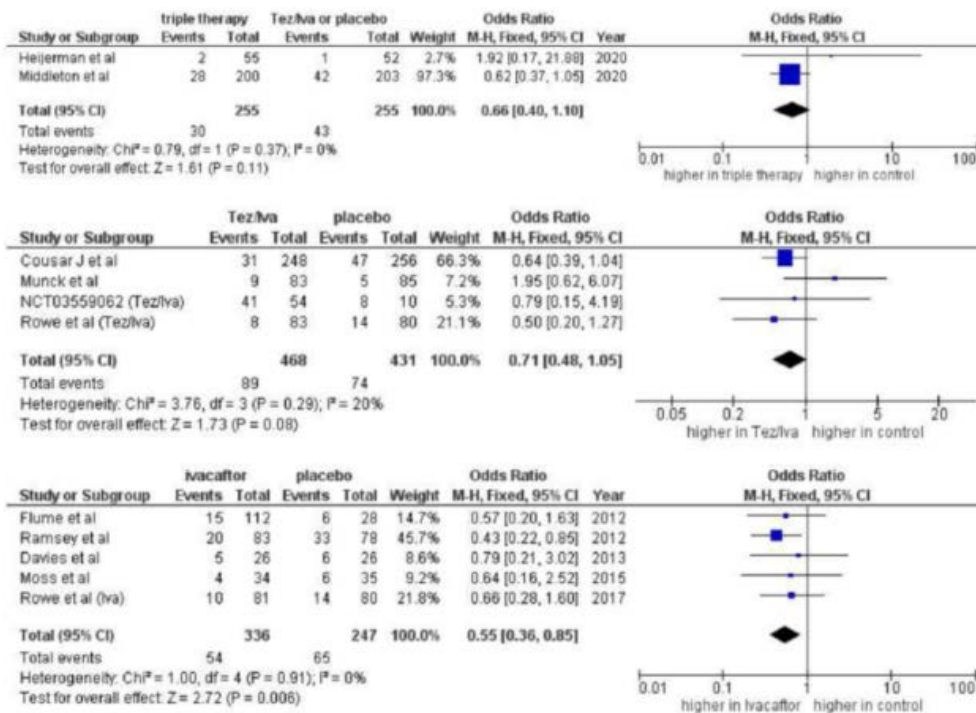
Fig. (15). Forest plot: Adverse events. **(A)** Triple therapy *vs.* Tez/IVA or placebo, **(B)** Tez/IVA combination therapy *vs.* control, **(C)** Ivacaftor *vs.* control. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Anmerkung/Fazit der Autoren

In children aged ≥ 6 years old, and adolescents with F508del_CFTR mutation, Elexacaftor-Tezacaftor-Ivacaftor tend to be more effective than first-generation therapy, demonstrating promising results by exhibiting significant improvement in lung function, body weight, and respiratory related quality of life.

Dawood SN et al., 2022 [1].

Newly Discovered Cutting-Edge Triple Combination Cystic Fibrosis Therapy: A Systematic Review

Fragestellung

This systematic review aims to discuss the efficacy and safety of the new triple therapy Trikafta with the help of data from various clinical trials.

Methodik

Population:

- children six years and above with CF

Intervention:

- triple combination therapy (Elexacaftor - Ivacaftor - Tezacaftor)

Komparator:

- nicht präspezifiziert

Endpunkte:

- nicht präspezifiziert

Recherche/Suchzeitraum:

- PubMed Central (PMC), Google Scholar, and Science Direct
- 2017-2022

Qualitätsbewertung der Studien:

- Cochrane RoB, SANRA 2, AMSTAR 2

Ergebnisse

Anzahl eingeschlossener Studien:

- N=10

Charakteristika der Population/Studien:

First Author, Year	Study Type	Inclusion Criteria	Sample Size (dropouts)	Intervention	Outcomes
Harry GM, 2019 [3]	RCT	Patients aged 12 years and above, homozygous for Phe508del mutation, with stable disease and ppFEV1 of 40 to 90	113 (6)	Participants were randomized 1:1 to four weeks of ELX/TEZ/IVA versus TEZ/IVA alone	The ELX/TEZ/IVA group showed improvements in ppFEV1, sweat chloride concentration, and CFQ-R RD score compared to the TEZ/IVA group. ELX/TEZ/IVA was well tolerated, with no discontinuations.
PG Middleton, 2019 [6]	RCT	Patients aged 12 years of age or older with CF and Phe508del–minimal function genotypes, ppFEV1 of 40 to 90% at screening, and had stable disease during the one-month screening period before the study began	403 (3)	Participants underwent randomization and received at least one dose of active treatment (ELZ/TEZ/IVA) or placebo	The ELZ/TEZ/IVA group resulted in a ppFEV1 that was 13.8 points higher at four weeks and 14.3 points higher through 24 weeks. The rate of pulmonary exacerbations was 63% lower, respiratory domain score on the CFQ-R RD 20.2 points higher, and a sweat chloride concentration 41.8 mmol per liter lower.
Edith T, 2021 [7]	RCT	Children aged 6 to 11 years, with CF, and either F/F or F/MF genotypes.	66 (2)	Children weighing <30 kg received 50% of the ELX/TEZ/IVA adult daily dose, whereas children weighing >30 kg received the total adult daily dose	ELX/TEZ/IVA treatment improved the ppFEV1, CFQ-R RD score, lung clearance index 2.5, and sweat chloride; body mass index-for-age z-score increased over the 24-week treatment period when compared with the pretreatment baseline.
David P, 2022 [10]	RCT	CF patients aged 12 years or older with at least one Phe508del allele starting ELZ/TEZ/IVA for the first time	487 (7)	Assessments occurred before and 1, 3, and 6 months into ELZ/TEZ/IVA therapy.	Six months into ELZ/TEZ/IVA therapy, ppFEV1 improved from baseline, CFQ-R RD score improved by 20.4 points, and sweat chloride decreased. BMI also significantly increased.

TABLE 4: Main features of the randomized control trials chosen for this review

Four final randomized control trials with similar inclusion criteria were chosen for this review and have been summarized in this table.

Randomized control trial (RCT); Phenylalanine 508 deletion mutation (Phe508del); Percent predicted forced expiratory volume in one second (ppFEV1); Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA); Tezacaftor/Ivacaftor (TEZ/IVA); Cystic fibrosis questionnaire–revised respiratory domain (CFQ-R RD); Cystic fibrosis (CF); Homozygous for the Phe508del-cystic fibrosis transmembrane conductance regulator mutation (F/F); Heterozygous for the Phe508del-cystic fibrosis transmembrane conductance regulator mutation and a minimal function cystic fibrosis transmembrane conductance regulator mutation (F/MF); Body mass index (BMI).

First Author, Year	Study Type	Inclusion Criteria	Key points
Tewkesbury, 2021 [4]	Narrative Review	NR	Modulator therapies are likely to improve the course of the CF disease and its management
Marika, 2021 [8]		CF patients with Phe508del/unknown genotype	Treatment of ex vivo models of nasal epithelial cells with ELZ/TEZ/IVA showed excellent responsiveness
Jennifer, 2019 [2]		Patients aged 12 and above with genotype Phe508del/MF or Phe508del/Phe508del, stable CF disease, and FEV1 % between 40 and 90	Next-generation CFTR correctors VX-659 and VX-445, each in triple combination with tezacaftor and ivacaftor, improve CFTR function in vitro and have shown improvements in phase 2 studies in patients with CF with one or two Phe508del-CFTR alleles.
Andrea, 2020 [11]		Patients aged six years and above, phase 2 and phase 3 trials published from 2005 to 2020	Most studies assessed ppFEV1, safety, and tolerability of ELX/TEZ/IVA as their primary outcome, and all showed clinical improvement
Anielo, 2021 [12]	Systematic Review	NR	CFTR modulators have been shown to change the clinical course of the CF in patients heterozygous for Phe508, especially if started at a young age
Dagenais, 2021 [13]		Full manuscripts or conference abstracts of observational studies, case series, and case reports from 2012 to 2020, participants that had a diagnosis of CF that received at least one dose of a CFTR modulator (i.e., IVA, LUM/IVA, TEZ/IVA, or ELX/TEZ/IVA) in the real-world setting, and reported adverse events that occurred while participants were receiving the CFTR modulator.	The types of adverse events reported generally aligned with what has been observed in clinical trials. It is necessary to monitor these effects in people with CF on CFTR modulators in the real-world setting to help better understand potential adverse events and patient characteristics that may be associated with a higher risk of specific adverse events.

TABLE 5: Main features of the narrative and systematic reviews accepted for the review

A total of two narrative reviews and four systematic reviews were included in this review. The details of the included studies are summarized in this table.

Not reported (NR); Cystic fibrosis (CF); Phenylalanine 508 deletion mutation and an unknown genotype (Phe508del/unknown genotype); Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA); Phenylalanine 508 deletion mutation and a minimal function CFTR mutation (Phe508del/MF); Homozygous for phenylalanine 508 deletion mutation (Phe508del/Phe508del); Forced expiratory volume in one second (FEV1); Cystic fibrosis transmembrane conductance regulator (CFTR); Chloride channel agonist currently only used in clinical trials (VX-659); Elexacaftor (VX-445); Phenylalanine 508 deletion mutation-cystic fibrosis transmembrane conductance regulator (Phe508del-CFTR); Percent predicted forced expiratory volume in one second (ppFEV1); Phenylalanine 508 gene mutation (Phe508); Ivacaftor (IVA); Lumacaftor/Ivacaftor (LUM/IVA); Tezacaftor/Ivacaftor (TEZ/IVA).

<u>Qualität der Studien:</u>

Quality Assessment Tool	Type of Study	Total Score	Accepted Score (>70%)	Number of Accepted Studies (#)
CCRBT	RCTs	7	5	4; Harry GM et al. 2019[3], PG Middleton et al. 2019[6], Edith T et al. 2021 [7], David P et al. 2022 [10].
SANRA 2	Narrative Review	12	9	2; Tewkesbury et al. 2021 [4], Marika et al. 2021 [8].
AMSTAR 2	Systematic Review, Meta-Analysis	16	12	4; Jennifer et al. 2019 [2], Andrea et al. 2020 [11], Anielo et al. 2021 [12], Dagenais et al. 2021 [13].

TABLE 3: Details of the quality assessment and the tools used for the final articles accepted for this review

Cochrane collaboration risk of bias tool (CCRBT); Randomized controlled trials (RCTs); Scale for the assessment of narrative review articles 2 (SANRA 2); assessment of multiple systematic reviews 2 (AMSTAR 2).

Studienergebnisse:

First Author, Year	Phase of RCT	Study Duration	Population	Genotype	N	Outcomes
Harry GM, 2019 [3]	III	Eight weeks - Four weeks tezacaftor/ivacaftor run-in - Four weeks trial	Children 12 years or older with 40-90% ppFEV1 and stable disease during the screening period	F/F	n = 52 (tezacaftor, ivacaftor)	Δ ppFEV1: +0.4 Δ Sweat Cl-: +1.7 Δ CFQ-R RD: -1.4
					n = 55 (elexacaftor, tezacaftor, ivacaftor)	Δ ppFEV1: 10.4 Δ Sweat Cl-: -43.4 Δ CFQ-R RD: +16.0
P.G. Middleton, 2019 [6]	III	24 weeks	Children 12 years or older with 40-90% ppFEV1 and stable disease during screening period	F/MF	n = 203 (placebo)	Δ ppFEV1 at 4 weeks: -0.2 Δ ppFEV1 at 24 weeks: -0.4 Δ Sweat Cl-: -0.4 Δ CFQ-R RD: -2.7 Δ BMI: +0.09
					n = 200 (elexacaftor, tezacaftor, ivacaftor)	Δ ppFEV1 at 4 weeks: +13.6 Δ ppFEV1 at 24 weeks: +13.9 Δ Sweat Cl-: -42.2 Δ CFQ-R RD: +17.5 Δ BMI: +1.13 Rate Ratio PEx: 0.37
Edith T., 2021 [7]	III	26 weeks - Two weeks pharmacokinetics study - 24 weeks open label study	Children aged six to eleven years	F/MF	n = 37 (elexacaftor, tezacaftor, ivacaftor)	Δ ppFEV1: + 9.1 Δ CFQ-R RD: + 6.9 Δ LCI2.5: -1.72 Δ Sweat Cl-: -55.1
				F/F	n = 29 (elexacaftor, tezacaftor, ivacaftor)	Δ ppFEV1: + 11.2 Δ CFQ-R RD: + 7.0 Δ LCI2.5: -1.64 Δ Sweat Cl-: -70.4

TABLE 6: Clinical trials summary

Randomized controlled trial (RCT); Percentage predicted forced expiratory volume in 1 s (ppFEV1); Phe508del/Phe508del (F/F); Sweat chloride (sweat Cl-); Cystic fibrosis quality of life-revised, respiratory domain (CFQ-R RD); Phe508del/minimal function (F/ MF); Body mass index (BMI); Pulmonary exacerbation (PEx); Lung clearance index (LCI-).

Anmerkung/Fazit der Autoren

In summary, the development of triple therapy has undoubtedly revolutionized the treatment of CF patients. Larger groups of patients have been given a chance at better standards of life, owing to Trikafta. With very few reported side effects, the future of this medication looks promising. However, as new treatments become available, their long-term safety must be assessed for healthcare providers to treat patients effectively. Although the potential adverse events of these medications have been explored in clinical trials, data from real-life experiences with CF patients using CFTR modulators should be shared to establish a more comprehensive conclusion. Furthermore, there remains a sizeable minority of patients who do not qualify for/cannot obtain these medications, which provides future research objectives for CF researchers.

Wang Y et al., 2022 [12].

Efficacy and Safety of Triple Combination Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Patients With Cystic Fibrosis: A Meta-Analysis of Randomized Controlled Trials

Fragestellung

Cystic fibrosis is a rare, recessive, progressive genetic disease caused by dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Small molecules have recently been developed to treat the molecular consequences of CFTR mutations and restore CFTR protein function. However, the data on triple combination therapy (mainly from Vertex Pharmaceuticals, which is most tested in clinical trials) are limited. This meta-analysis was aimed to assess the efficacy and safety of this therapy according to different mutation genotypes and comparators.

Methodik

Population:

- ptients diagnosed with CF with at least one p.Phe508del CFTR mutation

Intervention:

- triple combination therapy (next-generation corrector plus corrector plus potentiator) for CF

Komparator:

- placebo treatment or active control therapy

Endpunkte:

- primary outcomes included the absolute change from baseline in predicted forced expiratory volume in 1 s (ppFEV1), absolute change from baseline in sweat chloride concentration and absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score;
- secondary outcomes included adverse events

Recherche/Suchzeitraum:

- PubMed, Web of Science and Cochrane Library
- before 31 December 2021

Qualitätsbewertung der Studien:

- Cochrane RoB tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=6

Charakteristika der Population/Studien:

TABLE 1 | The main characteristics of included studies.

Author	Year	Setting	Treatment duration	Triple therapy	Placebo/Acitive placebo	No. of patients included in analysis		Genotypes
						Triple therapy	Placebo or active placebo	
Davies	2018	Multicenter	4 weeks	VX-659(400 mg) TEZ[a](100 mg) IVA[b](300 mg)	Triple placebo or Placebo + TEZ(100 mg)+IVA(300 mg)	40	28	F/MF[c] and F/F[d]
Keating	2018	Multicenter	4 weeks	VX-445(ELX) (200 mg) TEZ(100 mg) TEZ(100 mg)	Triple placebo or Placebo + TEZ(100 mg)+IVA(300 mg)	42	19	F/MF and F/F
Heijerman	2019	Multicenter	4 weeks	ELX[e](200 mg) TEZ(100 mg) IVA(300 mg)	TEZ(100 mg)+IVA(300 mg)	55	52	F/F
Middleton	2019	Multicenter	24 weeks	ELX(200 mg) TEZ(100 mg) IVA(300 mg)	Triple placebo	200	203	F/MF
Barry	2021	Multicenter	8 weeks	ELX(200 mg) TEZ(100 mg) IVA(300 mg)	TEZ(100 mg)+IVA(300 mg) or IVA(300 mg)	132	126	F-gating[f]/RF[g]
Sutharsan	2021	Multicenter	24 weeks	ELX(200 mg) TEZ(100 mg) IVA(300 mg)	TEZ(100 mg)+IVA(300 mg)	87	88	F/F

[a]TEZ: tezacaftor.
[b]IVA: ivacaftor. .
[c]F/MF: p.Phe508del-minimal function.
[d]F/F: p.Phe508del-p.Phe508del.
[e]ELX: elexacaftor (VX-445)
[f]F-gating: p.Phe508del-gating.
[g]RF: p.Phe508del-residual function.

Qualität der Studien:

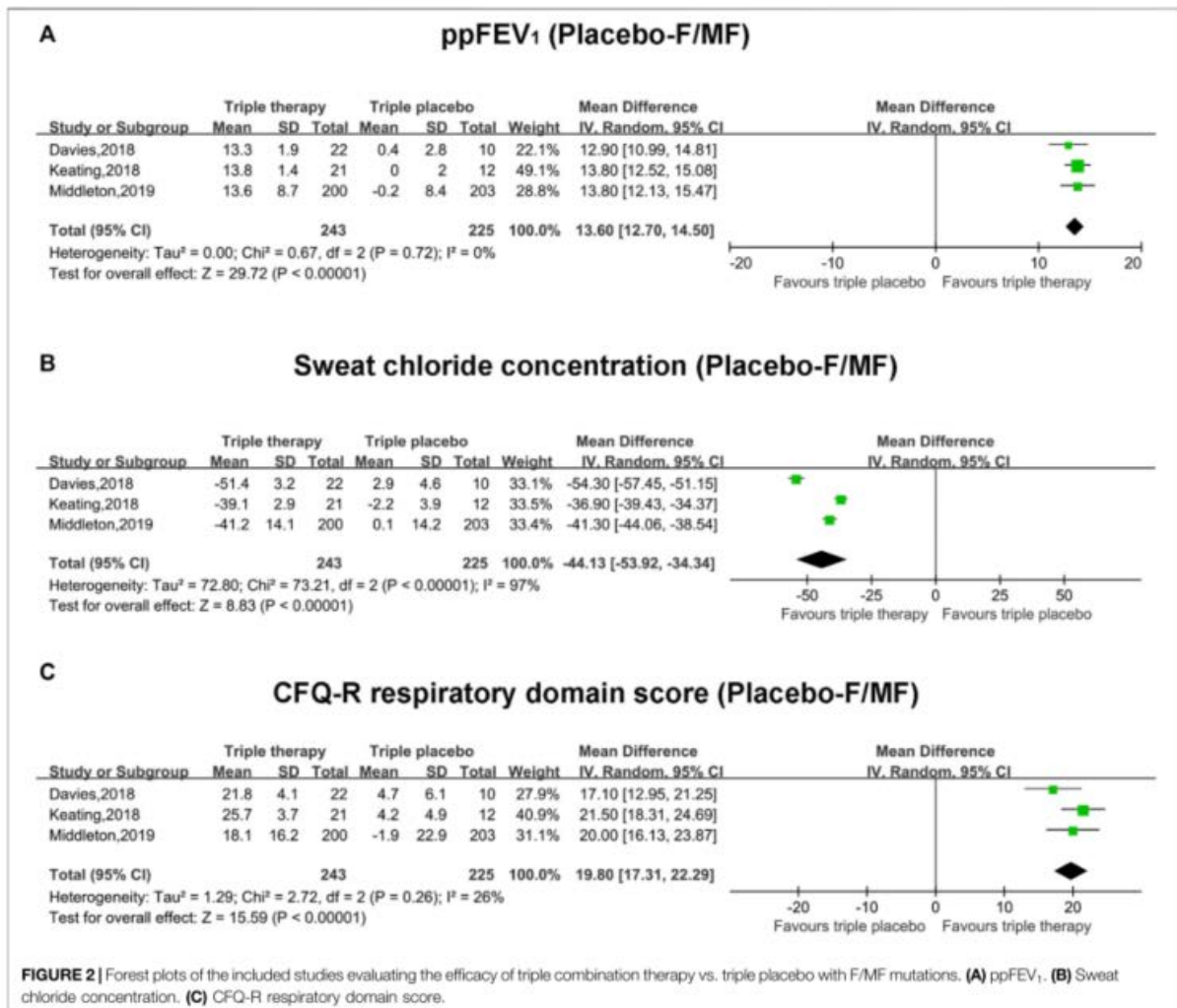**Supplementary Table 3 Risk of bias assessment of RCTs using the Cochrane Collaboration tool**

Study	Random sequence generation	Allocation concealment	Performance bias	Detection bias	Attrition bias	Reporting bias
Davies	Low	Low	Low	Low	Low	Low
Keating	Low	Low	Low	Low	Low	Low
Heijerman	Low	Low	Low	Low	Low	Low
Middleton	Low	Low	Low	Low	Low	Low
Barry	Low	Low	Low	Low	Low	Low

RCT, Randomized controlled trial

Studienergebnisse:

- Pooled Analysis of Primary Outcomes (ppFEV1, Sweat Chloride Concentration and CFQ-R Score) With Triple Placebo Comparator and F/MF Mutation
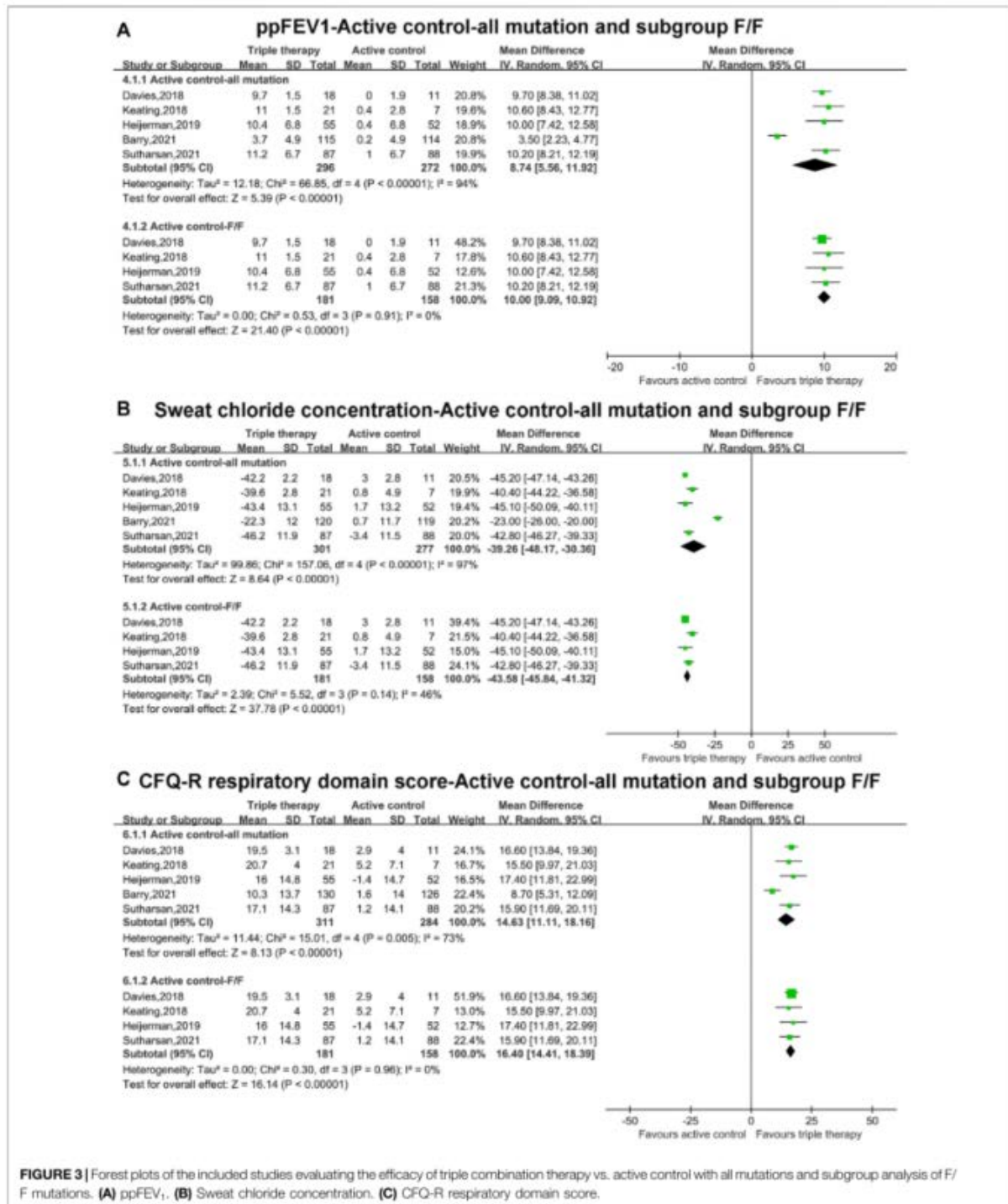
The pooled estimate of theabsolutechange inppFEV1 in the triple combination therapy group was significantly higher than that of the triple placebo group (mean difference, MD, 13.6; 95% CI, 12.7–14.5), and the heterogeneity was significantly small (I2 =0%) (Figure 2A). The pooled estimate of the absolute change in the sweat chloride concentration in the triple combination therapy group was clearly lower than that in the triple placebo group (MD, −44.13; 95% CI, −53.92 to −34.34); however, the heterogeneity was significantly high (I2 =97%, p < 0.001) (Figure 2B). Moreover, the pooled outcome of CFQ-R was much higher in the triple combination therapy group than the triple placebo group (MD, 19.8; 95% CI, 17.31–22.29), with relatively unclear heterogeneity (I2 = 26%) (Figure 2C).

FIGURE 2 | Forest plots of the included studies evaluating the efficacy of triple combination therapy vs. triple placebo with F/MF mutations. **(A)** ppFEV₁. **(B)** Sweat chloride concentration. **(C)** CFQ-R respiratory domain score.

- Pooled Analysis of Primary Outcomes (ppFEV1, Sweat Chloride Concentration and CFQ-R Score) With Active Control Comparator and all Mutations and Subgroup Analysis of F/F Mutations

The pooled estimate of the absolute change in ppFEV1 in the triple combination therapy group was significantly higher than that in the active group (MD, 8.74; 95% CI, 5.56–11.92), but the heterogeneity was significant (I2 =94%, p < 0.001) (Figure 3A). After the data from Barry et al. (Barry et al., 2021), containing F-gating or RF mutations, were omitted, subgroup analysis was conducted in patients with F/F mutations. The pooled estimate ofppFEV1 in thetriplecombination therapy group was still higher than that in the active group (MD, 10.00; 95% CI, 9.09–10.92). Moreover, the heterogeneity became non-significant (I2 =0%) (Figure 3A). The pooled estimate of the absolute change in sweat chloride concentration in the triple combination therapy group was clearly lower than that in the active group (MD, −39.26; 95% CI, −48.17 to −30.36), with clear heterogeneity (I2 =97%, p < 0.001) (Figure 3B). Subgroup analysis indicated that the pooled estimate of the sweat chloride concentration in the triple combination therapy group was lower than that in the active group in patients with F/F mutations (MD, −43.58; 95% CI, −45.84 to −41.32), and the heterogeneity was not clear (I2 =46%)(Figure 3B). The pooled outcome of the absolute change in CFQ-R in the triple combination therapy group was significantly higher than that in the active group (MD, 14.63; 95% CI, 11.11–18.16), and the heterogeneity was significant (I2 = 73%, p = 0.005) (Figure 3C). Subgroup analysis was conducted in patients with F/F mutations, and the

pooled estimate of CFQ-R in the triple combination therapy group was still clearly higher than that in the active group (MD, 16.40; 95% CI, 14.41–18.39). In addition, the heterogeneity became non-significant (I2 = 0%) (Figure 3C).

FIGURE 3 | Forest plots of the included studies evaluating the efficacy of triple combination therapy vs. active control with all mutations and subgroup analysis of F/F mutations. (A) ppFEV₁. (B) Sweat chloride concentration. (C) CFQ-R respiratory domain score.

- Adverse Events

Between the Triple Combination Therapy Group and Placebo/ Active Control Group The pooled incidence of any adverse events in the triple combination therapy group was nearly the same as that in the placebo group (RR, 0.96; 95% CI, 0.92–1.01), with insignificant heterogeneity (I2 =0%) (Figure 4A). Similarly, the pooled incidence of any adverse events in the triple combination therapy group was equivalent to that in the

active group (RR, 0.98; 95% CI, 0.90–1.06), without clear heterogeneity (I2 =0%) (Figure 4B). Most of these adverse events were considered mild or moderate in the triple combination therapy group and placebo/active control group (Tables 2, 3). Furthermore, no clear differences were observed in adverse events leading to discontinuation of the trial regimen among the patients in the triple combination therapy group and placebo/active control

FIGURE 4 | Forest plots of the included studies evaluating the safety according to any adverse events in triple combination therapy vs. triple placebo or active control. (A) Any adverse events (compared with triple placebo with F/MF). (B) Any adverse events (compared with active control with all mutations).
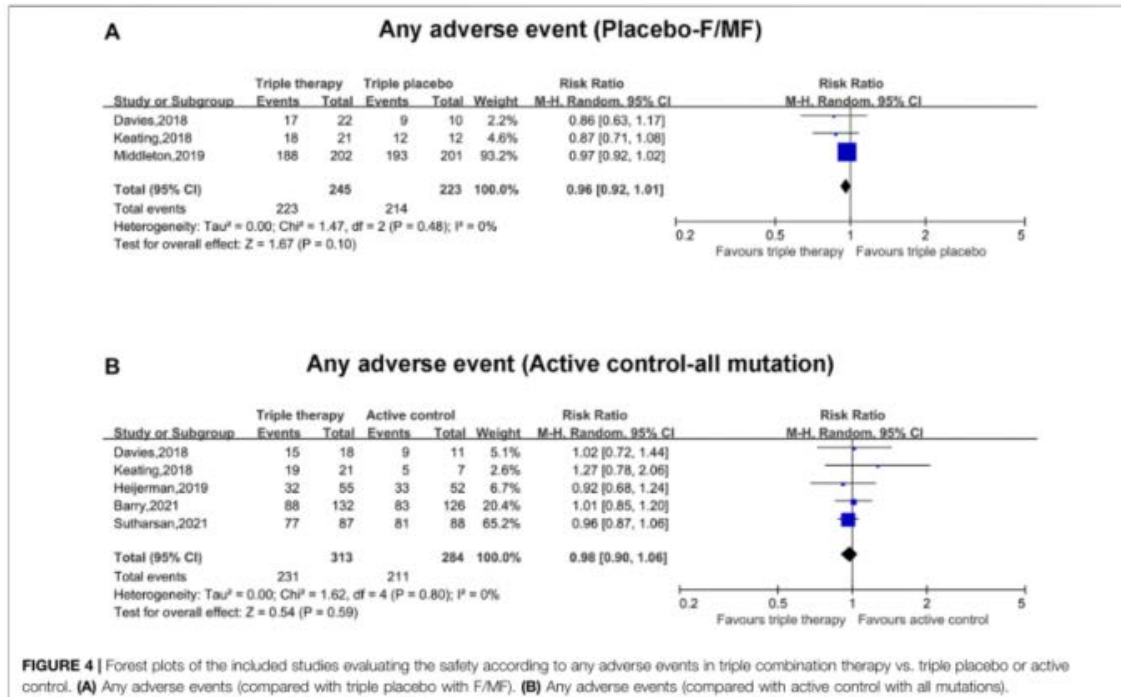
TABLE 2 | Adverse event for placebo control with p.Phe508del-minimal function genotype.

Adverse event	Davies		Keating		Middleton	
	Number of patients (percent)					
	Triple therapy (N = 22)	Placebo (N = 10)	Triple therapy (N = 21)	Placebo (N = 12)	Triple therapy (N = 202)	Placebo (N = 201)
Any adverse event	17 (77)	9 (90)	18 (86)	12 (100)	188 (93.1)	193 (96.0)
Maximum severity of adverse event						
Mild	6 (35)	5 (56)	13 (72)	5 (42)	67 (33.2)	53 (26.4)
Moderate	10 (59)	4 (44)	5 (28)	6 (50)	102 (50.5)	125 (62.2)
Severe	1 (6)	0	0	1 (8)	19 (9.4)	14 (7.0)
Serious adverse event	1 (5)	3 (30)	0	2 (17)	28 (13.9)	42 (20.9)
Adverse event leading to discontinuation of the trial regimen	0	0	0	0	2 (1.0)	0
Most common adverse events						
Cough	4 (18)	1 (10)	7 (33)	1 (8)	34 (16.8)	77 (38.3)
Infective pulmonary exacerbation of cystic fibrosis	4 (18)	2 (20)	2 (10)	4 (33)	44 (21.8)	95 (47.3)
Headache	4 (18)	0	NA	NA	35 (17.3)	30 (14.9)
Oropharyngeal pain	4 (18)	0	NA	NA	20 (9.9)	25 (12.4)
Sputum increased	3 (14)	0	5 (24)	3 (25)	40 (19.8)	39 (19.4)
Hemoptysis	NA	NA	2 (10)	2 (17)	11 (5.4)	28 (13.9)

Anmerkung/Fazit der Autoren

CFTR modulators in triple combination achieve better clinical results than placebo and active control, and result in comparable adverse events.

Kommentare zum Review

Anteil der Kinder nicht berichtet. Keine Subgruppenauswertung für Kinder

Habib AR et al., 2019 [3].

A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis.

Fragestellung

to evaluate the impact of CFTR modulators on lung function and other clinically important outcomes including pulmonary exacerbations, hospitalizations, respiratory symptoms, nutritional status, and adverse events in individuals with CF.

Methodik

Population:

- patients with CF

Intervention:

- CFTR modulators (e.g. potentiators, correctors, translational read-through agents)

Komparator:

- Placebo

Endpunkte:

- Primary outcome: Change in percent-predicted forced expiratory volume in one second (ppFEV1)

- Secondary efficacy outcomes: pulmonary exacerbations (PEx), hospitalization due to PEx, respiratory symptoms (i.e., Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory domain), and nutritional status (i.e., body mass index and weight).

- Adverse events, serious adverse events (including deaths) leading to treatment discontinuation, and the prevalence of elevated liver function tests (LFTs)

Recherche/Suchzeitraum:

- From January 1, 2005 to March 31, 2018. Online databases searched included: MEDLINE, EMBASE, ACP Journal Club, Cochrane Central Register for Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Cochrane Methodology Register (CMR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), and NHS Economic Evaluation Database (NHSEED).

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- eight phase 3 and six phase 2 studies

Charakteristika der Population:

Generic name	Genotypes investigated	Type of CFTR Modulator	No. of Studies
Ataluren	Nonsense mutation ≥ 1 allele	Translational readthrough agent – promotes ribosomal readthrough of premature termination codons to enable the production of full-length, functional CFTR	1
Ivacaftor (IVA)	F508del homozygous; F508del heterozygous G551D ≥ 1 allele; R117H ≥ 1 allele	CFTR "potentiator" – increases CFTR channel open probability (i.e., the fraction of time that the channel remains open)	5
Lumacaftor (LUM)	F508del homozygous	CFTR "corrector" – corrects CFTR misprocessing to increase the amount of cell surface-localized protein	2
Lumacaftor-ivacaftor (LUM-IVA)	F508del homozygous; F508del heterozygous	Combination CFTR corrector and potentiator	5
Tezacaftor (TEZ)	F508del homozygous	CFTR "corrector" – corrects CFTR misprocessing to increase the amount of cell surface-localized protein	1
Tezacaftor-ivacaftor (TEZ-IVA)	F508del homozygous; F508del/G551D	Combination CFTR corrector and potentiator	2

Table 1. CFTR Modulators Investigated in Phase 2 and 3 Clinical Trials. Abbreviations: CFTR = cystic fibrosis transmembrane conductance regulator.

Qualität der Studien:

- Most studies were considered 'low risk' for selection, performance, and attrition bias.
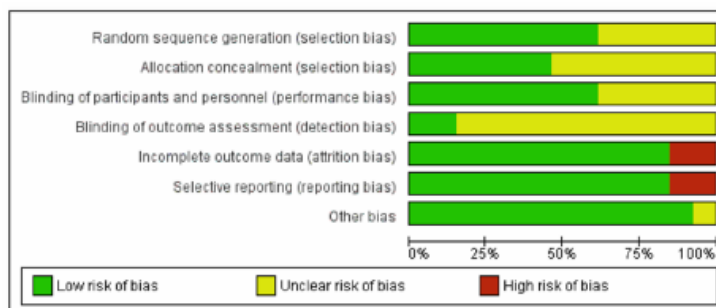
Studienergebnisse:

- Primary outcome (ppFEV1):

  o Of all the CFTR modulators examined to date, individuals with a G551D mutation treated with IVA experienced the largest improvement in ppFEV1 compared to placebo (n = 2 studies; n = 213; weighted absolute mean difference 10.8, 95% CI: 9.0–12.7) with no heterogeneity (I2 = 0%) in results between studies.

  o For F508del homozygous individuals 12 years and older, ppFEV1 significantly improved with LUM-IVA and TEZ-IVA compared to placebo. The effect size was similar for TEZ-IVA (n = 2 studies; n = 535; weighted absolute mean difference 4.0, 95% CI: 3.2–4.8) and higher dose LUM-IVA (n = 3 studies; n = 755; weighted absolute mean difference 3.4, 95% CI: 2.4–4.4).

  o For individuals 6–11 years, there was a mild increase in ppFEV1 for LUM-IVA compared to placebo (n = 1 study; n = 204; absolute mean difference 2.4, 95% CI: 0.4–4.4)19. No significant treatment effect was observed with IVA or TEZ alone, and there was a trend toward worsening in ppFEV1 for F508del homozygous individuals treated with higher doses of LUM (Fig. 3A).

  o For F508del heterozygous individuals, there was no significant improvement in ppFEV1 on LUM or LUM-IVA. In a small study involving individuals with F508del/G551D, TEZ-IVA did not lead to a significant improvement in ppFEV1 compared to IVA alone.

- o For individuals with the R117H mutation on at least one allele, IVA did not lead to an overall improvement in ppFEV1 compared to placebo, but there was a significant improvement in a pre-defined subgroup analysis restricted to adults (n = 50; absolute mean difference 5.0, 95% CI 1.2–8.8).

  - o For individuals with a nonsense mutation on at least one allele, ataluren did not result in a significant relative improvement in ppFEV1 compared to placebo.

- Secondary outcomes

  - o Pulmonary exacerbations (PEx): Of all the CFTR modulators examined, individuals (≥12 years old) with a G551D mutation receiving IVA derived the greatest reduction in PEx risk compared to placebo (n = 1 study; n = 161; OR 0.39, 95% CI: 0.21–0.74). LUM-IVA and TEZ-IVA also significantly reduced the risk of PEx compared to placebo in F508del homozygous individuals (≥12 years old) but the risk reduction was less than that observed with IVA in G551D. In comparison to placebo, no significant reduction in PEx risk was observed for F508del homozygous individuals or individuals with the R117H mutation on at least one allele receiving IVA, nor for individuals with a nonsense mutation receiving ataluren.

  - o Pulmonary exacerbations (PEx) requiring hospitalization: LUM-IVA reduced the risk of PEx requiring hospitalization in F508del homozygous individuals. TEZ-IVA also significantly reduced the rate of PEx leading to hospitalization compared to placebo (n = 1 study; n = 504; rate ratio 0.53, 95% CI 0.34–0.82) but a risk ratio could not be calculated. Individuals with the G551D mutation on at least one allele treated with IVA also experienced a reduction in the risk of PEx requiring hospitalization but this was not statistically significant.

  - o CFQ-R respiratory domain: Compared to placebo, CFQ-R Respiratory domain scores improved to a similar extent for IVA treated individuals (≥6 years old) with the G551D mutation on at least one allele (n = 3 studies; n = 236; weighted absolute mean difference: 7.2, 95% CI: 3.3–11.1), IVA treated individuals ≥18 years old with at least one R117H mutation (n = 1 study; n = 69; absolute mean difference: 8.4, 95% CI: 2.2–14.6), and for LUM-IVA treated F508del heterozygous individuals ≥18 years old (n = 1 study; n = 125; absolute mean difference: 6.5, 95% CI 1.4–11.6).

  - o CFQ-R Respiratory domain scores also significantly improved with TEZ-IVA and LUM-IVA in F508del homozygous individuals (≥12 years old) but the mean difference did not exceed the minimal clinically important difference (MCID) for LUM-IVA. Furthermore, there was no significant improvement in CFQ-R Respiratory domain scores for patients 6–11 years old on LUM-IVA compared to placebo.

  - o There was worsening of the CFQ-R Respiratory domain score for F508del homozygous and heterozygous individuals (≥18 years old) on LUM alone. In a small phase 2 study involving individuals with F508del/G551D, TEZ-IVA did not lead to significant improvement in the CFQ-R Respiratory domain compared to IVA alone. For individuals with a nonsense mutation on at least one allele, ataluren did not modify CFQ-R Respiratory domain score compared to placebo.

  - o Nutritional outcomes (BMI and weight): For individuals with at least one G551D mutation (≥6 years old), significant improvements in weight were observed on IVA compared to placebo (n = 2 studies; n = 213; weighted absolute mean difference: 2.8 kg, 95% CI: 1.8–3.8). For F508del homozygous individuals (≥12 years old), a clinically modest but statistically significant increase in BMI was observed for both doses of LUM-IVA compared to placebo; however, no significant treatment effect was seen in individuals 6–11 years on LUM-IVA. TEZ-IVA did not lead to improvement in BMI compared to placebo in individuals 12 years and older. For

F508del heterozygous individuals (≥18 years old), LUM-IVA did not result in significant improvement in weight or BMI compared to placebo26. There were no significant improvements in BMI compared to placebo among IVA treated individuals with an R117H mutation or ataluren treated individuals with a nonsense mutation (data not shown).

- o Adverse event reporting: CFTR modulators were generally well tolerated compared to placebo. For studies involving F508del homozygous and heterozygous individuals, those assigned to LUM had increased dyspnea and "abnormal respiration" compared to placebo. F508del homozygous and heterozygous subjects assigned to LUM and LUM-IVA also had more respiratory-related adverse events leading treatment discontinuation compared to placebo. For the one study involving individuals with a nonsense mutation, subjects receiving ataluren had increased incidence of acute kidney injury compared to placebo (15% vs. <1%) resulting in higher rates of treatment discontinuation.

- o The prevalence of LFT abnormalities was generally similar between treatment and placebo, however there were a few exceptions. A greater proportion of G551D patients had severe ALT elevations (>8x ULN) on IVA compared to placebo (3.6% vs 0%). Milder elevations in AST (2–3X ULN) were observed for G551D patients on IVA and ALT or AST (>3X ULN) in F508del homozygous children aged 6–11 on LUM-IVA compared to placebo.

Fazit der Autoren

In conclusion, based on randomized placebo-controlled parallel design trials, CFTR potentiation with IVA in individuals with a G551D mutation is safe, and results in robust clinical benefits compared to placebo and to date is superior to the effects observed with CFTR modulators in other CF genotypes. The effects of TEZ-IVA and LUM-IVA in F508del homozygous individuals are comparable with respect to the magnitude of change in ppFEV1 and PEx risk reduction but TEZ-IVA is safer and leads to greater improvement in respiratory symptoms.

Kommentar zum Review

- Keine Subgruppenanalysen nach Alter

Wu HX et al., 2019 [13].

Efficacy and Safety of CFTR Corrector and Potentiator Combination Therapy in Patients with Cystic Fibrosis for the F508del-CFTR Homozygous Mutation: A Systematic Review and Meta-analysis.

Fragestellung

to assess the efficacy and safety of CFTR corrector and potentiator combination therapy on ppFEV1, BMI and CFQ-R respiratory domain score in CF patients with the F508del-CFTR homozygous mutation.

Methodik

Population:

- CF patients with the F508del-CFTR mutation

Intervention/Komparator:
- CFTR corrector and potentiator combination therapy vs. Placebo

Endpunkte:
- ppFEV1, the CFQ-R respiratory domain score, BMI, AEs

Recherche/Suchzeitraum:
- Web of Science, Cochrane Central Register of Controlled Trials, Medline, and Embase to October 26, 2018

Qualitätsbewertung der Studien:
- Cochrane Approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:
- Five RCTs, including a total of 1637 participants with the F508del-CFTR homozygous mutation
- 1035 were allocated to receive combination therapy, while 582 were administered placebo

Qualität der Studien:
- All RCTs were at low risk of bias. No study was excluded for low quality (GRADE).

Studienergebnisse:
- Primary analysis revealed that combination therapy increased ppFEV1 (MD 2.38, 1.62–3.15,
- P\0.00001), improved CFQ-R respiratory domain score (MD2.59, 0.96–4.22, P = 0.002) and BMI (MD 0.21, 0.03–0.39, P = 0.02) in CF patients with the F508del-CFTR mutation.
- In secondary analysis, combination therapy had no impact on the number of participants reporting AEs (OR 0.88, 0.58–1.33, P = 0.53), but increased the proportion of discontinued treatments due to AEs (OR 2.71, 1.3–5.63, P = 0.008).

Anmerkung/Fazit der Autoren

This study shows that CFTR corrector and potentiator combination therapy has an acceptable safety profile and shows improvement in lung function, nutritional status and clinical score in CF subjects homozygous for F508del. It also indicates the combination therapy potential as a novel, effective regimen for CF with F508del homozygous mutation.

Kommentar zum Review

Keine Subgruppenanalysen nach Alter

3.3 Leitlinien

Hammermann J et al., 2020 [7] [5] [6].

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

S3-Leitlinie: Mukoviszidose bei Kindern in den ersten beiden Lebensjahren, Diagnostik und Therapie.

Zielsetzung/Fragestellung

Damit die Vorteile des neu eingeführten Neugeborenen-Screenings durch die frühere Diagnose und den früheren Therapiebeginn für die Patienten tatsächlich in Lebenszeit und -qualität umgesetzt werden können und um die Versorgung von Kindern mit Mukoviszidose in den ersten beiden Lebensjahren zu optimieren, soll mit dieser Leitlinie eine Orientierungshilfe für die sinnvolle und notwendige Diagnostik und Behandlung zur Verfügung gestellt werden.

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:

- systematische Literaturrecherchen in der MEDLINE und der Cochrane Library: 2017

LoE/GoR

Evidenzlevel	Therapiestudien (auch Beobachtungsstudien)	Diagnostikstudien
1a	Systematischer Review von RCTs	Systematischer Review von Level 1 Diagnostikstudien
1b	Einzelne RCTs	Kohortenstudien mit guten Referenzstandards zur Validierung eines diagnostischen Tests
2a	Systematischer Review von Kohortenstudien	Systematischer Review von Level 2 Diagnostikstudien
2b	Einzelne Kohortenstudien	Explorative Kohortenstudien mit guten Referenzstandards
3a	Systematische Reviews von Fallkontrollstudien	Systematische Reviews von Level 3 Diagnostikstudien
3b	Einzelne Fallkontrollstudien	Nicht konsekutiv durchgeführte Studie oder Studie ohne konsistent angewandte Referenzstandards
4	Fallserien; Grundlagenarbeiten	Fallkontrollstudien mit schlechtem oder nicht-unabhängigem Referenzstandard
5	Expertenmeinung, (nicht systematischer) Review	Expertenmeinung

Bei methodischen Mängeln oder hohem Verzerrungsrisiko wurde dem Evidenzlevel ein „-" beigefügt.

Empfehlungsgrad	Definition
A	Starke Empfehlung (soll)
B	Empfehlung (sollte)
0	Empfehlung offen (kann)

Empfehlungen

Wann und wie sollte mit der Therapie begonnen werden?

- Physiotherapie soll zeitnah nach Diagnosestellung begonnen werden. [Empfehlungsgrad: A]

- Bestandteile der Therapie sollten die Sekretmobilisation, die Förderung körperlicher Aktivität und die Schulung der Inhalationstherapie sein, insbesondere die Anleitung der Sorgeberechtigten in die selbständige Durchführung. [Empfehlungsgrad: B]

- Die physiotherapeutischen Behandlungen sollen von Physiotherapeuten durchgeführt werden, die eine Zusatzqualifikation in atemtherapeutischen Techniken erworben haben, z.B. in Deutschland „Grundkurs Physiotherapie bei chronischen Lungenerkrankungen und Mukoviszidose". [Empfehlungsgrad: A]

- Eine Inhalation mit atemwegserweiternden Medikamenten (z.B. Salbutamol) kann vor der Physiotherapie durchgeführt werden. [Empfehlungsgrad: 0]

- Inhalation mit Dornase alfa kann durchgeführt werden. [Empfehlungsgrad 0]

- Eine Inhalation von hypertoner Kochsalzlösung soll durchgeführt werden. [Empfehlungsgrad A]

- Beta-2-Mimetika sollten vorher angewendet werden, wenn es klinische Hinweise auf eine Bronchialobstruktion gibt. [Empfehlungsgrad B]

- Inhalationen mit kurzwirksamen ß2-Sympathomimetika können durchgeführt werden. [Empfehlungsgrad: 0]

- Bei Erstnachweis von S. aureus (Penicllin- oder Methicillin-sensibel oder Methicillin-resistenter S. aureus; PSSA, MSSA oder MRSA) soll eine antibiotische Therapie mit

gegen S. aureus empfohlenen, sensibel getesteten Antibiotika erfolgen. [Empfehlungsgrad A]

- Bei wiederholtem Nachweis von S. aureus (PSSA, MSSA oder MRSA) soll nur bei pulmonaler Exazerbation antibiotisch behandelt werden. [Empfehlungsgrad A]
- Eine antibiotische Dauerprophylaxe soll nicht durchgeführt werden [Empfehlungsgrad A]
- Bei Erstnachweis von H. influenzae soll eine antibiotische Therapie mit gegen H. influenzae gerichteten Antibiotika durchgeführt werden. [Empfehlungsgrad A]
- Bei Erregern wie S. maltophilia und A. xylosoxidans sollte eine antibiotische Therapie mit gegen die entsprechenden Erreger gerichteten Antibiotika durchgeführt werden. [Empfehlungsgrad B]
- Bei wiederholtem Nachweis dieser Erreger soll bei pulmonaler Exazerbation antibiotisch behandelt werden. [Empfehlungsgrad A]
- Eine prophylaktische antibiotische Therapie, um eine Kolonisation mit diesen gramnegativen Erregern zu verhindern, sollte nicht durchgeführt werden. [Empfehlungsgrad B]
- Bei erstem Nachweis von Pseudomonas aeruginosa soll eine frühe Eradikation mittels Tobramycin inhalativ für 4 Wochen ODER mittels Ciprofloxacin p.o kombiniert mit Colistin inhalativ über 3 Wochen erfolgen. Für den Fall, dass eine Inhalation nicht möglich ist, sollte eine intravenöse Kombinationstherapie als Möglichkeit in Betracht gezogen werden (Übernommen aus S3 – Leitlinie „Lungenerkrankung bei Mukoviszidose", Modul 1) [Empfehlungsgrad: A]
- Bei Patienten mit chronischer Pseudomonas aeruginosa-Infektion soll eine inhalative antibiotische Suppressionstherapie durchgeführt werden (Übernommen aus S3 – Leitlinie „Lungenerkrankung bei Mukoviszidose", Modul 2) [Empfehlungsgrad: A]
- Eine generelle Therapie der Lungenerkrankung bei Mukoviszidose sollte weder mit inhalativen noch mit oralem NAC erfolgen. [Empfehlungsgrad B]
- Eine Nasenspülung mit physiologischer Kochsalzlösung sollte regelmäßig durchgeführt werden. [Empfehlungsgrad B]
- Wegen des unklaren Sicherheitsprofils und der Notwendigkeit von Spiegelbestimmungen sollte eine Langzeittherapie mit Ibuprofen nicht durchgeführt werden. [Empfehlungsgrad B]
- Eine Langzeittherapie mit Montelukast soll bei einer alleinigen Indikation Mukoviszidose nicht durchgeführt werden. [Empfehlungsgrad A]
- Eine Langzeittherapie mit inhalativen Steroiden soll wegen fehlender Wirksamkeit und wegen möglicher Nebenwirkungen bei einer alleinigen Indikation Mukoviszidose nicht durchgeführt werden. [Empfehlungsgrad A]
- Eine Langzeitbehandlung mit oralen Steroiden soll wegen der damit verbundenen Nebenwirkungen bei einer alleinigen Indikation Mukoviszidose nicht durchgeführt werden. [Empfehlungsgrad A]

Mutationsspezifische Therapien (CFTR-Modulatoren)

Das bessere Verständnis der Biologie und Funktion des CFTR Proteins hat in den letzten Jahren zur Zulassung mutationsspezifische Therapien für Kinder über zwei Jahren u.a. für Patienten mit homozygoter F508del-Mutation und Gatingmutationen geführt [5]. Eine mutationsspezifische Therapie bei Kindern in den ersten Lebensjahren ist mit der Hoffnung verbunden, die frühe Lungenerkrankung und die exokrine Pankreasfunktion zu

verbessern. Dem stehen offene Fragen nach Sicherheit, Wirksamkeit und altersadaptierter Dosierung und Applikationsform gegenüber. Für Kinder in den ersten beiden Lebensjahren Altersgruppe liegen nur Studienergebnisse für Ivacaftor vor.

Ivacaftor: Für Kinder zwischen 12 und 24 Monaten mit mindestens einer Gating Mutation (G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, oder G1349D) und einem Gewicht von mindestens sieben kg liegt eine offene, nicht randomisierte Studie mit 19 Studienteilnehmern und einer Studiendauer von 24 Wochen (ARRIVAL, [243], Evidenzlevel 2b) vor. Als wichtigste Nebenwirkung fand sich ein Transaminasenanstieg >5xULN in 11,1% (2/18). Der mittlere Abfall der Chloridkonzentration im Schweiß nach 24 Wochen lag bei – 73,5 mmol/l. Es wurde ein Anstieg der faekalen Pankreaselastase im Stuhl bei sechs von neun Patienten von < 50µg/g Stuhl auf ≥ 200µg/g Stuhl und ein Abfall erhöhter Trypsin, Lipase und Amylasewerte im Serum berichtet. Die Studienergebnisse haben zu einer Zulassung durch die European Medicines Agency im November 2018 geführt.

Empfehlung:

Kinder im Alter zwischen 12-24 Monaten mit mindestens einer Gating Mutation (G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, oder G1349D) und einem Gewicht von mindestens 7 kg sollten Ivacaftor als mutationsspezifische Therapien erhalten. [Empfehlungsgrad B]

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2023) am 10.05.2023

#	Suchfrage
1	[mh "cystic fibrosis"]
2	(cystic NEXT fibrosis):ti,ab,kw
3	mucoviscidosis:ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from May 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 10.05.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	cystic fibrosis[mh]
2	cystic fibrosis[tiab]
3	mucoviscidosis[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR

#	Suchfrage
	lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	(#5) AND ("2018/05/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 10.05.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	cystic fibrosis[mh]
2	cystic fibrosis[tiab]
3	mucoviscidosis[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2018/05/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 10.05.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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

Verfahrens-Nr.: 2023-B-121-z

Verfasser	
Name der Institution	Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ) Gesellschaft für Pädiatrische Pneumologie (GPP) Arbeitsgemeinschaft der Ärzte im Mukoviszidose e.V. (AGAM) Forschungsgemeinschaft Mukoviszidose (FGM)
Datum der Erstellung	2. Juni 2023

Indikation
„zur Behandlung von Kindern im Alter von 1 bis < 2 Jahren mit Zystischer Fibrose (CF), die homozygot bezüglich einer F508del Mutation sind."

Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Voranstellen möchten wir, dass diese Stellungnahme zum Behandlungsstandard bei 12 bis 23 Monate alten Kindern mit Mukoviszidose (Cystische Fibrose, CF) mit homozygotem Nachweis der F508del-CFTR-Mutation (F/F) durch Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ), die AG CF der Gesellschaft für Pädiatrische Pneumologie (GPP), die Arbeitsgemeinschaft der Ärzte (AGAM) und die Forschungsgemeinschaft Mukoviszidose (FGM) im Mukoviszidose e.V. gemeinschaftlich konsentiert wurde und stellvertretend für die vorgenannten Fachgremien eingereicht wird. Daher ist im weiteren Dokument von „wir" die Rede, wenn diese Fachgremien gemeint sind.

Die CF ist eine angeborene Multiorganerkrankung mit Folgeproblemen v.a. an den oberen und unteren Atemwegen, Leber und Gallenwegen, Pankreas, Darm, Geschlechtsorganen und den Schweißdrüsen. Die hieraus resultierenden Probleme für den individuellen Patienten sind unterschiedlich stark ausgeprägt, sodass die für die angefragte Altersgruppe mit dem Genotyp F/F bislang zur Verfügung stehende rein symptomatische Therapie sich in ihrer Intensität an dem aktuellen Gesundheitszustand des jeweiligen Kindes orientiert (s. auch Antwort auf nächste Frage). Entsprechend der S2-Leitlinie zur Diagnostik und Therapie der CF in den ersten beiden Lebensjahren (1) gibt es jedoch Therapieempfehlungen, die für alle Kinder mit dem vorgenannten CFTR-Genotyp gelten und die wir nun nach Organsystemen gegliedert auflisten werden (die entsprechende Literatur ist in der vorgenannten awmf-Leitlinie sehr übersichtlich dargestellt und zusammengefasst, weshalb wir für Details auf diese frei zugängliche Leitlinie verweisen möchten):
- Obere Atemwege: Nasenpflege mit Nasenspülungen mittels iso- oder hypertoner Kochsalzlösung (NaCl)
- Untere Atemwege: Tägliche Inhalation mit NaCl 6% ab Diagnosestellung, ggf. nach vorheriger Inhalation mit einem bronchienerweiternden Medikament (z.B. Salbutamol); regelmäßige Atemphysiotherapie (professionell und mit/durch die

Eltern/Betreuungspersonen); an die aktuelle Infektsituation angepasste antibiotische Therapie (inhalativ, oral, intravenös)
- Leber/Galle: bei Hinweisen auf Galleabflussstörungen Gabe von Ursodeoxycholsäure
- Pankreas: bei exokriner Pankreasinsuffizienz (liegt typischerweise bei absoluter Mehrheit der CF-Patienten mit diesem Genotyp vor) Substitution von Pankreasenzymen zu jeder fetthaltigen Mahlzeit, Substitution fettlöslicher Vitamine
- Darm: bei Obstipationsneigung Gabe von stuhlerweichenden Präparaten wie Macrogol zur Prävention eines distalen intestinalen Obstruktionssyndroms (DIOS)
- Schweißdrüsen: Salzsubstitution, v.a. bei hohen Außen- oder Körpertemperaturen

Es liegen Daten zum Verlauf der Erkrankung von Kindern mit CF in den ersten Lebensjahren aus longitudinalen Beobachtungsstudien vor, die den Verlauf der frühen CF-Lungenerkrankung bei Kindern im Vorschulalter unter best-supportive-care (symptomatischer Therapie) mit Gasauswaschverfahren (multiple-breath washout, MBW) zur Erhebung des LCI2,5 und Magnetresonanztomografie (MRT) der Lunge untersucht haben.
Hierbei zeigt sich in der Untersuchung von Stanojevic et al. an 2-5jährigen Kindern mit CF, dass diese bei regelmäßigen Untersuchungen mittels MBW über ein Jahr stets höhere (=schlechtere) LCI2,5-Werte hatten als gesunde Gleichaltrige (2). Im Mittel lagen die LCI2,5-Werte bei den Kindern mit CF, welche mit best-supportive-care behandelt wurden, zu jedem Untersuchungszeitpunkt im pathologischen Bereich und zeigten zudem eine Verschlechterung über die Zeit (2). Die LCI2,5-Werte der gesunden Vorschulkinder waren zu jedem Zeitpunkt im Normalbereich und zeigten keine Änderung über das Jahr der Beobachtung (2). Dies unterstreicht, dass die CF-Lungenerkrankung auch schon im Vorschulalter nachweisbar und progredient ist und der LCI2,5 hierfür ein geeigneter Endpunkt ist, um lungenkranke von lungengesunden Vorschulkindern zu unterscheiden.
Darüber hinaus haben Stahl et al. kürzlich gezeigt, dass die CF-Lungenerkrankung in der hier betrachteten Altersgruppe mittels MRT nachweisbar und über die ersten Lebensjahre unter best-supportive-care progredient ist (3). Hierbei sind die morphologischen und funktionellen Veränderungen, die mittels MRT erkennbar werden, bei Kindern nach klinischer Diagnosestellung der CF stärker ausgeprägt als bei solchen, welche über das CF-Neugeborenenscreening (CF-NGS) identifiziert wurden (3). Betrachtet man jedoch die Rate der jährlichen Verschlechterung über die ersten Lebensjahre, so ist diese bei den Kindern, die über das CF-NGS identifiziert wurden, vergleichbar zu denen mit klinischer Diagnosestellung, was dafür spricht, dass effektivere Therapieoptionen als die symptomatischen Behandlungen notwendig sind, um das Voranschreiten der CF-Lungenerkrankung zu reduzieren oder gänzlich zu verhindern (3). Diese Untersuchung bestätigt, dass es schon früh im Leben der CF-Patienten pulmonale Veränderungen gibt, die bei gesunden Gleichaltrigen nicht auftreten, und dass diese mittels MRT festgestellt werden können. Sowohl das MBW als auch das MRT sind im Vorschulalter multizentrisch durchführbar und können daher als Endpunkte in klinischen Studien genutzt werden (4, 5).

Anmerkung zur Sinnhaftigkeit einer frühen kausalen Therapie:
Ein möglichst frühes Eingreifen in das Fortschreiten dieser schweren Erberkrankung macht medizinisch außerordentlich Sinn, um strukturelle Schäden in den verschiedenen betroffenen Organen zu verhindern. Dies zeigt sich auch an der Tatsache, dass eine initial schlechtere Lungenfunktion im Kindesalter ein wichtiger Prädiktor für einen schlechteren Krankheitsverlauf im weiteren Leben darstellt (6, 7). Best-supportive-care bei CF beinhaltet bisher ausschließlich symptomatische Therapieansätze, die den Krankheitsprogress schlechter adressieren als kausale Therapieansätze, z.B. in Form der CFTR-Modulatoren, die den Basisdefekt der CF behandeln (8). Aus diesem Grund ist es wahrscheinlicher, dass CFTR-Modulatoren eher als symptomatische Therapieansätze geeignet sind, den Krankheitsverlauf nachhaltig zu verändern. Es ist zu erwarten, dass durch die Therapie des CF-Basisdefekts Morbidität und Mortalität der Betroffenen effektiver reduziert werden können, aber auch krankheitsrelevante ökonomische Kosten beeinflusst werden

können. So werden z.B. die momentan in der CF-Therapie zentralen inhalativen Antibiotika, die einen beträchtlichen Kostenfaktor darstellen, erst bei Patienten benötigt, die eine chronische Besiedlung mit typischen Bakterien aufzeigen. Diese chronische Besiedlung wird durch strukturelle Schäden der Lunge begünstigt, so dass frühe Therapien, die strukturelle Lungenschädigungen verhindern oder verlangsamen können, geeignet sein können, eine Pathogenbesiedlung und damit die Notwendigkeit dieser kostenintensiven Therapeutika hinauszuzögern oder bei ausreichend frühzeitigem Beginn gar ganz zu verhindern.

In diesem Zusammenhang verweisen wir außerdem auf das Ziel des 2016 flächendeckend in Deutschland eingeführten CF-Neugeborenenscreenings (9). Durch das CF-NGS, das die Diagnosestellung des überwiegenden Teils der CF-Patienten in den ersten 8 Wochen des Lebens ermöglichen soll, soll sichergestellt werden, dass die Patienten Zugang zu den empfohlenen CF-typischen Therapien erhalten, damit durch eine frühzeitige, möglichst effektive Therapie, Morbidität, Mortalität und krankheitsbedingte Folgekosten reduziert werden können. Es ist in diesem Zusammenhang nicht nachvollziehbar, dass therapeutische Ansätze wie die CFTR-Modulatoren, die sehr viel proximaler in den pathogenetischen Prozess eingreifen als symptomatische Therapien und somit das Potential haben, diese Ziele in besonderem Maße zu beeinflussen, den jüngeren Patienten nicht zu Verfügung stehen sollen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Wie oben ausgeführt, kann der Verlauf der CF und der beim individuellen Patienten beteiligten Organsysteme sehr unterschiedlich sein. Kommt es trotz der oben aufgeführten „Basistherapie" zu Beschwerden in einem Bereich, wird aktuell versucht, die symptomatische Therapie zu intensivieren, z.B. für die unteren Atemwege durch die Hinzunahme von rekombinanter humaner DNase (rhDNase) zur inhalativen mukolytischen Therapie. Jedoch sind die möglichen symptomatischen Maßnahmen begrenzt, weshalb bereits vielfach Anträge auf sog. off-label-use von CFTR-Modulatoren zur kausalen Therapie auch von Kindern dieser Altersgruppe gestellt wurden. Hier zeigte sich eine gute Verträglichkeit und Wirksamkeit bei Kindern in diesem jungen Vorschulalter. Dies ist im Einklang mit unserer langjährigen Erfahrung zu CFTR-Modulatoren in verschiedenen Altersgruppen sowie mit den Ergebnissen der jeweiligen Zulassungsstudien. So zeigt sich bereits bei 2-5jährigen Kindern mit CF, F/F, eine Verbesserung im Lung Clearance Index (LCI), einem Lungenfunktionsparameter, der die Gleichmäßigkeit der Lungenbelüftung beurteilt, unter kausaler Therapie mit der CFTR-Modulatorkombination Lumacaftor/Ivacaftor. Zudem zeigte sich eine höhere Wahrscheinlichkeit einer Befundverbesserung im Lungen-MRT unter der Therapie mit Lumacaftor/Ivacaftor bei den 2-5jährigen Kindern (10) im Vergleich zur Placebo-Gruppe, die lediglich mit der Standardtherapie behandelt wurde. Darüber hinaus ist anzumerken, dass der Anteil der Patienten mit mind. einer pulmonalen Exazerbation in der VX16-809-121-Placebogruppe bei 62,5% und in der LUM/IVA-Gruppe bei 42,9% lag. Obwohl dieser Unterschied formal nicht signifikant ist, weist er einen sehr eindeutigen Trend auf und ist höchst patientenrelevant, da er eine Reduktion von 30% feststellt, wodurch u.a. die Lebensqualität der Patienten deutlich verbessert wird.

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