Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-038 Baloxavir marboxil

Stand: April 2020

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

Baloxavir marboxil
zur Behandlung der Influenza

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
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:	
Baloxavir marboxil Xofluza®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Xofluza ist indiziert zur Behandlung der Influenza bei Patienten ab 12 Jahren einschließlich Patienten mit hohem Risiko, Influenza-bedingte Komplikationen zu entwickeln. Xofluza ist indiziert zur Postexpositions-Prophylaxe der Influenza bei Personen ab 12 Jahren.
Oseltamivir J05AH02 (Tamiflu®)	Therapie der Influenza Tamiflu ist für die Behandlung von Erwachsenen und Kindern, einschließlich reifer Neugeborener, mit influenzatypischen Symptomen indiziert, wenn das Influenza-Virus in der Bevölkerung auftritt. Die Wirksamkeit konnte nachgewiesen werden, wenn die Behandlung innerhalb von zwei Tagen nach erstmaligem Auftreten der Symptome begonnen wurde. [Stand FI 02/2019]
Zanamivir J05AH01 (Relenza®/ Dectova®)	Relenza ist indiziert zur Behandlung der Influenza A und B bei Erwachsenen und Kindern (ab 5 Jahren) mit typischen Influenza-Symptomen, wenn Influenza in der Bevölkerung auftritt. [Stand FI 01/2019]
Amantadin N04BB01 (generisch)	Chemoprophylaxe und Chemotherapie der **Virusgrippe Typ A**: Chemoprophylaxe der Virusgrippe Typ A bei Einzelpersonen und Gruppen, wenn und solange Infektionsgefahr besteht. Chemotherapie der Virusgrippe Typ A: Die Behandlung mit Amantadin ist so rasch wie möglich nach Ausbruch der Erkrankung zu beginnen und sollte 1-2 Tage über das Abklingender Symptome hinaus fortgeführt werden. Hinweis: Voraussetzung der Anwendung von Amantadin der Prophylaxe und Therapie der Virusgrippe A ist eine ärztliche Kontrolle der Therapie sowohl von Einzelpersonen als auch von Kollektiven während des gesamten Behandlungszeitraums. [Stand FI Amantadin ABZ 01/2019]

Quellen: AMIS-Datenbank, Fachinformationen Stand 02/2020

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-038 (Baloxavir marboxil)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. März 2020

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Abkürzungsverzeichnis

AE	adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	ECRI Guidelines Trust
EM	Effect measure
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ILI	influenza-like illness
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITTI	the intention-to-treat infected
KI	Konfidenzintervall
LoE	Level of Evidence
LRTC	lower respiratory tract complication
NAI	neuraminidase inhibitor
NI	neuraminidase inhibitor
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RMST	Restricted mean survival time
RR	Relatives Risiko
SAE	Serious adverse events
SIGN	Scottish Intercollegiate Guidelines Network
TCM	Traditional chinese medicine
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WMD	Weighted mean difference

1 Indikation

Behandlung der Influenza

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Influenza durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 25.02.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1101 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 4 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Systematische Reviews

Qiu S et al., 2015 [3].

Effectiveness and safety of oseltamivir for treating influenza: an updated meta-analysis of clinical trials

Fragestellung

The aim of this study was to determine the effect of oseltamivir on the duration of influenza and the prevention of serious complications and hospitalization by systematically reviewing updated clinical trials published in both Chinese and English.

Methodik

Population:

- diagnosed as having influenza with epidemiological exposure history

Intervention:

- oseltamivir

Komparator:

- placebo or other drugs

Endpunkte:

- duration of fever, duration of symptoms, complications, adverse events, hospitalization, and antibiotic usage

Recherche/Suchzeitraum:

- We searched for relevant articles published in PubMed, Wanfang Data and the China National Knowledge Infrastructure database. The last search was updated in February 2015.

Qualitätsbewertung der Studien:

- The revised Jadad scale was applied for quality assessment. The maximum score was 7, indicating the highest quality study. Only studies with Jadad score > 1 were included in this meta-analysis.

Ergebnisse

Anzahl eingeschlossener Studien:

- In total, 12 eligible articles were included in the meta-analysis, including 6 published in English [19–24] and 6 in Chinese [25–30]

Charakteristika der Population:

A total of 107 712 influenza patients were included in the studies, including 46 466 in the experimental group and 61 246 in the control group. Four studies recruited influenza-like cases, while the other eight studies included patients with confirmed influenza. Oseltamivir was

prescribed to patients at 75 mg/bid or 150 mg/qd. The patients in the control group were treated with placebo, traditional Chinese medicine (TCM) or drugs other than oseltamivir.

Table I. Main characteristics of the eligible studies.

First author	Year	Inclusion criteria[a]	Exclusion criteria[a]	Oseltamivir dose (mg/day)	No. of cases in experiment group	No. of cases in control group	Age (years)	Outcome[b]	Follow-up (days)[c]
Aver'ianov [19]	2012	1, 2, 3, 4	NA	150	29	23	NA	①⑨	7
Blumentals [20]	2007	2	5, 10	NA	36 751	36 751	≥13	③⑦	14
Barr [21]	2007	2	5	NA	4447	20 407	1–12	⑤⑥⑦	30
Kaiser [22]	2003	1, 3	NA	150	2023	1541	13–97	③④⑤⑥	28
Nicholson [23]	2000	1	NA	150/300	798	396	NA	①⑥	8
Dobson [24]	2015	1, 2, 3, 4	NA	150	1565	1295	NA	②③④⑤⑦⑧	21
Deng [25]	2004	1	5, 6, 10, 12	NA	599	577	NA	①③④⑤	10
Chen [26]	2007	3, 4	5, 6, 7, 8, 9, 10, 11, 12	150	22	25	NA	②③④⑥	8+
Li [27]	2011	1, 2, 3, 4	5, 7, 8, 9, 10	150	123	122	18–70	①②⑥	5+
Lin [28]	2004	2, 3, 4	8, 9, 10, 11	150	27	29	NA	①②③④⑤⑥⑧	21
Liu [29]	2011	2	5, 7, 8	150	46	44	14–51	①③④	8+
Yao [30]	2005	2, 4	6, 8, 9, 10, 11, 12	150	36	36	NA	①②④⑥	9+

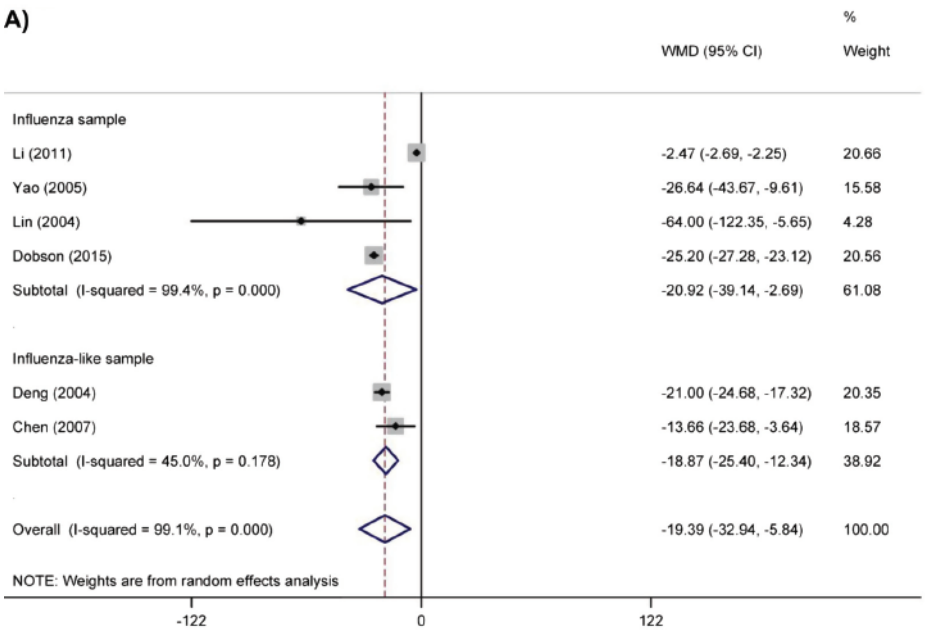
[a]Inclusion and exclusion criteria: 1, treated within 48 h of the onset of symptoms; 2, a definitive diagnosis as influenza; 3, temperature > 37.8°C; 4, two or more flu symptoms; 5, flu with pneumonia; 6, patients with symptoms > 48 h; 7, patients with other severe diseases, metabolic diseases, and immunodeficiency; 8, being vaccinated against flu within 1 year; 9, patients with bacterial infections; 10, pregnant or breast-feeding women; 11, alcohol or drug abuser; 12, patient with mental symptoms.
[b]Outcome: ① duration of fever; ② duration of symptoms; ③ complications; ④ adverse reactions; ⑤ hospitalization; ⑥ use of antimicrobial drugs; ⑦ occurrence of pneumonia; ⑧ health economic index; ⑨ use of antifebrile drugs.
[c]+symbol indicates that symptoms were recorded until all symptoms disappeared after the end of the follow-up period.

Qualität der Studien:

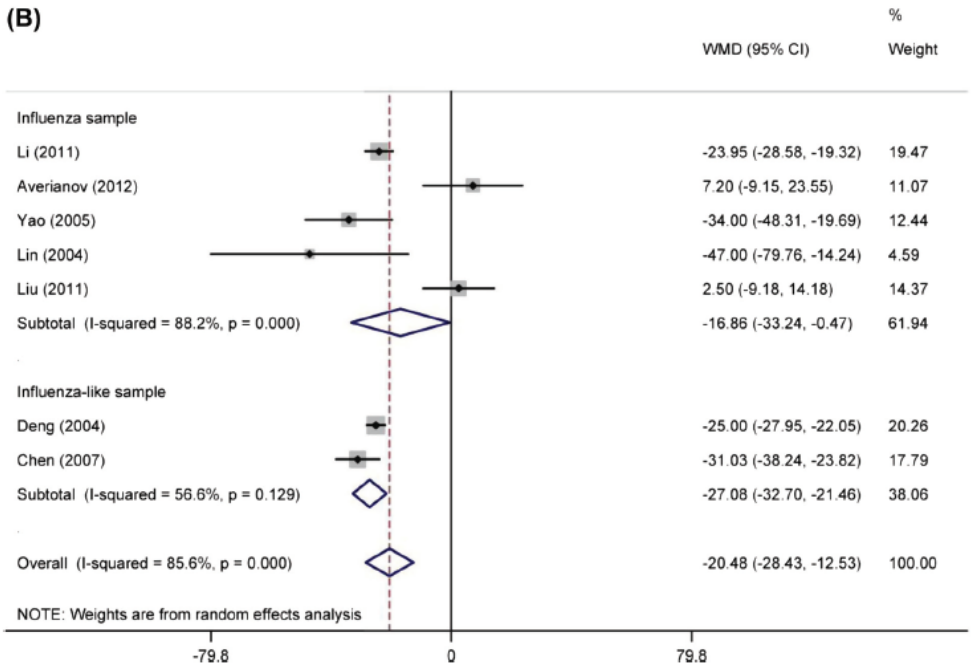
- According to the revised Jadad scale, six studies had high quality, while six studies had relatively low quality

Studienergebnisse:

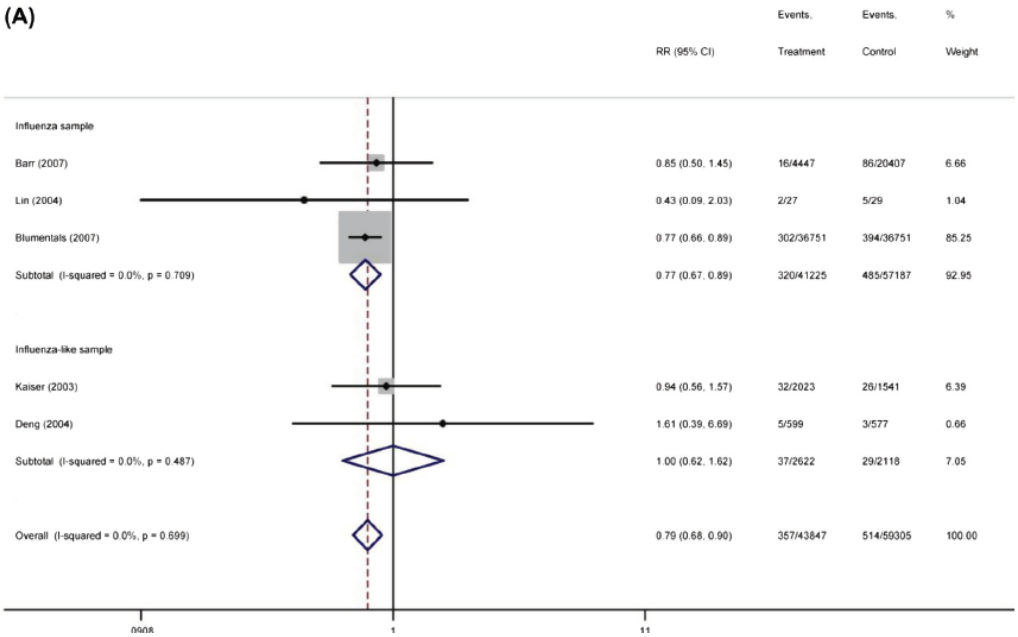
- duration of symptoms
  - The combined WMD was –19.39 (95% CI, –32.94, –5.84; p = 0.005) for the symptoms, indicating a positive effect of oseltamivir in shortening the duration of both symptoms and fever



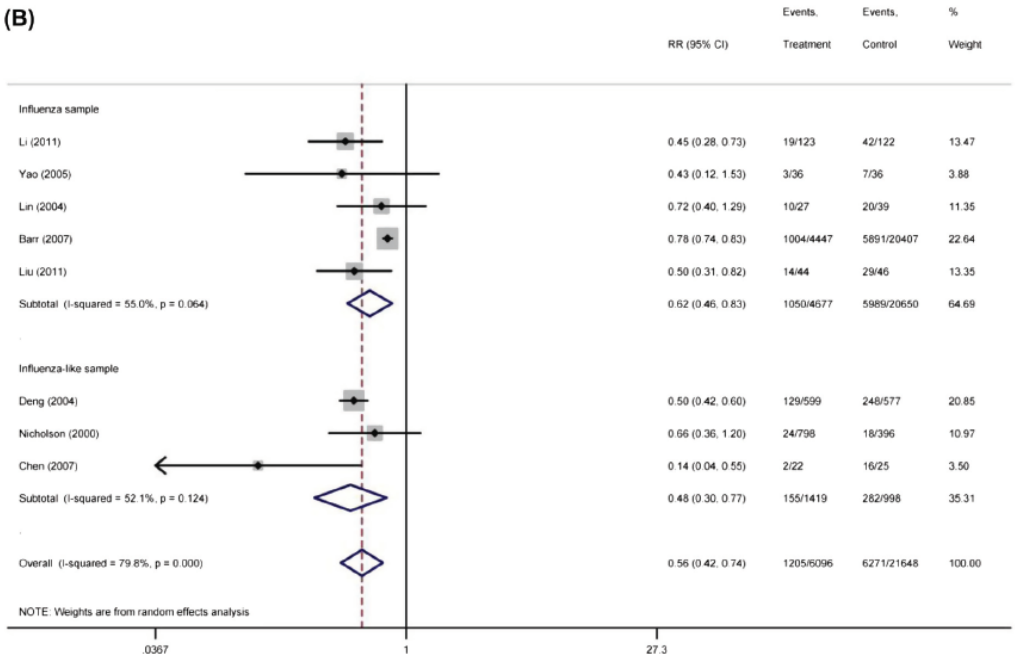
- duration of fever
  - The combined WMD was –20.48 (95% CI, –28.43, –12.53; p < 0.001) for the fever, indicating a positive effect of oseltamivir in shortening the duration of both symptoms and fever



- hospitalization
  - oseltamivir could significantly lower the risk of hospitalization (RR, 0.79; 95% CI, 0.68, 0.90; p < 0.001)



- antibiotic usage
  - antibiotics usage in the oseltamivir group was significantly lower than that in the control group (RR, 0.56; 95% CI, 0.42, 0.74; p < 0.001)



- complications
  - oseltamivir significantly reduced the risk of developing nonspecific complications (RR, 0.58; 95% CI, 0.35, 0.95; p = 0.032) and otitis media (RR, 0.78; 95% CI, 0.65, 0.93; p = 0.006) but not the occurrence of pneumonia (RR, 0.58; 95% CI, 0.30, 1.13; p = 0.112)
- adverse reactions
  - The adverse reactions reported during antiviral treatment included nausea, vomiting, diarrhea, kidney damage, and mental reactions. Six articles (7050 patients) reported the adverse reactions of oseltamivir. The fixed effect model showed no significant difference in the incidence of adverse reactions between the oseltamivir and control groups (RR, 1.01; 95% CI, 0.95, 1.09; p = 0.710)

Anmerkung/Fazit der Autoren

Based on this meta-analysis combining 12 eligible clinical trials, we found that oseltamivir not only shortened the duration of fever and symptoms but also reduced the risk of hospitalization, the occurrence of both otitis media and nonspecific complications, and antibiotic usage. No significantly elevated risk of adverse drug reactions was observed among patients treated with oseltamivir.

Our analysis found that oseltamivir could significantly reduce the hospitalization rate and antibiotic usage. Previous observational studies have demonstrated a clinical benefit of NAIs, including reduced mortality and hospitalization, in patients with influenza [40,41]. However, in a Cochrane Collaboration study, oseltamivir and zanamivir were found to have limited effects in decreasing symptoms and did not reduce the hospitalization rate or the risk of serious influenza complications [42]. When performing a cumulative meta-analysis on the effect of oseltamivir on patient hospitalization rates, we find that oseltamivir is associated with a modest protection against hospitalization but that it appeared to be underutilized in patients with the highest hospitalization risk. Patients with longer hospital stays tend to be treated with more antibiotics [43]. In the meta-analysis by Hernán and Lipsitch published in 2011, oseltamivir reduced antibiotic usage in healthy adults by 28% (95% CI, 11–42%) [34]. However, antibiotics should

not be prescribed routinely during flu treatment [44]. The use of oseltamivir in patients without antibacterial drugs does not increase the risk of concurrent bacterial infections.

[42] Ebell MH. Oseltamivir and zanamivir have limited effect on symptoms and do not reduce hospitalisation or serious complications of influenza. Evid Based Med 2014;19:211.

Kommentare zum Review

Die Kontrollgruppen erhielten Placebo, TCM oder andere medikamentöse Therapien. Welche Kontrollintervention in den Studien durchgeführt wurde ist nicht dokumentiert und es gibt keine Subgruppenanalysen.

Malosh RE et al., 2018 [2].

Efficacy and Safety of Oseltamivir in Children: Systematic Review and Individual Patient Data Meta-analysis of Randomized Controlled Trials.

Fragestellung

Oseltamivir has been used to treat children with influenza for nearly 2 decades, with treatment currently approved for infants aged ≥2 weeks. However, efficacy and safety remain controversial. Newer randomized, placebo-controlled trials (RCTs), not included in previous meta-analyses, can add to the evidence base.

Methodik

Population:

- children with influenza virus infection

Intervention:

- oseltamivir

Komparator:

- placebo

Endpunkte:

- duration of illness in hours

Recherche/Suchzeitraum:

- We searched PubMed, MEDLINE, Embase, and the Cochrane Library for clinical trials published between 1 January 1997 and 1 May 2016

Qualitätsbewertung der Studien:

- The risk of bias was evaluated using the Cochrane tool to describe the data quality from each trial

Ergebnisse

Anzahl eingeschlossener Studien:

- 5

Charakteristika der Population:

Table 1. Description of Randomized Controlled Trials of Efficacy of Oseltamivir in Pediatric Populations

Trial	WV15758 [24]	WV15759/WV15871 [25]	NV16871 [26]	NCT00707941 [27]	NCT00593502 [28]
Description	Otherwise healthy children (1–12 y) <48 h of symptom onset	Children with asthma (≥6 y–≤12 y) <48h of symptom onset	Children with asthma (≥6 y–≤17 y) <48 h of symptom onset	Age +1y, no upper age limit (89% <18 y, ~80% ≤10y) within 5 days symptom onset	Children (1–3 y), early treatment (≤24 h of symptom onset)
Location	United States, Canada	Europe, Israel, United States, Canada, Argentina, Australia, Chile, China, New Zealand, South Africa	Europe, Israel	Bangladesh	Finland
Numbers of intention-to-treat patients	695 (planned = 680)	334 (planned = 500)	329 (planned = 392)	796 (<48 h from onset)[a]	408 (planned = 308)
Number (%) intention-to-treat infected patients	452 (65%) (planned = 340) -217 oseltamivir -235 placebo	179 (54%) (planned = 250) -84 oseltamivir -95 placebo	94 (29%) (planned = 196) -43 oseltamivir - 51 placebo	796 (<48 h from onset)[a] -398 oseltamivir -396 placebo	98 (24%) (planned = 154) -37 oseltamivir -61 placebo
Randomization	1:1 Stratified by presence/absence of acute otitis media (baseline clinical diagnosis)	1:1 Stratified by class of asthma (mild or moderate/severe).	1:1 Stratified by class of asthma (mild or moderate/severe) and time from onset of influenza symptoms to treatment start	1:1 Stratified by <48 h and 48+ h since symptom onset; permuted blocks with variable length between 2 and 8	1:1 Randomized in blocks of 4; randomization, labeling and packaging of study drugs performed by Roche
Laboratory assays for detection of influenza	Virus culture, serology	Virus culture, serology	Virus culture, serology	RT-PCR, virus isolation	Virus culture, time-resolved fluoroimmunoassay, RT-PCR
Duration of illness definition	Time from illness onset to presence of mild or no cough, nasal congestion/runny nose, afebrile, return to normal activity	Time from illness onset to presence of mild or no cough, nasal congestion/runny nose, afebrile, return to normal activity	Time from illness onset to resolution of influenza symptoms	Time from illness onset to resolution of major symptoms (fever, tachypnea, difficult/noisy breathing, cough, and any danger sign)	Time from illness onset to presence of mild or absent cough and rhinitis, afebrile, return to normal activities

Abbreviation: RT-PCR, real-time polymerase chain reaction.

Overall 1190 patients enrolled and randomized, 796 patients randomized <48 hours from onset eligible for inclusion in meta-analysis. Separate randomization for those enrolled >48 hours from onset.

Studienergebnisse:

- Duration of illness
  - Overall, there was a significant reduction in the duration of illness among those who received timely oseltamivir treatment (RMST difference, −17.6 hours; 95% CI, −34.5 to −0.7 hours
- Complications
  - In the ITTI population (n = 1598) there were fewer cases of LRTC >48 hours after first study drug intake in the oseltamivir group compared to the placebo group (29/770 [4%] vs 38/828 [5%]; relative risk [RR], 0.75; 95% CI, 0.37, 1.52), but the difference was not statistically significant (Figure 3). There was evidence of a 34% reduction in risk of developing otitis media in the ITTI population (RR, 0.66; 95% CI, 0.47–0.95). In the ITT population with complete data on complications (n = 2458), the effect of treatment on developing otitis media was attenuated and no longer significant (RR, 0.98; 95% CI, 0.77, 1.26). There were too few hospitalizations to reach meaningful conclusions (ITTI 4/770 [0.5%] oseltamivir compared to 3/825 [0.3%] placebo).
- Safety
  - We found an increased RR of vomiting in the treatment group (RR, 1.63; 95% CI, 1.30, 2.04), but no evidence of an increased risk of nausea, diarrhea, or SAEs among 2558

patients in the safety population (Table 3). SAEs were very rare in both the oseltamivir (11/1074 [1%]) and placebo (4/1078 [0.4%]) groups. In the trials that recorded data, there was also no difference in withdrawal from treatment (26/676 [4%] oseltamivir vs 27/682 [4%] placebo; P = ·93) and withdrawal due to an adverse event (8/676 [1%] vs 8/682 [1%]; P = ·99) by treatment group.

Anmerkung/Fazit der Autoren

In the current analysis, we demonstrated a reduction in the duration of illness of approximately 18 hours among children who received timely oseltamivir treatment compared to placebo. In addition, we found that treatment reduced the risk of otitis media and that there was little evidence of safety issues, except for vomiting. A recent meta-analysis of all adult RCTs found a reduction in duration of illness in the ITTI population of 25 hours.

The major outliers in this analysis were the trials that included only children with asthma. The pooled estimate for the 3 trials that did not specifically enroll asthma patients was a reduction in illness duration of 29.9 hours, which is closer to that found in the adult meta-analysis.

Kommentare zum Review

Financial support. This study was funded by the Multiparty Group for Advice on Science (MUGAS) Foundation through an unrestricted grant from Roche Pharmaceuticals. Neither party had a role in analysis, interpretation, reporting, or the decision to submit for publication. We thank Roche for providing the data and answering data specific queries.

Boikos C et al., 2017 [1].

Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009-15

Fragestellung

To review systematically the published literature evaluating neuraminidase inhibitor (NI) safety and effectiveness in situations of pandemic and novel/variant influenza.

Methodik

Population:

- influenza in all patient populations

Intervention:

- neuraminidase inhibitor (NI) oseltamivir, zanamivir, peramivir and/or laninamivir. For inclusion, studies of NIs must have been used in the context of pandemic influenza (defined as any influenza A/H1N1 strains circulating in 2008–2009 or 2009–2010 influenza seasons) or novel/variant influenza (defined as influenza strains endemic in avians or swine, not endemic in humans) treatment, prophylaxis and/or outbreak control

Komparator:

- administration of another influenza antiviral drug class, regimen or NI; standard of care at the time the study was conducted; placebo; or no treatment for influenza.

Endpunkte:

- The primary outcome of interest for NI effectiveness in prophylaxis/outbreak control was secondary transmission. For NI effectiveness in treatment, outcomes included mortality (distinguishing between all-cause and influenza-related, if possible), pneumonia, ICU admission, hospitalization, secondary transmission, severe influenza infection (defined as either ICU admission or death), duration of fever (or time to afebrile), time to resolution of symptoms(duration of disease) and effectiveness of NIs in relation to timing of administration (either after symptomon set or presentation for medical care was also evaluated). For NI safety (for either treatment, prophylaxis or outbreak control) the primary outcomes of interest were all reported adverse events (AEs). Secondary outcomes included for NI effectiveness in treatment, prophylaxis or outbreak control were viral shedding, viral load and development of resistance.

Recherche/Suchzeitraum:

- Six databases were searched for published articles: BIOSIS Previews, CINAHL, EMBASE, MEDLINE, PubMed and Web of Science. Searches were limited to studies published from 1 April 2009–31 October 2015

Qualitätsbewertung der Studien:

- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for rating the quality of evidence were used to assess the quality of each study. We specifically evaluated the risk of bias (selection bias,measurement error and residual confounding) in RCTs and observational studies, and checked for any additional risk of bias in RCTs arising fromrandomsequence generation, allocation concealment and blinding. Each study was assessed for the presence/absence of confounding, measurement error and selection bias (as determined by reviewers). We also evaluated the imprecision and indirectness of the outcomes of interest

Ergebnisse

Anzahl eingeschlossener Studien:

- In total, 165 articles were included in this systematic review
- Ninety-four per cent (155 of 165) of the included studies were observational and the remainder were experimental.
- Approximately 63%(104 of 165) of included studies were retained for the analysis of the effect of NI treatment

Charakteristika der Population:

- Roughly 88% (145 of 165) of studies included participants with laboratory-confirmed influenza (most commonly by RT-PCR); however, the diagnostic methods that authors used varied widely by study
- In the majority of studies, the study population exclusively received oseltamivir (107 of 165; 65%); in four studies (2%) authors evaluated the effect of peramivir alone; and in the remaining 54 (33%) it was either unclear whether study participants received several NIs or one NI exclusively.

Qualität der Studien:

- We deemed selection bias to be unlikely in roughly half (77 of 165) of the included studies and likely/unclear in 40% (61 of 165). Furthermore, measurement error was considered likely in 37% (61 of 165) of all included studies and unclear (or possible) in 35% (57 of 165) of studies.
- We judged that the included studies were generally of low quality based upon presence of confounding, measurement error and/or selection bias

Studienergebnisse:

NIs for treatment

- Mortality
  - Seven studies reported at least one adjusted measure (an EM reported from an RCT or adjusted for at least one confounder) of the effect of NIs versus no treatment on mortality in the context of pandemic/novel influenza. In a general population, four of seven studies reported a statistically significant protective effect of NIs against mortality. In children, only the study by Yang et al. presented an adjusted EM that favoured the use of NI treatment for the outcome of mortality in this population; however, this was not statistically significant.
- Hospitalization
  - Three studies (2%) presented an adjusted effect estimate evaluating NI treatment on hospitalization (Figure 5).97,109,140 In children, the studies by Lera et al.97 and Shi et al.140 both reported an EM favouring NI treatment for the outcome of hospitalization. In a general population, the study by Marra et al.109 reported a similar result.
- ICU admission
  - Two studies57,124 reported adjusted EMs evaluating NI treatment for the outcome of ICU admission. In children, Hagerman et al.57 presented adjusted effect estimates in favour of oseltamivir use for the outcome of ICU admission. In a general population, Poeppl et al.124 presented adjusted effect estimates in favour of oseltamivir use for the outcome of ICU admission.
- Pneumonia
  - One study168 reported an adjusted EM evaluating NI treatment on the outcome of pneumonia. In a general population, Yu et al.168 reported an EM that favoured NI treatment compared with no treatment for the outcome of pneumonia (Figure 5).
- Duration of fever
  - One study, Saito et al.,135 presented two adjusted EMs (for oseltamivir and zanamivir respectively) evaluating the effect of NI treatment on duration of fever in children. Both EMs favoured NI treatment compared with no treatment, but only the adjusted EM for oseltamivir treatment was statistically significant.
- Time to resolution of influenza symptoms
  - In one study,125 authors reported an adjusted effect estimate evaluating the effect of NI treatment of the time-to resolution of influenza symptoms. In adults, Pop-Vicas et al.125 found that days to antiviral initiation was independently associated with prolonged influenza, defined as an influenza-like illness (ILI) lasting beyond 7 days (data not shown in Pop-Vicas et al. article; adjusted in a multivariable regression model)

Anmerkung/Fazit der Autoren

Overall, approximately half (34 of 62, 55%) of all statistical analyses comparing NI treatment with no treatment were statistically significant, favouring the use of NIs for all outcomes with limited significant evidence opposing their use. Evaluating adjusted estimates only, NIs are likely effective in reducing mortality and may be effective in reducing pneumonia, in the general population. Furthermore, there was a trend in the evidence supporting NI treatment for the reduction of severe influenza, hospitalization, ICU admission and fever duration (in a general population, children and adults).

In all studies, a statistically significantly decreased risk, odds or lower R0 were reported in individuals who received NIs as prophylaxis (both pre- and post-exposure) compared with those that did not (in a general population and in adults) with the exception of one observational study conducted in adult healthcare personnel workers.

However, the results of this review must be interpreted with caution as they are based on a small number of studies that are of very poor methodological quality. Knowledge gaps remain regarding NI effectiveness and safety for specific populations, namely Aboriginal people, high-risk individuals (living with chronic and/or immune conditions) and the elderly (>65years old).

3.2 Leitlinien

Uyeki TM et al., 2019 [4].

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza.

Leitlinienorganisation/Fragestellung

These clinical practice guidelines are an update of the guidelines published by the Infectious Diseases Society of America (IDSA) in 2009. The guidelines consider the care of children, pregnant and postpartum women, and nonpregnant adults and include special considerations for patients who are severely immunocompromised such as hematopoietic stem cell and solid organ transplant recipients. The target audience includes primary care clinicians, obstetricians, emergency medicine providers, hospitalists, and infectious disease specialists. The guidelines may be also useful for occupational health physicians and clinicians working in long-term care facilities. It adds new information on diagnostic testing, use of antivirals, and considerations of when to use antibiotics and when to test for antiviral resistance, and presents evidence on harm associated with routine use of corticosteroids.

Methodik

Grundlage der Leitlinie

Die Leitlinie ist ein Update einer Leitlinie aus dem Jahr 2009. Es wird angegeben, dass sich die Leitlinienerstellung an der Originalleitlinie orientierte. Die Leitlinie aus dem Jahr 2009 entspricht einer hochwertigen Leitlinie entsprechend S3 Klassifizierung der AWMF. Ob ein systematisches Vorgehen auch für das Update zugrunde liegt ist nicht dokumentiert.

Harper SA, Bradley JS, Englund JA, et al; Expert Panel of the Infectious Diseases Society of America. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:1003–32.

- Repräsentatives Gremium, keine Patientenbeteiligung.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche für die Originalleitlinie von 2009 dargelegt, unklar, ob die Suche auch im Update systematisch war. Systematische Bewertung der Evidenz.
- Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig. Die Verbindung zu der zugrundeliegenden Evidenz ist nicht explizit dargestellt.
- Keine Angaben zur Überprüfung der Aktualität.

Recherche/Suchzeitraum:

- Originalleitlinie 2009: Literature searches of the Medline database were performed for relevant English-language literature from the period 1966–2008.
- Keine Angaben zum Update.

LoE und GoR

Category and Grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from 1 or more properly randomized controlled trials
II	Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Adapted from the Canadian Task Force on the Periodic Health Examination [6].

TREATMENT

Which Patients With Suspected or Confirmed Influenza Should Be Treated With Antivirals?

18. Clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza, irrespective of influenza vaccination history, who meet the following criteria:

• Persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization (A-II).

• Outpatients of any age with severe or progressive illness, regardless of illness duration (A-III).

• Outpatients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients (A-II).

• Children younger than 2 years and adults ≥65 years (A-III).

• Pregnant women and those within 2 weeks postpartum (A-III).

19. Clinicians can consider antiviral treatment for adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history, who are either:

• Outpatients with illness onset ≤2 days before presentation (C-I).

• Symptomatic outpatients who are household contacts of persons who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised (C-III).

• Symptomatic healthcare providers who care for patients who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised (C-III).

For Patients Who Are Recommended to Receive Antiviral Treatment for Suspected or Confirmed Influenza, Which Antiviral Should Be Prescribed, at What Dosing, and for What Duration?

20. Clinicians should start antiviral treatment as soon as possible with a single neuraminidase inhibitor (NAI) (either oral oseltamivir, inhaled zanamivir, or intravenous peramivir) and not use a combination of NAIs (A-1).

21. Clinicians should not routinely use higher doses of US Food and Drug Administration–approved NAI drugs for the treatment of seasonal influenza (A-II).

22. Clinicians should treat uncomplicated influenza in otherwise healthy ambulatory patients for 5 days with oral oseltamivir or inhaled zanamivir, or a single dose of intravenous peramivir (A-1).

23. Clinicians can consider longer duration of antiviral treatment for patients with a documented or suspected immunocompromising condition or patients requiring hospitalization for severe lower respiratory tract disease (especially pneumonia or acute respiratory distress syndrome [ARDS]), as influenza viral replication is often protracted (C-III).

In a Patient With Suspected or Confirmed Influenza, When Should Bacterial Coinfection of the Upper or Lower Respiratory Tract Be Considered, Investigated, and Treated?

24. Clinicians should investigate and empirically treat bacterial coinfection in patients with suspected or laboratory-confirmed influenza who present initially with severe disease (extensive pneumonia, respiratory failure, hypotension, and fever), in addition to antiviral treatment for influenza (A-II).

25. Clinicians should investigate and empirically treat bacterial coinfection in patients who deteriorate after initial improvement, particularly in those treated with antivirals (A-III).

26. Clinicians can consider investigating bacterial coinfection in patients who fail to improve after 3–5 days of antiviral treatment (C-III).

If a Patient With Influenza Does Not Demonstrate Clinical Improvement With Antiviral Treatment or Demonstrates Clinical Deterioration During or After Treatment, What Additional Testing and Therapy Should Be Considered?

27. Clinicians should investigate other causes besides influenza virus infection in influenza patients who fail to improve or deteriorate despite antiviral treatment (A-III).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, February 2020) am 20.02.2020

#	Suchfrage
1	[mh "influenza, human"]
2	[mh "influenzavirus A"]
3	[mh "influenzavirus B"]
4	#1 OR #2 OR #3
5	influenza:ti,ab,kw OR infleunzas:ti,ab,kw
6	grippe:ti,ab,kw
7	flu:ti,ab,kw
8	#5 OR #6 OR #7
9	#4 OR #8
10	#9 with with Cochrane Library publication date from Feb 2015 to Feb 2020

Systematic Reviews in Medline (PubMed) am 20.02.2020

#	Suchfrage
1	influenza, human[mh]
2	influenzavirus A[mh]
3	influenzavirus B[mh]
4	#1 OR #2 OR #3
5	influenza[tiab] OR influenzas[tiab]
6	grippe[tiab]
7	flu[tiab]
8	#5 OR #6 OR #7
9	#4 OR #8
10	(#9) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence)))

	AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
11	((#10) AND ("2015/02/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 20.02.2020

#	**Suchfrage**
1	influenza, human[mh]
2	influenzavirus A[mh]
3	influenzavirus B[mh]
4	#1 OR #2 OR #3
5	influenza[tiab] OR influenzas[tiab]
6	grippe[tiab]
7	flu[tiab]
8	#5 OR #6 OR #7
9	#4 OR #8
10	(#9) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
11	(#10) AND ("2015/02/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])
13	(#12) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Referenzen

1. **Boikos C, Caya C, Doll MK, Kraicer-Melamed H, Dolph M, Delisle G, et al.** Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009-15. J Antimicrob Chemother 2017;72(6):1556-1573.

2. **Malosh RE, Martin ET, Heikkinen T, Brooks WA, Whitley RJ, Monto AS.** Efficacy and safety of oseltamivir in children: systematic review and individual patient data meta-analysis of randomized controlled trials. Clin Infect Dis 2018;66(10):1492-1500.

3. **Qiu S, Shen Y, Pan H, Wang J, Zhang Q.** Effectiveness and safety of oseltamivir for treating influenza: an updated meta-analysis of clinical trials. Infect Dis (Lond) 2015;47(11):808-819.

4. **Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al.** Clinical practice guidelines by the infectious diseases society of america: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. Clin Infect Dis 2019;68(6):895-902.