Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2021-B-292 Luspatercept

Stand: November 2021

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

Luspatercept
[Behandlung von Erwachsenen mit nicht transfusionsabhängiger Anämie aufgrund von Beta-Thalassämie]

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.	Erythrozytentransfusionen
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:	
Luspatercept B03XA06 Reblozyl®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Behandlung von erwachsenen Patienten mit nicht transfusionsabhängiger Anämie aufgrund von Beta-Thalassämie
Deferasirox V03AC03 Exkjade®	EXJADE ist angezeigt zur Behandlung der chronischen Eisenüberladung auf Grund häufiger Transfusionen (≥ 7 ml/kg/Monat Erythrozytenkonzentrat) bei Patienten mit Beta-Thalassämia major im Alter von 6 Jahren und älter. EXJADE ist auch angezeigt zur Behandlung der chronischen, transfusionsbedingten Eisenüberladung, wenn eine Deferoxamin-Therapie bei folgenden Patientengruppen kontraindiziert oder unangemessen ist: – bei Kindern im Alter zwischen 2 und 5 Jahren mit Beta-Thalassämia major mit Eisenüberladung auf Grund häufiger Transfusionen (≥ 7 ml/kg/Monat Erythrozytenkonzentrat), – bei Erwachsenen, Kindern und Jugendlichen im Alter von 2 Jahren oder älter mit Beta-Thalassämia major mit Eisenüberladung auf Grund seltener Transfusionen Transfusionen (< 7 ml/kg/Monat Erythrozytenkonzentrat), – bei Erwachsenen, Kindern und Jugendlichen im Alter von 2 Jahren und älter mit anderen Anämien. EXJADE ist auch angezeigt zur Behandlung der chronischen Eisenüberladung, wenn eine Deferoxamin-Therapie bei Patienten mit nicht-transfusionsabhängigen Thalassämie-Syndromen im Alter von 10 Jahren und älter, die eine Chelat-Therapie benötigen, kontraindiziert oder unangemessen ist.
Deferipron V03AC02 Deferipron Lipomed	Die Monotherapie mit Deferipron Lipomed ist zur Therapie der Eisenüberlast bei Patienten mit Thalassaemia major indiziert, wenn eine aktuelle Chelattherapie kontraindiziert oder ungeeignet ist. Deferipron Lipomed in Kombination mit einem anderen Chelatbildner (siehe Abschnitt 4.4) ist bei Patienten mit Thalassaemia major indiziert, wenn eine Monotherapie mit einem Eisenchelatbildner ineffektiv ist oder wenn die Verhinderung oder Behandlung lebensbedrohender Eisenüberlast (vor allem des Herzens) eine schnelle oder intensive Korrektur rechtfertigt (siehe Abschnitt 4.2).
Deferoxamin V03AC01	Behandlung der chronischen Eisenüberladung, z. B.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Desferal®	– Transfusionshämosiderosen, insbesondere bei Thalassaemia major, sideroblastischer Anämie, autoimmunhämolytischer Anämie und anderen chronischen Anämien; – primärer (idiopathischer) Hämochromatose bei Patienten, deren Begleiterkrankungen (z. B. schwere Anämie, Herzerkrankungen, Hypoproteinämie) einen Aderlass ausschließen; – Eisenüberladung bei Patienten mit Porphyria cutanea tarda; Behandlung der akuten Eisenvergiftung.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-292 (Luspatercept)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. September 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AEs	Adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CT	computerized tomography
DFO	desferrioxamine
DFP	deferiprone
DFX	deferasirox
DM	Diabetes Mellitus
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IGT	Impaired Glucose Tolerance
KI	Konfidenzintervall
LIC	liver iron concentration
LoE	Level of Evidence
LVEF	left ventricular ejection fraction
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SCT	stem cell transplantation
SD	standard deviations
SF	serum ferritin
SIGN	Scottish Intercollegiate Guidelines Network
TM	thalassemia major
TRIP	Turn Research into Practice Database
UIE	urine iron excretion
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit nicht transfusionsabhängiger Anämie aufgrund von Beta-Thalassämie.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Thalassämie* 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), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.startpage.com) 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 17.09.2021 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 170 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 vier Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Bollig C et al., 2017 [1].

Deferasirox for managing iron overload in people with thalassaemia.

Fragestellung

To assess the effectiveness and safety of oral deferasirox in people with thalassaemia and iron overload.

Methodik

Population:

- People with thalassaemia regardless of age, type of thalassaemia (e.g. thalassaemia major, thalassaemia intermedia) and setting (e.g. country, primary or secondary care), who have developed iron overload (defined as ferritin levels of over 1000 ng/mL on at least two occasions in individuals with transfusion-dependent thalassaemia and over 300 ng/mL in those with non-transfusion-dependent thalassaemia). People with thalassemia who have undergone stem cell transplantation (SCT) are excluded.

Intervention/Komparator:

- For oral deferasirox (all schedules and doses) the following comparisons were considered:
  - deferasirox compared with no therapy or placebo in people with transfusion-dependent thalassaemia;
  - deferasirox compared with no therapy or placebo in people with non-transfusion-dependent thalassaemia;
  - deferasirox compared with another iron-chelating treatment (i.e. deferoxamine or deferiprone or any combination thereof) in people with transfusion-dependent thalassaemia;
  - deferasirox compared with another iron-chelating treatment (i.e. deferoxamine or deferiprone or any combination thereof) in people with non-transfusion-dependent thalassaemia.

Endpunkte:

- primär: overall mortality
- sekundär: Reduced end-organ damage due to iron deposition; Measures of iron overload; Measures of iron excretion; AEs; Participant satisfaction

Recherche/Suchzeitraum:

- Bis 2015

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

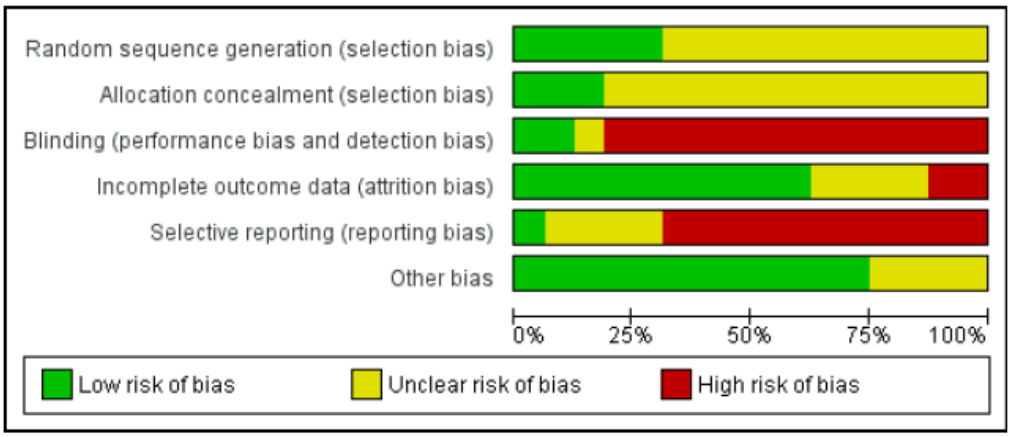
Anzahl eingeschlossener Studien:

- Sixteen studies involving 1807 randomised participants
- Twelve two-arm studies compared deferasirox to placebo (two studies) or deferoxamine (seven studies) or deferiprone (one study) or the combination of deferasirox and deferoxamine to deferoxamine alone (one study). One study compared the combination of deferasirox and deferiprone to deferiprone in combination with deferoxamine. Three three-arm studies compared deferasirox to deferoxamine and deferiprone (two studies) or the combination of deferasirox and deferiprone to deferiprone and deferasirox monotherapy respectively (one study). One four-arm study compared two different doses of deferasirox to matching placebo groups.

Qualität der Studien:

- The quality of included studies comparing deferasirox to deferoxamine in peoplewith transfusion-dependent thalassaemia wasmoderate to low, mainly due fact that the investigators and participants knew which interventions had been assigned to which participants, the small number of participants included in the studies and the use of a surrogate markers (measures used in place of a hard clinical end point) instead of patient-important outcomes. For the comparison of deferasirox to placebo in people with non-transfusion-dependent thalassaemia, the quality of the evidence was moderate to very low based on only one small study. For the other comparisons, the quality of the evidence was low to very low, mainly due to the inclusion of even fewer participants. Ideally, further randomised studies looking at patient-important, long-term outcomes and rarer adverse events, should be conducted.

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



Studienergebnisse:

- Nine studies (1251 participants) provided data for deferasirox versus standard treatment with deferoxamine. Data suggest that a similar efficacy can be achieved depending on the ratio of doses of deferoxamine and deferasirox being compared. In the phase III study, similar or superior efficacy for the intermediate markers ferritin and liver iron concentration (LIC) could only be achieved in the highly iron overloaded subgroup at a mean ratio of 1 mg of deferasirox to 1.8 mg of deferoxamine corresponding to a mean dose of 28.2 mg per day and 51.6 mg per day respectively.
- The pooled effects across the different dosing ratios are: serum ferritin, mean difference (MD) 454.42 ng/mL (95%confidence interval (CI) 337.13 to 571.71) (moderate quality

evidence); LIC evaluated by biopsy or SQUID,MD 2.37 mg Fe/g dry weight (95% CI 1.68 to 3.07) (moderate quality evidence) and responder analysis, LIC 1 to < 7 mg Fe/g dry weight, risk ratio (RR) 0.80 (95% CI 0.69 to 0.92) (moderate quality evidence). The substantial heterogeneity observed could be explained by the different dosing ratios.

- Data on mortality (low quality evidence) and on safety at the presumably required doses for effective chelation therapy are limited.
- Patient satisfaction was better with deferasirox among those who had previously received deferoxamine treatment, RR 2.20 (95% CI 1.89 to 2.57) (moderate quality evidence).
- The rate of discontinuations was similar for both drugs (low quality evidence).
- For the remaining comparisons in people with transfusion-dependent thalassaemia, the quality of the evidence for outcomes assessed was low to very low, mainly due to the very small number of participants included.
- Four studies (205 participants) compared deferasirox to deferiprone; one ofwhich (41 participants) revealed a higher number of participants experiencing arthralgia in the deferiprone group, but due to the large number of different types of adverse events reported and compared this result is uncertain.
- One study (96 participants) compared deferasirox combined with deferiprone to deferiprone with deferoxamine. Participants treated with the combination of the oral iron chelators had a higher adherence compared to those treated with deferiprone and deferoxamine, but no participants discontinued the study.
- In the comparisons of deferasirox versus combined deferasirox and deferiprone and that of deferiprone versus combined deferasirox and deferiprone (one study, 40 participants), and deferasirox and deferoxamine versus deferoxamine alone (one study, 94 participants), only a few patient-relevant outcomes were reported and no significant differences were observed.
- One study (166 participants) included people with non-transfusion dependent thalassaemia and compared two different doses of deferasirox to placebo. Deferasirox treatment reduced serum ferritin, MD -306.74 ng/mL (95% CI -398.23 to -215.24) (moderate quality evidence) and LIC, MD -3.27 mg Fe/g dry weight (95% CI -4.44 to -2.09) (moderate quality evidence), while the number of participants experiencing adverse events and rate of discontinuations (low quality evidence) was similar in both groups.
- No participant died, but data on mortality were limited due to a follow-up period of only one year (moderate quality evidence).

Anmerkung/Fazit der Autoren

Deferasirox offers an important treatment option for people with thalassaemia and secondary iron overload. Based on the available data, deferasirox does not seem to be superior to deferoxamine at the usually recommended ratio of 1 mg of deferasirox to 2 mg of deferoxamine. However, similar efficacy seems to be achievable depending on the dose and ratio of deferasirox compared to deferoxamine. Whether this will result in similar efficacy and will translate to similar benefits in the long term, as has been shown for deferoxamine, needs to be confirmed. Data from randomised controlled trials on rare toxicities and long-term safety are still limited. However, after a detailed discussion of the potential benefits and risks, deferasirox could be offered as the first-line option to individuals who show a strong preference for deferasirox, and may be a reasonable treatment option for people showing an intolerance or poor adherence to deferoxamine.

3.2 Systematische Reviews

Dou H et al., 2019 [3].

Effectiveness and Safety of Deferasirox in Thalassemia with Iron Overload: A Meta-Analysis

Fragestellung

to carry out an up-to-date meta-analysis to include recently published works and comprehensively assess the efficacy and safety of DFX in thalassemia with iron overload.

Methodik

Population:

- thalassemia patients with iron overload (defined as serum ferritin [SF] levels above 1,000 µg/L on at least 2 occasions) regardless of age, gender, or race;

Intervention:

- DFX

Komparator:

- DFO or placebo

Endpunkte:

- overall mortality, any AEs

Recherche/Suchzeitraum:

- Embase, Medline, Cochrane, and Chinese Biomedical Literature (CBM) databases from January 1990 to May 2018

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Six articles reporting RCTs with a total of 1,102 included patients were eligible for inclusion

Charakteristika der Population:

Table 1. Baseline characteristics of the included studies

First author [ref.], year	Experimental participants	Control treatment	Control patients	Duration, weeks	Dosage form (DFX)	Criteria for adverse events	
						standard of serum creatinine increases	standard of ALT increases
Nisbet-Brown [20], 2003	17	placebo	5	2	Exjade	not mentioned	not mentioned
Cappellini [21], 2006	296	DFO	290	52	Exjade	>1× ULN	twice the ULN
Piga [16], 2006	48	DFO	23	48	Exjade	above the ULN	ALT >250 U/L
Taher [19], 2012	110	placebo	56	52	Exjade	>33% above baseline and above the ULN	ALT >5× ULN and >2× baseline
Pennell [18], 2014	98	DFO	99	52	Exjade	33% above baseline and above the ULN	>5× ULN and 2× baseline
Hassan [17], 2016	30	DFO	30	52	Exjade	33% above baseline, not above the ULN	not mentioned

DFO, deferoxamine; DFX, deferasirox; ULN, upper limit of normal; ALT, alanine aminotransferase.

Qualität der Studien:

- Five of the 6 RCTs clearly described the randomization methods used, and 2 RCTs described the process of allocation concealment. Double-blinding was mentioned in 4 RCTs, and the blinding methods used were described. Meanwhile, 2 RCTs used an open-label design. Incomplete outcome data were reported in 2 RCTs, and 1 study revealed a withdrawal rate of more than 20%. Only 1 study reported all the outcomes described in the Methods section. The included RCTs were not defined regarding other biases.

Table 2. Risk of bias for each study

First author [ref.], year	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias
Nisbet-Brown [20], 2003	L	L	L	L	L	U	U
Piga [16], 2006	L	U	L	L	H	H	U
Cappellini [21], 2006	U	U	H	L	U	U	U
Taher [19], 2012	L	L	L	L	L	U	U
Pennell [18], 2014	L	U	L	L	U	L	U
Hassan [17], 2016	L	U	H	U	U	L	U

L, low risk; U, unclear; H, high risk.

Studienergebnisse:

- No differences in mortality.
- DFX was not better than DFO in lowering SF and LIC, with an exception that high DFX dose (> 30 mg/kg/day) was superior to DFO in LIC.
- AEs such as gastrointestinal problems appeared to be more common with DFX. DFX does not seem to be superior to DFO at low dose. Similar efficacy seems to be achievable depending on dose. However, the convenient oral administration of DFX has a higher compliance rate.

Anmerkung/Fazit der Autoren

Overall, based on the above data, DFX does not seem to be superior to DFO at low dose. However, similar efficacy as with DFO is achievable depending on DFX dose (≥30 mg/kg/day). Actually, DFX could be offered as first-line option to individuals with intolerance or poor adherence to DFO or a strong preference for DFX.

Kommentare zum Review

- only 6 RCT were included / some results were based on very few studies
- heterogeneity might be present, affecting the results of this meta-analysis

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Sridharan K et al., 2018 [4].

Efficacy and safety of iron chelators in thalassemia and sickle cell disease: a multiple treatment comparison network meta-analysis and trial sequential analysis

Fragestellung

To compare the efficacy and safety of desferrioxamine (DFO), deferiprone (DFP), deferasirox (DFX) and silymarin in patients with either thalassemia or sickle cell disorder through network meta-analysis.

Methodik

Population:

- patients with either thalassemia or sickle cell disorder with iron overload

Intervention:

- any of the iron chelator

Komparator:

- any other iron-chelating agent or placebo
  - Agents included: DFO, DFP, DFX, DFP/DFO, DFX/DFO, DFP/DFO sequential therapy, DFO/Silymarin, DFX/Silymarin, and DFP/Silymarin

Endpunkte:

- Primary: end of treatment serum ferritin values.
- Secondary: Liver iron concentrations (LICs), mortality, left ventricular ejection fraction (LVEF), urine iron excretion (UIE), adverse events, neutropenia, agranulocytosis, changes in serum ferritin, and number of patients discontinuing treatment

Recherche/Suchzeitraum:

- Medline (through PubMed) and Cochrane CENTRAL were searched for the clinical studies with the below-mentioned criteria and the literature search was completed on August 5, 2017.

Qualitätsbewertung der Studien:

- Cochrane Approach /GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 32 were included in the systematic review and meta-analysis
- Studies compared the following interventions: DFP with DFO (n = 7); DFX with DFO (n = 5); DFP/DFO with DFO (n = 6); DFX with placebo (n = 3); DFO/Silymarin with DFO (n = 3); and one each compared DFP/DFO sequential therapy with DFO, DFP/DFO with DFP, DFP/DFO with DFX/DFO, DFX/Silymarin with DFX, DFP/Silymarin with DFP, and DFP/DFO sequential with DFP. Two studies had three arms comparing DFP/DFO with DFP and DFO.

Qualität der Studien:

- Risk of bias assessment revealed a high risk of bias in at least one domain for most of the included studies

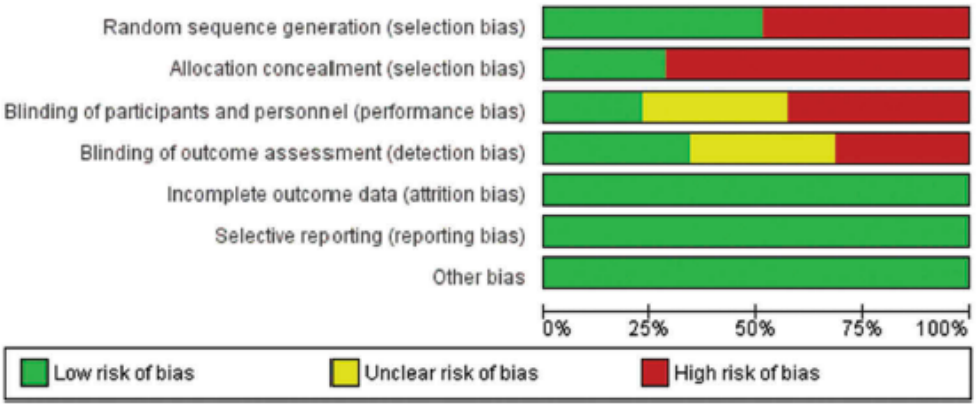

Figure 2. Network plot of the comparisons for end of treatment serum ferritin.
Large majority of the included studies compared DFP, DFX, and DFP/DFO with DFO.

- Grading the evidence: Grading of the evidence for key comparisons was carried out based on imprecision, indirectness, publication bias, and risk of bias of the included studies. Due to serious limitations in the imprecision, publication bias and risk of bias, the strength of evidence was observed to be very low for most of the comparisons.

Studienergebnisse:

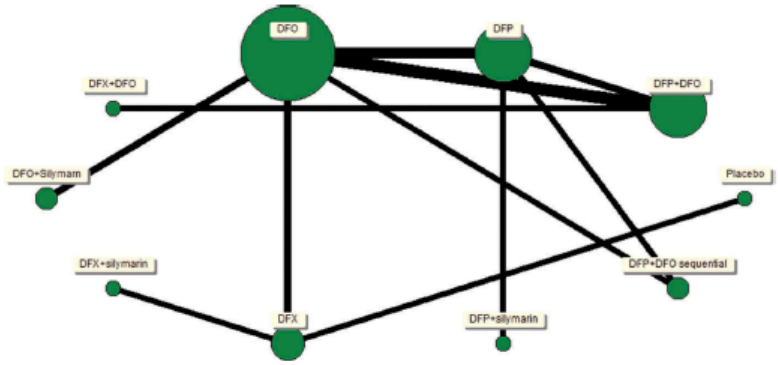

Figure 3. Summary of risk of bias of the included studies.
Red circle with *minus* symbol indicates absence of reporting of that specific domain, green circle with *plus* symbol indicates reporting, and yellow circle with question mark indicates an unclear risk.

- Primary endpoint:
  - Nineteen studies (with 1229 participants) were analyzed for any significant differences in the end of treatment serum ferritin. MTC estimates revealed no significant differences in the serum ferritin levels for any of the iron chelators with placebo.
  - However, DFX/DFO was associated with significantly lower serum ferritin levels than DFO (WMD = −1232 [−1948, −516]), DFX (WMD = −3064 [−5560, −567]), DFO/DFP (WMD = −406 [−756, −55]), and DFO/Silymarin (WMD = −1164 [−2001, −327])
  - Similarly, DFP/Silymarin was observed with lower serum ferritin levels than DFP {WMD = −271 [−356, −185]), DFX/Silymarin was associated with better serum ferritin levels than DFX (−728 [−1003, −453]) and DFO (WMD = −596 [−1156, −35]). DFO/DFP with better serum ferritin levels than DFX (WMD = −958 [−1751, −166]).

- Secondary endpoints:
  - The direct comparison pooled estimates revealed significantly lower serum ferritin levels with DFP/DFO compared to DFO (WMD = −826 [−1450, −201.7).
  - MTC estimates for the secondary outcome measures were compared against DFO for all other interventions. DFX/DFO was associated with lower LIC than DFO but DFO was observed with better LIC than DFO/Silymarin. LVEF was significantly better with DFO/DFP and DFO/DFP sequential therapy than DFO alone.
  - In addition, DFO/DFP was observed with lower adverse event rates compared to DFO. Due to clinical heterogeneity and lack of appropriate clinical trials, pooled estimates could not be generated for differences in the cardiac iron status between the interventions.

Anmerkung/Fazit der Autoren

To conclude, we have generated pooled estimates through both MTCs between various iron chelators. However, evaluation of combined chelator therapy has largely been experimental so far and more caution should be placed with the interpretation of this meta-analysis. The results might change with the advent of randomized clinical trials in the future.

Kommentare zum Review

- no literature from EMBASE
- although the effect on serum ferritin has been considered as the primary outcome, it is also an acute phase reactant; dose differences between the interventions were not analyzed;
- effect of chelator on the cardiac iron status could not be analyzed;
- publication bias could not be tested for most of the interventions;
- Risk of bias of the large majority of the studies was observed to be high in most of the domains and TSA could not be performed for any other iron chelator except for DFP/DFO-combined therapy.

3.3 Leitlinien

De Sanctis V et al., 2016 [2].

International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A)

The ICET-A Recommendations for the Diagnosis and Management of Disturbances of Glucose Homeostasis in Thalassemia Major Patients.

Leitlinienorganisation/Fragestellung

The International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) planned the current project to formulate recommendations for accurate diagnosis and effective management of abnormalities of glucose homeostasis in patients with TM.

Methodik

Grundlage der Leitlinie

- A group of endocrinologists, haematologists and paediatricians, members of the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) convened to formulate recommendations for the diagnosis and management of abnormalities of glucose homeostasis in thalassemia major patients on the basis of available evidence from clinical and laboratory data and consensus practice.
  - systematic search of PubMed and Google Scholar from May 2006 through September 2016
  - Two chairmen (VDS and ATS) appointed an expert panel of pediatricians, endocrinologists, and haematologists, selected for their expertise in research and the clinical treatment of thalassemia. This advisory committee, chaired by nine clinicians to support the systematic review of the literature and to guarantee the accuracy of the process, suggested the use of a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of the US family medicine and primary care journals (ie, American Family Physician, Family Medicine, Journal of Family Practice, and BMJ USA).
  - Evidence was graded using a 3-point scale based on the quality of methodology (e.g., randomized control trial, case control, prospective/retrospective cohort, case series, etc.) and the overall focus of the study as follows:

    I. Good-quality patient-oriented

    II. Limited-quality patient-oriented evidence

    III. Other evidence, including consensus guidelines, opinion, case studies, or disease oriented evidence.

    The strength of recommendation was ranked as follows:

    A. Recommendation based on consistent and good-quality patient-oriented evidence.

    B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.

    C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

Recommendations

Management of β-Thalassemia Major:

- Current practice is to start chelation therapy after transfusion of 5-10 units of blood (approximately 1-2 gr/Fe), or when the ferritin level rises above 1,000 µg/l. (I,C)
- Serum ferritin has been used to start, formulate and monitor chelation therapy, but it is now known to be an imprecise indicator of total body iron burden since it can yield inappropriate results in the presence of inflammation, abnormal liver function or ascorbate deficiency. Despite these reservations, trends in serum ferritin concentrations serve as a reasonable, cost efficient and readily applicable surrogate marker for the iron load. (I,C)
- LIC estimation using MRI shows excellent correlation with that obtained from liver biopsy and is an accurate method to assess liver iron content and proportional iron stores.(I,A)
- Pancreatic imaging has a potential role in the assessment of iron deposition and for the prediction of the development of glycemic abnormalities. (I,B)
- Prospective data are needed to prove the validity of pancreatic MRI imaging for the assessment of effects of different chelators as well as their doses; more evaluation is required before this measurement can be recommended for routine use. (II,C)

Management of IGT and DM in Thalassemia Major:

- Intensive iron-chelation therapy and prevention and treatment of chronic hepatitis C are now the most important issues in managing impairment of glucose homeostasis in patients with transfusion dependent β-thalassemia. (II,A)
- Management of DM should be individualised.(II,C)
- During initiation of insulin, blood glucose monitoring both pre- and post-prandially as well as at bedtime and overnight may help to determine dosage requirements.(II,A)
- Patients with diabetes who are on insulin should perform self-monitored blood glucose testing at least three times a day.(II,A)
- Continuous glucose monitoring (CGMS) is under investigation as a potential new measure of prandial glucose control, especially in the more difficult cases. (II,A)
- Patients with TM should strive to attain plasma glucose goals as per the ADA recommendations for all people with diabetes.(I,A)
- There is limited published data on the efficacy and safety of oral antidiabetic agents. (II,A)
- Glycated hemoglobin A1c reflects a mean glycemia over the preceding 3 months (erythrocyte life span). In diabetes management, the target value is set below 6.5%, to reduce the risk of chronic complications. However, HbA1c is a poor marker in subjects with diabetes and hemoglopinopathies.(I,A) Fructosamine determination is useful for monitoring diabetes in these patients.(I,A)
- TM women with normal glucose tolerance pre-pregnancy should still be advised that they may develop glucose intolerance later in pregnancy, and that repeat OGTT should be performed at both 12–16 and 24–28 weeks gestation with measures at 0, 1 and 2 h using the specific gestational diabetes criteria.(I,A)
- Women with diabetes who are planning to become pregnant should be informed that establishing good glycaemic control before conception and continuing this throughout pregnancy will reduce the risk of miscarriage, congenital malformation, stillbirth and

neonatal death. It is important to explain that risks can be reduced but not eliminated. (I,A)

- TM women with pre-existing diabetes should have pre-pregnancy counselling and planning to aim for optimal glycemic control before and throughout pregnancy to minimize adverse pregnancy outcomes. (I,A)
- All pregnant patients with DM should regularly be monitored for the development of complications. (I,A)
- Plasma glucose levels should be monitored closely during the peri-partum period and until hospital discharge. (II,C)
- Chelation treatment should be interrupted during pregnancy.(I,C)
- Diabetic patients with TM should regularly be seen by a specialized multidisciplinary team with expertise in both diabetes and TM, including ongoing diabetes self-management education.(I,A) The team should include an endocrinologist and dietician with experience in TM. (I,C)

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 09 of 12, September 2021) am 17.09.2021

#	Suchfrage
1	[mh Thalassemia]
2	*thalass*mi*:ti,ab,kw
3	((mediterranean OR cooley OR erythroblastic) AND an*mia*):ti,ab,kw
4	{OR #1-#3}
5	#4 with Cochrane Library publication date from Sep 2016 to present

Systematic Reviews in Medline (PubMed) am 17.09.2021

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	Thalassemia[mh]
2	thalassemi*[tiab] OR thalassaemi*[tiab]
3	(mediterranean[tiab] OR cooley[tiab] OR erythroblastic[tiab]) AND (anemi*[tiab] OR anaemi*[tiab])
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw]

#	Suchfrage
	OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	((#5) AND ("2016/09/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 17.09.2021

verwendete Suchfilter ohne Änderung:

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

#	Suchfrage
1	Thalassemia[mh]
2	thalassemi*[tiab] OR thalassaemi*[tiab]
3	(mediterranean[tiab] OR cooley[tiab] OR erythroblastic[tiab]) AND (anemi*[tiab] OR anaemi*[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 ("2016/09/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.09.2021

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

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

- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

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

Referenzen

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A **Rethlefsen M, Kirtley S, Waffenschmidt S, Aula AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMAStatement for Reporting Literature Searches in Systematic Reviews. BMC 2021; 10:39. https://doi.org/10.1186/s13643-020-01542-z

B **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-6. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO