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-051 Avatrombopag

Stand: Mai 2020

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

Avatrombopag **Primäre Immunthrombozytopenie** **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.	Splenektomie
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:	
Avatrombopag ATC-Code Doptelet®	Anwendungsgebiet laut Beratungsanforderung: Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). <u>Inoffizielle Übersetzung:</u> Doptelet ist indiziert zur Behandlung der primären chronischen Immunthrombozytopenie (ITP) bei erwachsenen Patienten, die gegenüber anderen Behandlungen (z.B. Kortikosteroide, Immunglobuline) refraktär sind.
Kortikosteroide	
Dexamethason H02AB02 Dexamethason JENAPHARM® Generisch	– […] – Orale Anfangsbehandlung von **Autoimmunerkrankungen**, wie systemischer Lupus erythematodes (insbesondere viszerale Formen), – […] (FI Stand September 2019)
Prednisolon H02AB06 Prednisolon JENAPHARM® Generisch	[…] angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad […] <u>Hämatologie/Onkologie:</u> – autoimmunhämolytische Anämie, Idiopathische thrombozytopenische Purpura (Morbus Werlhof), akute intermittierende Thrombozytopenie – […] (FI Stand Juni 2018)
Methylprednisolon H02AB04 Methylprednisolon JENAPHARM® Generisch	Erkrankungen, die einer systemischen Therapie mit Glukokortikoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad zum Beispiel: […] <u>Blutkrankheiten/Tumorerkrankungen</u> – Autoimmunhämolytische Anämie (FI Stand August 2019)
Prednison	[…] angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach

II. Zugelassene Arzneimittel im Anwendungsgebiet	
H02AB07 Prednison acis® Generisch	Erscheinungsform und Schweregrad […] <u>Hämatologie/Onkologie:</u> – autoimmunhämolytische Anämie, Idiopathische thrombozytopenische Purpura (Morbus Werlhof), akute intermittierende Thrombozytopenie – […] (FI Stand August 2017)
Weitere Wirkstoffe	
Immunoglobuline J06BA02 Flebogamma DIF®	[…] <u>Immunmodulation bei Erwachsenen, Kindern und Jugendlichen (2 – 18 Jahre) bei:</u> – Primärer Immunthrombozytopenie (ITP) bei Patienten mit hohem Blutungsrisiko oder vor Operationen zur Korrektur der Thrombozytenzahl. (FI Stand Juli 2019)
Humanes Thrombozyten-konzentrat	Die Gabe von Thrombozytenkonzentraten ist indiziert zur Behandlung einer Blutungsneigung, bedingt durch eine schwere Thrombozytopenie infolge thrombozytärer Bildungsstörungen, im Notfall auch bei Umsatzstörungen, jedoch nicht bei einer niedrigen Thrombozytenzahl allein. Damit durch die Zufuhr von Plättchen eine Besserung der thrombozytär bedingten Blutungsneigung zu erwarten ist, sollte vor der Behandlung zunächst deren Ursache abgeklärt werden. (FI Stand September 2013)
Eltrombopag B02BX05 Revolade®	Revolade ist für die Behandlung von Patienten im Alter von 1 Jahr und älter mit primärer Immunthrombozytopenie (ITP) indiziert, wenn diese 6 Monate oder länger nach Diagnosestellung andauert und die Patienten gegenüber anderen Therapien refraktär sind (z. B. Kortikosteroide, Immunglobuline) (siehe Abschnitte 4.2 und 5.1). (FI Stand Februar 2019)
Romiplostim B02BX04 Nplate®	Nplate ist für die Behandlung von Patienten mit chronischer immun-(idiopathischer) thrombozytopenischer Purpura (ITP) im Alter von 1 Jahr oder älter indiziert, die gegenüber anderen Therapien refraktär sind (z. B. Kortikosteroide, Immunglobuline; siehe Abschnitte 4.2 und 5.1) (FI Stand Januar 2018)
Azathioprin L04 AX01 Azathioprin dura® generisch	[…] Azathioprin ist angezeigt in schweren Fällen der folgenden Erkrankungen bei Patienten, die Kortikosteroide nicht vertragen oder Steroid-abhängig sind und bei denen trotz hoher Dosen von Kortikosteroiden keine ausreichende therapeutische Wirkung erzielt werden kann: […] – chronisch refraktäre idiopathische thrombozytopenische Purpura […] (FI Stand November 2019)
Fostamatinib B02BX09 Tavlesse®	Tavlesse is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1).

II. Zugelassene Arzneimittel im Anwendungsgebiet	

Quellen: AMIS-Datenbank, Fachinformationen (Stand: April 2020)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-051 (Avatrombopag)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	19. März 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DXM	Dexamethasone monotherapy
ELT	Eltrombopag
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ITP	Immunthrombozytopenie
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	Odds Ratio
rhTPO	human thrombopoietin
RTX	Rituximab
ROM	Romiplostim
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TPO-RAs	Thrombopoietin-receptor agonists
WHO	World Health Organization

1 Indikation

Behandlung der primären chronischen Immunthrombozytopenie (ITP) bei erwachsenen Patienten, die gegenüber anderen Behandlungen (z.B. Kortikosteroide, Immunglobuline) refraktär sind.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Immunthrombozytopenie* durchgeführt. 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, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 19.05.2019 durchgeführt, die Folgerecherche am 02.03.2020. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 310 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 7 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

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3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es liegen keine Beschlüsse vor.

3.2 Cochrane Reviews

Es konnten keine relevanten CR im vorliegenden AWG identifiziert werden.

3.3 Systematische Reviews

Elgebaly AS et al., 2017 [2].

Tolerability and efficacy of eltrombopag in chronic immune thrombocytopenia: meta-analysis of randomized controlled trials

Fragestellung

The aim of this meta-analysis is to synthesize evidence from published randomized controlled trials (RCTs) about the safety and efficacy ofeltrombopag for both adult and children with ITP.

Methodik

Population:

- patients having chronic ITP

Intervention:

- Eltrombopag

Komparator:

- Placebo

Endpunkte:

- overall platelet response defined as platelet counts of at least 50 x 109/L in the absence of rescue therapy, incidence of significant bleeding (WHO grades II-IV) according to WHO bleeding scale, incidence of any bleeding (WHO grades I-IV), number of cases needed to rescue treatment, and adverse events

Recherche/Suchzeitraum:

- PubMed, Scopus, Web of Science, and Cochrane Central
- Zeitraum: k.A.

Qualitätsbewertung der Studien:

- The quality of the retrieved RCTs was assessed according to Cochrane Handbook of Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs (N=611 patients)

Charakteristika der Population:

- population was patients (adults or children) with a clinical diagnosis of chronic ITP and a platelet count less than 30 x 10^9/L

Qualität der Studien:

- The quality of the included studies was from moderate to high quality according to the Cochrane risk of bias assessment tool.

Studienergebnisse:

- Efficacy analysis.
  - Overall effect estimate favored eltrombopag group in terms of the overall platelet response (RR = 3.42; 95% CI [2.51-4.65]; P < .0001), pooled studies were homogenous (I^2 = 22%; P = .27);
  - incidence of significant bleeding (WHO grades II-IV; RR = 0.56; 95% CI: 0.41-0.77; P = .0004), pooled studies were homogenous (I^2 = 0%; P = .40);
  - number of cases needed to rescue treatment (RR = 0.45; 95% CI: 0.32-0.65; P < .0001), pooled studies were homogenous (I^2 = 38%; P = .20);
  - incidence of any bleeding (RR = 0.74; 95% CI: 0.66-0.83; P < .00001); I^2 = 0%; P = .48
- adverse events
  - total number of adverse events reported in both groups did not differ significantly; the frequency of adverse events was not higher in the eltrombopag group when compared to placebo (RR: 0.95; 95% CI [0.871.05]; P = .32).
  - Thromboembolic events: Among the 6 included studies, only RAISE and Tomiyama et al studies reported the occurrence of thromboembolic events in eltrombopag group, 2% and 7% (1 patient), respectively. All remaining studies stated that no thromboembolic events were recorded during the course of the study.

Anmerkung/Fazit der Autoren

Eltrombopag is a tolerable and effective drug for the management of chronic ITP in children and adults.

Kommentare zum Review

Patientenpopulation: Kinder und Erwachsene eingeschlossen

Zhang J et al., 2018 [7].

Eltrombopag versus romiplostim in treatment of adult patients with immune thrombocytopenia: a systematic review incorporating an indirect-comparison meta-analysis

Fragestellung

Therefore, this study aims to evaluate the efficacy and safety of ELT versus ROM for adultpatients with ITP using an indirect-comparison meta-analysis.

Methodik

Population:

- Participants were adult (≥ 18 years) with ITP

Intervention:

- thrombopoietin-receptor agonists (ELT or ROM irrespective of dosage and schedule)

Komparator:

- placebo

Endpunkte:

- overall platelet response (primary outcome), defined as achieving at least once platelet response (≥ 50×109/L) during treatment; incidence of overall and serious adverse events (SAEs); durable platelet response, defined as maintaining platelet counts ≥ 50×109/L for at least 60% ofthe duration of TPO-RAs treatment or for six or more weeks during the final eight weeks of TPO-RAs treatment; incidence of clinically significant bleeding (WHO Grade 2–4 or rated as severe, life threatening, or fatal); all bleeding events; and proportion of patients who received rescue treatment

Recherche/Suchzeitraum:

- PubMed, Embase and Cochrane Library, Clinical Trials.gov, China National Knowledge Infrastructure, and Chinese Biomedical Literature Database
- earliest records to May 2017

Qualitätsbewertung der Studien:

- checklist developed by Cochrane Collaboration

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs (786 participants)

Charakteristika der Population:

- All patients were aged ≥18 years old, with disease duration more than 3 months and baseline platelet count less than 30×109/L.

Qualität der Studien:

- seven studies had low risk ofselection bias for central randomization while the other two was unclear because the method ofrandomization and allocation concealment were not reported
- All studies had low risk of performance bias and detection bias, as both patients and study personnel were masked.
- All studies had low risk ofattrition bias, as there was no loss to follow-up or the missing data were dealt with properly (e.g. applying ITT analysis which underestimated the efficacy of the medication).
- All studies had low risk ofreporting bias since they were registered in ClinicalTrials. gov and had reported all predesigned outcomes.
- Considering all studies supported by pharmaceutical industry, the bias caused by conflict of interest was unclear.

Studienergebnisse:

- Five studies (606 patients) evaluated the efficacy and safety of ELT in comparison to placebo
- Four studies (180 patients) evaluated the efficacy and safety of ROM

- Overall platelet response
  - was reported in all studies (five for ELT and four for ROM) including 785 patients (ITT).
  - the heterogeneity was not statistically significant (I^2 = 32%, P = 0.21 and I^2 = 4%, P = 0.37, respectively).
  - The pooled results with a fixed-effect model showed that proportion of patients achieving overall response was significantly higher in the TPO-RAs group than in the placebo group (RR = 4.07, 95%CI: 2.91–5.70 for ELT and RR = 8.81, 95%CI: 4.01–19.35 for ROM, respectively).
  - However, the result of indirect comparison indicated that the overall response between ELT and ROM was not significantly different (RR = 0.59, 95%CI: 0.24–1.45).
- Safety
  - Eight studies (764 participants) reported the overall incidence of any AEs reported in patients receiving TPO-RAs or placebo.
  - The pooled analysis showed that the incidence was not significantly different between two groups (RR = 1.05, 95%CI: 0.84–1.32 for ELT and RR = 1.05, 95%CI: 0.97–1.14 for ROM).
  - And the result of indirect comparison also showed that the overall incidence ofany AEs in ELT group was similar to that in ROM group (RR = 0.98, 95%CI: 0.79–1.21).

Anmerkung/Fazit der Autoren

Eltrombopag and romiplostim might be equivalent in efficacy and safety for adult ITP, however, physicians should still take into account drug cost and comorbidities of the specific patient while making decisions on the treatment of ITP with TPO-RAs.

Wang J et al., 2018 [6].

Efficacy and safety of the combination treatment of rituximab and dexamethasone for adults with primary immune thrombocytopenia (ITP): a meta-analysis

Fragestellung

To conduct a meta-analysis, assessing the efficacy and safety of the combination treatment of dexamethasone and rituximab for adults with ITP (primary immune thrombocytopenia).

Methodik

Population:

- patients with ITP

Intervention:

- rituximab and dexamethasone combination treatment (RTX+DXM)

Komparator:

- dexamethasone monotherapy (DXM)

Endpunkte:

- OR (overall response) rate, CR (complete response) rate, PR (partial response) rate, SR (sustained response) rate, R (relapse) rate, change in Treg cell count (mean [SD]), and AE (adverse event)

Recherche/Suchzeitraum:

- Pubmed, Embase, Cochrane, China National Knowledge (CNKI), Wanfang database, and Sino Med.
- Suchzeitraum: k.A.

Qualitätsbewertung der Studien:

- GRADE pro scale (Grading of Recommendations Assessment, Development and Evaluation) was used to assess the quality of the evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs

Charakteristika der Population:

- Participants <18 years old.

Qualität der Studien:

- None of the 11 trials was stopped early or funded by industry.
- Adequate randomization was reported by all of the selected trials, with only three trials specifying the randommethod.
- A total of 19 outcomes were assessed by GRADE pro software, ofwhich 32% (6/19) was scaled as high level, 47% (9/19) was moderate level, and 21% (4/19) was low level

Studienergebnisse:

- Overall Response Rate
  - The comparison of OR rate at week 4 was conducted in six trials (n=435).
  - OR rate was significantly higher in combination arm than that in monotherapy arm (RR=1.23, 95% CI: 1.03-1.48, and P=0.03).
  - However, high heterogeneity was found in pooled analysis (P=0.01, I^2=65%)
- Complete Response Rate
  - Six studies (n=435) reported the CR rate at week 4 without significant heterogeneity (P=0.10, I^2=45%).
  - Pooled analysis by using a Fixed-effect model showed that CR rate at week 4 in combination arm was significantly higher than that in monotherapy arm (RR=2.06, 95% CI: 1.63-2.62, and P<0.00001)
- Partial Response Rate
  - PR rate at week 4 was reported by six studies (n=435), pooled analysis of which turned out homogenous (P=0.27, I^2=22%).

  - Analysis conducted by a Fixed-effect model showed that PR rate at week 4 in monotherapy arm was significantly higher than that in combination arm (RR=0.66, 95% CI: 0.49-0.88, P=0.005)
- Sustained Response Rate
  - SR rate at month 6 (n=296) and month 12 (n=274) was reported by three studies, respectively, both of which showed no significant heterogeneity (P=0.76, I2=0%; P=0.15, I^2=47%).
- Safety Profile
  - Only three trials (n=286) reported serious AE. Through a Fixed-effect method, no heterogeneity was observed (P=0.67, I^2=0%), and no significant difference was found either (RR=1.93, 95% CI: 1.00-3.71, and P=0.05)

Anmerkung/Fazit der Autoren

Dexamethasone combined with rituximab can provide a better long-term response in the treatment of adults with ITP and will not increase the risk of adverse effects.

Kommentare zum Review

Zulassung: Rituximab off label

Arai Y et al., 2017 [1].

Efficacy of Dexamethasone for Acute Primary Immune Thrombocytopenia Compared to Prednisolone: A Systematic Review and Meta-analysis

Fragestellung

We conducted a systematic review and meta-analysis, and evaluated the efficacy (long-term SR, short-term overall response [OR], and relapse) and safety (short- and long-term adverse events) of Dex compared with PSL as an initial therapy for ITP.

Methodik

Population:

- patients with acute primary ITP

Intervention:

- Dexamethasone

Komparator:

- Prednisolone

Endpunkte:

- The primary outcome was the incidence of SR (platelet count [Plt] > 30 x 109/L for 6 months without concomitant treatments after thecompletionofthefinal therapy);

- the secondary outcomes included the OR (Plt > 30 x 10^9/L) and complete response (CR; Plt > 100 x 109/L) at an early time point (on day 14 or 28 of the first therapy), relapse after therapy (loss of response or bleeding episodes), and the incidence of adverse effects.

Recherche/Suchzeitraum:

- MEDLINE (via PubMed) (1950 to January 2017) and Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2016, Issue 12)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs totaling 704 patients with acute primary ITP

Charakteristika der Population:

- All the RCTs included only adult patients; children younger than 16 years were not included.
- The median age of the participants ranged from24 to 46 years.
- one study included relapsed ITP cases (5 out of 36 cases), and in the other study 3 patients (out of total 22 patients) were secondary ITP due to lymphoid malignancy.
- Secondary thrombocytopenia patients due to hepatitis viral infection, systemic lupus erythematosus, and pregnancy were clearly excluded in these RCTs.

Qualität der Studien:

- All the studies lacked sufficient blinding of participants and personnel (classified as “high risk”), which can work as a potential bias to the intervention group (Dex arm).

Studienergebnisse:

- Sustained Response
  - Seven RCTs with 668 patients presented data on SR. One study14 defined SRas Plt > 50 x 10^9/L, and the RR shownin this study was integrated in our analysis as it was.
  - The pooled results demonstrated no significant difference between the two arms (RR, 1.13; 95% CI, 0.94–1.36; p = 0.21)
  - This tendency was the same if analyzed with the random-effects model (RR, 1.23; 95% CI, 0.84–1.79; p = 0.28).
  - Subgroup analyses showed that four studies using Dex with posttherapy (two or more courses of Dex in all patients irrespective of the initial response, or Dex administration followed by consolidation and/or tapered corticosteroid therapy)6,7,13,14 showed a significantly higher incidence of SR compared with that of the PSL arm (N ¼ 231; RR, 1.82; 95% CI, 1.38–2.41; p < 0.01;

- Early Overall Response and Complete Response
  - Data regarding the incidence of early OR were extracted from all eight studies, including a total of 704 patients.

- The pooled results indicated that Dex significantly increased early OR (RR, 1.11;95% CI, 1.01–1.22; p = 0.03). The random-effects model indicated the same tendency (RR, 1.19; 95% CI 1.04– 1.37; p = 0.01).

- Relapse
  - Time-to-event data were not available except for one study.14 In each study, relapse was defined as the loss of response or the appearance of bleeding episodes, and the judgement of relapse was not related to whether the secondary therapeutic intervention was initiated or not.

Anmerkung/Fazit der Autoren

Use of Dex with posttherapy instead of PSL may be more beneficial as the initial therapy. Studies comparing Dex with other new strategies are essential to determine the most suitable therapeutic regimens for acute ITP.

Kommentare zum Review

- Die eingeschlossenen Studien wurden hauptsächlich in asiatischen Ländern (China, Korea und Thailand) sowie im Iran und in Deutschland durchgeführt und zwischen 2009 und 2016 veröffentlicht.

Puavilai T et al., 2020 [5].

Treatment efficacy for adult persistent immune thrombocytopenia: a systematic review and network meta-analysis

Fragestellung

Persistent immune thrombocytopenia (ITP) patients require second-line treatments, for which information on clinical outcomes are lacking. A systematic review and network meta-analysis (NMA) were conducted.

Methodik

Population:

- patients with newly diagnosed, relapsed and persistent ITP

Intervention/ Komparator:

- TPORA monotherapy (i.e., recombinant human thrombopoietin (rhTPO), eltrombopag and romiplostim), monoclonal antibody (rituximab), immunosuppressive agents (i.e., azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, vincristine and vinblastine), or combination(s) of the aforementioned monotherapies.

Endpunkte:

- The primary outcome of interest was platelet response, i.e., achievement of platelet count ≥30 9 10^9/l or ≥50 9 10^9/l, as originally defined by each study, at 4–6 weeks after receiving second-line treatment.

- The 3 secondary outcomes were quantitative platelet count at 6 weeks after treatment, any bleeding and composite SAEs, including death, thrombosis (i.e., occurrence of arterial/venous occlusion), and serious infection (i.e., grade 3–4)

Recherche/Suchzeitraum:

- Studies were identified from MEDLINE (via PubMed) and Scopus databases. The search was performed up to 21 September 2018

Qualitätsbewertung der Studien:

- risk of bias was assessed using the Cochrane Collaboration's tool for RCTs (Higgins et al, 2011).
- Each item was graded as "low risk" or "high risk"; if there was insufficient information to judge, it was classified as "unclear".

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies (sample sizes ranging from 21 to 234)

Charakteristika der Population:

- adult persistent ITP patients (failing initial treatment within 3–12 months or longer)

Qualität der Studien:

- Most items were assessed as unclear because of insufficient information including random sequence generation (57,1%), allocation concealment (57,1%), blinding (85,7%) and other sources of bias (57,1%). However, all studies were judged low risk for selective outcome reporting.

Studienergebnisse:

- All studies were two-arm comparisons:
  - 5 studies for for eltrombopag versus placebo
  - 4 studies for romiplostim versus placebo
  - 2 studies for rituximab versus placebo
  - 1 study for rhTPO+ciclosporin versus rhTPO
  - 1 study for for rhTPO+rituximab versus rituximab
  - 1 study for for rhTPO+danazol versus danazol

Efficacy

- Platelet response
  - Fourteen studies reported platelet response as an outcome.
  - Two studies comparing rhTPO+danazol versus danazol and rhTPO+ciclosporin versus rhTPO were disconnected from other comparisons, and were therefore excluded from the network.
  - A network map was constructed for 12 studies (1313 subjects) consisting of 4 direct comparisons among 5 treatments (Fig 2A)
  - Among them, 11 studies used a platelet cut-off of 50 x 10^9/l, but 1 study (Arnold et al, 2012) used a platelet cut-off of 30 9 10^9/l.

- For all relative treatment comparisons (Table II, above diagonal line), eltrombopag and romiplostin provided the most effective outcomes compared with placebo, with the former having a slight (non-significant) advantage in terms of platelet response [RR = 1,10 (0,46; 2,67)].
- Both eltrombopag and romiplostim were significantly more effective than rituximab and rhTPO+rituximab with corresponding pooled RRs of 4,56 (1,89; 10,96) and 4,18 (1,21; 14,49) for eltrombopag; 4,13 (1,56; 10,94) and 3,79 (1,02; 14,09) for romiplostim. Eltrombopag was ranked as the best treatment for platelet response according to its SUCRA of 89,6, followed by romiplostim, rhTPO+rituximab, placebo and rituximab, respectively (Table III).
- There was no evidence of inconsistency effects (global v2 = 0,04, P = 0,850) or publication bias for platelet response

- Platelet response
  - Twelve studies reported platelet count as an outcome with 1301 subjects, which included 4 direct comparisons among 5 treatments (Fig 2B).
  - All possible pairwise comparisons were made (Table II, below diagonal line), indicating that romiplostim produced the most effective platelet count compared to placebo, followed by eltrombopag, rhTPO+rituximab and rituximab with pooled USMD of 81,66 x 10^9/l (49,63; 113,69), 53,79 x 10^9/l (28,27; 79,32), 49,11 x 10^9/l (-19,80, 118,01) and 26,87 x 10^9/l (-17,67; 71,40), respectively.
  - In 6 comparisons, none of the active drugs were statistically significantly associated with platelet count outcome.
  - Romiplostim ranked as the best treatment for platelet count (SUCRA = 92,8), followed by eltrombopag, rhTPO+rituximab, and rituximab, respectively (Table III).
  - There was no evidence of inconsistency effects (global v2 = 0,69, P = 0,407). There was evidence of publication bias for platelet count
- Any bleeding
  - Nine studies reported any bleeding outcome.
  - Data from these 9 studies (1042 subjects) included 3 direct comparisons among 4 treatments (Fig 2C).
  - All possible pairwise comparisons were made, which indicated that rituximab had the lowest risk for any bleeding when compared to placebo, followed by eltrombopag and romiplostim, with pooled RR of 0,76 (0,49, 1,18), 0,79 (0,65, 096) and 0,82 (0,59, 1,13), respectively.
  - However, all placebo and active controlled comparisons were not statistically significant, except eltrombopag versus placebo (Table IV, above diagonal line).
  - The highest probability of bleeding was found in placebo, followed by romiplostim, eltrombopag, and rituximab, respectively (Table III).
  - There was no evidence of inconsistency effects (global v2 = 0,99, P = 0,319) or publication bias (Figure S5C).

Safety

- Composit SAEs
  - Eleven studies reporting composite SAE outcome were included in the network with 1253 total subjects. These consisted of 4 direct comparisons among 5 treatments (Fig 2D).

- All possible pairwise comparisons were made (Table IV, below diagonal line), and rhTPO+rituximab had the highest risk of composite SAEs when compared to placebo followed by rituximab and eltrombopag with pooled RR of 4,54 (0,10, 210,26), 1,86 (0,17, 19,95) and 1,09 (0,34, 3,45), respectively.
- Romiplostim had the lowest composite SAEs when compared to placebo with a statistically significant pooled RR of 0,39 (0,17, 0,93).
- In addition, the latter 3 active treatments had non-significantly lower risk for composite SAEs than rhTPO+rituximab, with pooled RRs of 0,41 (0,02, 8,34), 0,24 (0,00, 13,11) and 0,09 (0,00, 4,40), respectively.
- The treatment with greatest probability for highest SAEs was rhTPO+rituximab, followed by rituximab, eltrombopag, placebo and romiplostim, respectively (Table III). There was no evidence of inconsistency effects (global v2 = 0,34, P = 0,562) or publication bias

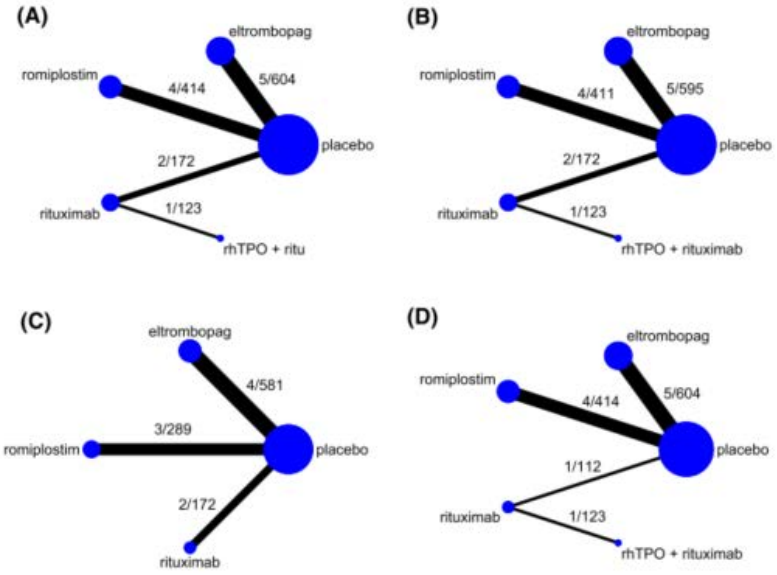

Fig 2. Network map for all outcomes. (A) Platelet response. (B) Platelet count. (C) Any bleeding. (D) Composite serious adverse events. The number of studies and patients, indicated above each line, are depicted by the size of nodes and line thickness, respectively. Ritu, rituximab; rhTPO, recombinant human thrombopoietin. [Colour figure can be viewed at wileyonlinelibrary.com]

Table III. The surface under the cumulative ranking curve and rank of each treatment for platelet response, platelet count, any bleeding and composite serious adverse events outcomes.

	Platelet response		Platelet count		Any bleeding		Composite serious adverse events	
Treatment	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Placebo	26·2	4	5·1	5	92·7	1	48·3	4
Eltrombopag	89·6	1	62·8	2	32·8	3	51·4	3
Romiplostim	84·5	2	92·8	1	42·2	2	8·1	5
Rituximab	20·8	5	32·8	4	32·3	4	62·6	2
rhTPO+rituximab	28·8	3	56·5	3	–	–	79·6	1

rhTPO, recombinant human thrombopoietin; SUCRA, surface under the cumulative ranking curve.

Anmerkung/Fazit der Autoren

In conclusion, romiplostim and eltrombopag may yield high efficacy and safety. Rituximab may not be beneficial due to lower efficacy and higher complications compared with the thrombopoietin receptor agonists. RCTs with long-term clinical outcomes are required.

Kommentare zum Review

3.4 Leitlinien

Neunert C et al., 2019 [3].

American Society of Hematology 2019 guidelines for immune thrombocytopenia

Leitlinienorganisation/Fragestellung

These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about the management of ITP.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; ASH formed a multidisciplinary guideline panel that included 8 adult clinical experts, 5 pediatric clinical experts, 2 methodologists with expertise in ITP, and 2 patient representatives.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; The panel was balanced to minimize potential bias from conflicts of interest.
- Systematische Suche, Auswahl und Bewertung der Evidenz; The panel reviewed the ASH 2011 guideline recommendations and prioritized questions.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including evidence-to-decision frameworks, to appraise evidence (up to May 2017) and formulate recommendations.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- systematic reviews of the literature that were updated or performed for these guidelines.
- To ensure that recent studies were not missed, searches (presented in supplemental File 5) were updated in May of 2017, and panel members were asked to suggest any studies that may have been considered missed and fulfilled the inclusion criteria for the individual questions.

LoE / GoR

- The strength of a recommendation is expressed as either strong (“the guideline panel recommends…”) or conditional (“the guideline panel suggests…”) and has the following interpretation:
- Strong recommendation
  - For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not.

  - For clinicians: Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
  - For policy makers: The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
  - For researchers: The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.
- Conditional recommendation
  - For patients: The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
  - For clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
  - For policy makers: Policy-making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
  - For researchers: This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related
- Interpretation of good practice statements
  - As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used.16 Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

<u>Sonstige methodische Hinweise</u>

- The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval was guided by ASH policies and procedures derived from the GIN-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.

Empfehlungen

Management of adults with ITP who are corticosteroid dependent or do not have a response to corticosteroids

ELTROMBOPAG VS ROMIPLOSTIM.

Recommendation 6

In adults with ITP for ≥3 months who are corticosteroid-dependent or unresponsive to corticosteroids and are going to be treated with a TPO-RA, the ASH guideline panel *suggests* either eltrombopag or romiplostim (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark**: Individual patient preference may place higher value on use of a daily oral medication or weekly subcutaneous injection.

SUMMARY OF EVIDENCE. We included all systematic reviews and RCTs comparing eltrombopag and romiplostim in adults with ITP. We found no studies that directly compared eltrombopag and romiplostim in this population; thus, eltrombopag and romiplostim represent different populations. We found 1 systematic review (and update) that indirectly compared eltrombopag and romiplostim; this review reported on durable response.[68,69] A second systematic review[70] compared romiplostim vs placebo and eltrombopag vs placebo for the outcomes of major bleeding and reduction or discontinuation of corticosteroids. No studies reported on overall HRQoL. The EtD framework is shown online at https://guidelines.gradepro.org/profile/D6D75FC4-6FBA-93B5-AFD38C23FC90D98E.

SECOND-LINE THERAPIES: SPLENECTOMY, TPO-RA, AND RITUXIMAB COMPARED 1 AGAINST THE OTHER.

Recommendation 7

In adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel *suggests* either splenectomy or a TPO-RA (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 8

In adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel *suggests* rituximab rather than splenectomy (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 9

In adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel *suggests* a TPO-RA rather than rituximab (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). **Remark:** These recommendations are the result of dichotomous evaluation of treatments that are often being considered simultaneously. Each of these second-line treatments may be effective therapy and therefore the choice of treatment should be individualized based on duration of ITP, frequency of bleeding episodes requiring hospitalization or rescue medication, comorbidities, age of the patient, medication adherence, medical and social support networks, patient values and preferences, cost, and availability. Patient education and shared decision-making are encouraged. If possible, splenectomy should be delayed for at least 1 year after diagnosis because of the potential for spontaneous remission in the first year. Patients who value avoidance of long-term medication may prefer splenectomy or rituximab. Patients who wish to avoid surgery may prefer a TPO-RA or rituximab. Patients who place a high value on achieving a durable response may prefer splenectomy or TPO-RAs.

Good practice statement

The treating physician should ensure that patients have appropriate immunizations prior to splenectomy and that they receive counseling regarding antibiotic prophylaxis following splenectomy. The treating physician should educate the patient on prompt recognition and management of fever and refer to current recommendations on pre- and postsplenectomy care.

SUMMARY OF EVIDENCE. We included all RCTs and all observational studies that had internal comparators. Due to the scarcity of RCTs for these questions, we also included all single-arm prospective studies of ≥50 adults with ITP who were treated with splenectomy, TPO-RAs, or rituximab. For splenectomy only, we included a systematic review published in 2004 and all retrospective studies of ≥100 patients published after 2004 due to the lack of prospective studies. We did not identify any RCTs directly comparing splenectomy, TPO-RAs, or rituximab with 1 another; thus, splenectomy, TPO-RAs, and rituximab arms represent different populations. Two retrospective cohort studies compared rituximab with splenectomy.77,78 Regarding splenectomy, we identified 1 systematic review,79 10 additional retrospective studies,80-89 and 1 prospective study.90 Ten studies reported data on response at 1 month,79-88 1 study reported on durable response,80 6 studies reported on remission,79,83,85,86,89,90 8reported on major bleeding,80-87 8 studies reported on infection,80-87 8studies reported on thrombosis,80-87 9 studies reported on operative complications,79,81-83,85-87,89,91,92
and 0 studies reported on
overall HRQoL for patients receiving splenectomy. Two additional retrospective comparisons of splenectomy with rituximab also provided data on remission.77,78 With respect to TPO-RAs, we identified 9 RCTs73,74,93-99 (TPO-RA vs a comparator other than rituximab or splenectomy). All 9 studies reported data on response within 1 month,73,74,93-99 3 studies reported on durable response,73,74,99 0 studies reported on remission, 7 studies reported on major bleeding,73,74,93-96,99 3 studies reported on infection,73,94,95 8 studies reported on thrombosis,73,74,93,95-99 and 3 reported on overall HRQoL74,95,99 for patients receiving TPO-RAs. Regarding rituximab, we identified 2 RCTs67,100 (rituximab vs comparator besides splenectomy or TPO-RA), 2 single-arm phase 2 studies,101,102 1prospective study,103 and 1 prospective registry study.104 Five studies reported data on response within 1month,67,100,102-104 3 studies reported on durable response,100,102,103 5 studies reported on remission,100-104 6 studies reported on infection,67,100-104 4 studies reported on major bleeding,67,100,102,104 2 studies reported on thrombosis,67,100 and 0 studies reported data on overall HRQoL for patients receiving rituximab. Two additional retrospective comparisons of splenectomy with rituximab also provided data on remission.77,78 The EtD framework for splenectomy compared with TPO-RAs is shown online at https://guidelines.gradepro.org/profile/6647F4D9-028E-C88F-9AF27697D58AB301. The EtD framework for splenectomy compared with rituximab is shown online at https://guidelines.gradepro.org/ profile/6ED06816-4D2A-3FA9-8A34-EC148BC0F509. The EtD framework for rituximab compared with TPO-RAs is shown online at https://guidelines.gradepro.org/profile/F6795F46-991E-E43A99FA-95F588C70354.

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Provan D et al., 2019 [4].

Updated international consensus report on the investigation and management of primary immune thrombocytopenia

Leitlinienorganisation/Fragestellung

The final document provides consensus recommendations on the diagnosis and management of ITP in adults, during pregnancy, and in children, as well as quality of-life considerations.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; The panel included 22 members with recognized clinical and research expertise in ITP representing North America (United States, 4; Canada, 1), Europe (13), Australia (1), China (2), and Japan (1). There were 3 pediatric hematologists and 18 adult hematologists (2 with expertise in obstetric hematology). Two members were experts in clinical trials methodology. There was 1 patient representative.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; Although 100% consensus was not attained on every recommendation, 85% of recommendations achieved 85% agreement within the expert group
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- A literature search of the electronic database PubMed was performed in July 2018.

- The following search terms were used: “immune thrombocytopenic purpura,”“idiopathic thrombocytopenic purpura,”“autoimmune thrombocytopenic purpura,” “autoimmune thrombocytopenia,”“idiopathic thrombocytopenia,” “immune thrombocytopenia,” and “ITP.”
- Corresponding MeSH terms were used, in addition to searching titles and abstracts.

LoE/GoR:

Table 1. Evidence levels

Evidence level	Definition
Ia	Evidence obtained from meta-analysis of RCTs
Ib	Evidence obtained from ≥1 RCT
IIa	Evidence obtained from ≥1 well-designed controlled study without randomization
IIb	Evidence obtained from ≥1 other type of well-designed quasi-experimental study*
III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlated studies, and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

*Refers to a situation in which implementation of an intervention is not under the control of the investigators, but an opportunity exists to evaluate its effect.

Table 2. Grading of evidence

Grade of recommendation	Definition	Level of evidence
A	Requires ≥1 RCT as part of a body of literature of overall good quality and consistency addressing specific recommendation	Evidence levels Ia, Ib
B	Requires the availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation	Evidence levels IIa, IIb, III
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.	Evidence level IV

Adapted from the National Guidelines Clearinghouse (www.guideline.gov).

Sonstige methodische Hinweise

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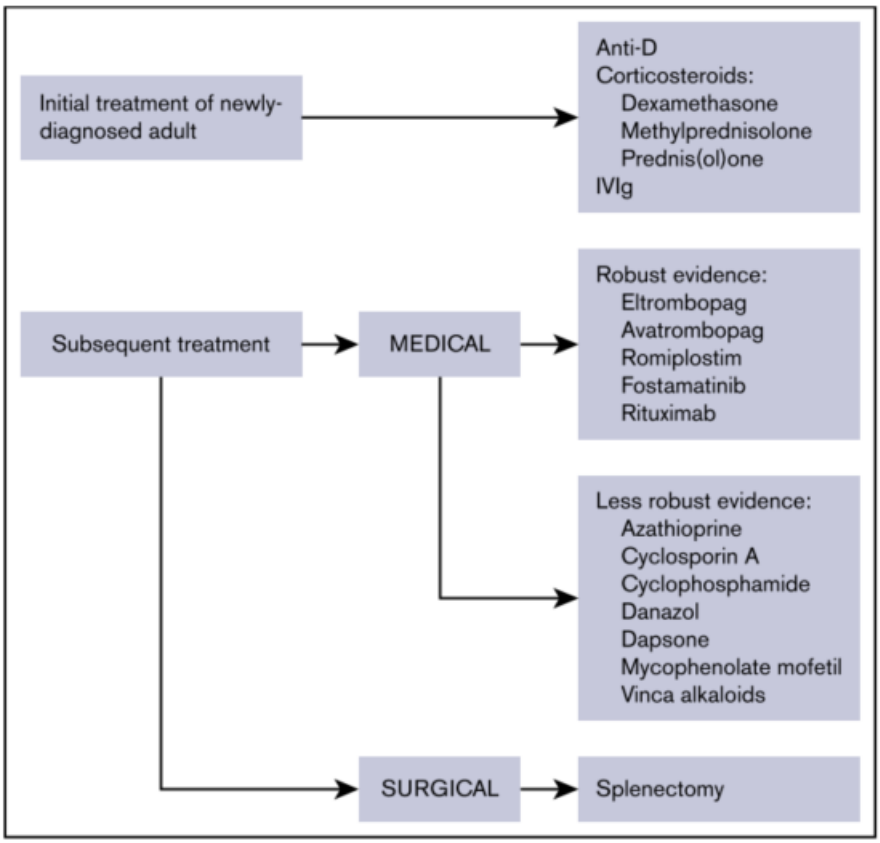
Empfehlungen



Goals of therapy

Recommendations for treatment goals

1. Treatment goals should be individualized to the patient and the phase of the disease.

2. Treatment should prevent severe bleeding episodes. 3. Treatment should maintain a target platelet level .20-30 3 10^9/L at least for symptomatic patients (because risk for major bleeding increases below this level).

4. Treatment should be with minimal toxicity.

5. Treatment should optimize health-related quality of life (HRQoL).

Subsequent treatment options for adult patients with persistent and chronic ITP - Medical therapies with robust evidence

Recommendation 1 (Grade A recommendation, evidence level Ib):

1. TPO-RAs (eltrombopag, avatrombopag, romiplostim) have provided excellent responses (.60%) in splenectomized and nonsplenectomized patients (Grade A recommendation, evidence level Ib). Response to continued TPO-RAs persists for up to 6 to 8 years117 and often allows other ITP therapy to be reduced or discontinued. Cessation of treatment will lead to the return of thrombocytopenia in most cases, but some patients (10%-30%) may achieve a durable response after TPO-RAs are tapered and withdrawn.

Recommendation 2 (Grade B recommendation, evidence level IIa and Grade C recommendation, evidence level IV)

2. Evidence from a systematic review of multiple uncontrolled trials and RCTs shows a response to rituximab in 60% of patients. Long-term durable responses occur in 20% to 25% of adult patients (Grade B recommendation, evidence level IIa). Prior to treatment, hepatitis B status should be determined, and vaccination against encapsulated gram-positive bacteria should be given (Grade C recommendation, evidence level IV).

Medical therapies with less robust evidence

Recommendation 3 (Grade B recommendation, evidence level IIa/IIb).

1. Immunosuppressive agents (including mycophenolate mofetil [MMF], cyclosporine A, and azathioprine) may be used in patients failing other therapies. Danazol and dapsone are "corticosteroidsparing" agents that may be particularly useful in some patients (eg, those in whom splenectomy is contraindicated or if other agents are unavailable) (Grade B recommendation, evidence level IIa/IIb).

Recommendations for surgical therapy for persistent and chronic ITP in adults

- Splenectomy is associated with long-term treatment-free remissions. It is recommended to wait ≥12 to 24 months from diagnosis before performing splenectomy because of the chance of remission or stabilization of a platelet count at a hemostatic level (Grade C recommendation).
- When available, indium-labeled autologous platelet scanning may be useful prior to splenectomy to confirm that the spleen is the main site of platelet sequestration (Grade B recommendation).
- Laparoscopic splenectomy is as effective as open splenectomy in terms of response and is more comfortable for the patient (Grade B recommendation).
- Postoperative thromboprophylaxis should be considered in patients undergoing splenectomy as long as the platelet count is >30 to 50 x 10^9/L (Grade C recommendation).
- Splenectomy should be performed by a surgeon experienced in identifying accessory splenic tissue, which is common and should be removed (Grade C recommendation).
- Appropriate vaccination against Streptococcus pneumoniae, Neisseria meningitidis,and Haemophilus influenzae must be provided ≥2 weeks before splenectomy and maintained according to national guidelines; recent treatment (within 6 months) with rituximab may impair vaccination efficacy.
- Patients should be informed of the long-term risks of splenectomy (increased rates of thrombosis, infection, and cancer) and educated to follow advice aimed at mitigating these complications (Grade C recommendation).
- Antibiotic prophylaxis should be given as per national guidelines (Grade C recommendation).

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ELTROMBOPAG. Several studies and 1 meta-analysis on eltrombopag have been published since the previous consensus recommendations. Chronic ITP. Eltrombopag has been well studied in patients with chronic ITP since the previous consensus recommendations.142-152

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AZATHIOPRINE. Limited published data were found since 2010. A retrospective study assessing treatment patterns in ITP patients in Sri Lanka could not demonstrate a significant response to azathioprine (evidence level III).183 Azathioprine has less of a role in patients who could try a TPO-RA or rituximab (supplemental Table 3).

SPLENECTOMY.

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3.5 Sonstige Quellen ohne systematische Evidenzbasierung

Es konnten keine ergänzenden Dokumente im vorliegenden AWG identifiziert werden.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 3 of 12, March 2020) am 05.03.2020

#	Suchfrage
1	[mh "Purpura, Thrombocytopenic, Idiopathic"]
2	(idiopathic OR immune OR autoimmune OR (auto NEXT immune) OR autoantibod* OR (auto NEXT antibod*) OR primary):ti,ab,kw
3	(thrombocytopeni* OR thrombocytopaeni*):ti,ab,kw
4	(werlhof* OR ITP):ti,ab,kw
5	#1 OR (#2 AND #3) OR #4
6	#5 with Cochrane Library publication date from March 2015 to present

Systematic Reviews in Medline (PubMed) am 05.03.2020

#	Suchfrage
1	purpura, thrombocytopenic, idiopathic[mh]
2	idiopathic[tiab] OR immune[tiab] OR autoimmune[tiab] OR auto-immune[tiab] OR autoantibod*[tiab] OR auto-antibod*[tiab] OR primary[tiab]
3	thrombocytopeni*[tiab] OR thrombocytopaeni*[tiab]
4	werlhof*[tiab] OR ITP[tiab]
5	#1 OR (#2 AND #3) OR #4
6	(#5) 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 studies[pt] OR validation studies[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]))))))
7	((#6) AND ("2015/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am am 05.03.2020

#	**Suchfrage**
1	purpura, thrombocytopenic, idiopathic[mh]
2	idiopathic[tiab] OR immune[tiab] OR autoimmune[tiab] OR auto-immune[tiab] OR autoantibod*[tiab] OR auto-antibod*[tiab] OR primary[tiab]
3	thrombocytopeni*[tiab] OR thrombocytopaeni*[tiab]
4	werlhof*[tiab] OR ITP[tiab]
5	#1 OR (#2 AND #3) OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(((#6) AND ("2015/03/01"[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]))

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