

Efficacy and Safety of Therapeutic Options in Children and Adolescents With Persistent or Chronic Primary Immune Thrombocytopenia: A Systematic Review

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Keywords

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Abstract

Background

Currently, there is no consensus on the treatment of persistent and chronic primary immune thrombocytopenia (ITP) in children. This systematic review evaluates the safety and efficacy of current therapeutic options.

Methods

A comprehensive literature search was performed across MEDLINE/PubMed, Elsevier databases (EMBASE, Scopus), Web of Science (WoS; core collection), and Cochrane (CENTRAL). We included articles published between 1995 and 2026, reporting on safety and/or efficacy of therapies in children and adolescents (<18 years) with persistent or chronic primary ITP.

Results

Ninety-four studies were included. Watchful waiting resulted in a complete remission rate of 14-76%. Of note, thrombopoietin receptor agonists demonstrated the best efficacy/safety balance: acceptable and durable response rates (40-78%) with favourable safety profiles. Splenectomy also yields high complete response rates, but carries a risk of life-threatening complications. Besides, rituximab, sirolimus and mycophenolate mofetil show good efficacy but safety data are scarce. In contrast, first-line therapies (corticosteroids, IVIG and anti-D) provide only short-term benefit whereas cyclosporine A, dapsone and interferon-alpha demonstrate inconsistent efficacy in addition to relevant side effects.

Conclusions

The choice of therapeutic options in paediatric persistent and chronic ITP is extensive. While watchful waiting may be appropriate for many patients, thrombopoietin receptor agonists appear to offer the most favourable efficacy/safety balance when pharmacological treatment is indicated. Long-term safety evaluation and comparative studies focusing on patient-centred outcomes remain warranted.

Introduction

Primary immune thrombocytopenia (ITP) is an acquired, immune-mediated disorder characterized by isolated thrombocytopenia (platelet count < 100 × 10⁹/L), and in contrast to secondary ITP, it is not caused by an underlying disease or medication use (1). The pathogenesis is complex, involving increased platelet destruction and/or impaired production, with contributions from humoral and T-cell-mediated cytotoxicity. Additionally, in some cases the concentration of endogenous thrombopoietin, which stimulates the growth and maturation of megakaryocyte progenitors, is lower than expected (2,3). Acute primary ITP occurs in 2–6 per 100,000 children annually and is usually self-limiting, though thrombocytopenia persists in 15–20% of cases (4-6). In 2009, consensus definitions for the duration of ITP have been established: 'newly diagnosed' (<3 months), 'persistent' (3–12 months) and 'chronic' (>12 months), as well as standardized criteria for treatment response (1). Although rare in

children, major complications such as intracerebral haemorrhage can be life-threatening, with significant mortality rates (2,7–9). Other bleeding events, such as severe epistaxis, gastrointestinal bleeding and menorrhagia, can significantly affect quality of life, limit daily activities and cause psychological stress for patients and families (10). Therefore, ITP treatment aims to prevent severe bleeding episodes and maintain quality of life. However, the management of persistent and chronic ITP remains controversial, as second-line therapies vary in efficacy and safety profiles. Yet, watchful waiting may also be appropriate for some patients. Besides, the current treatment paradigm is shifting from an exclusive focus on the platelet count to clinically relevant endpoints such as bleeding complications and quality of life (11). This systematic review summarizes the safety and efficacy of treatment options for children and adolescents with persistent or chronic ITP, to guide clinical decision-making and optimize outcomes.

Materials and methods

Search strategy and study selection

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. It was registered in the International Prospective Register of Systematic Review (PROSPERO) and can be accessed at <https://www.crd.york.ac.uk/PROSPERO/view/CRD42024574932>.

A systematic search was conducted on September 5th, 2024, in PubMed/MEDLINE, Elsevier databases (EMBASE (<https://www.embase.com>, Scopus), Web of Science (WoS; Core Collection) and Cochrane (CENTRAL). A second search was performed on February 22nd, 2026, to guarantee a complete and up-to-date literature overview. The full search strategy is shown in Supplementary Table 1. Reference lists of relevant articles and reviews were screened manually for additional eligible studies.

We included original human studies (randomized controlled trials (RCTs), cohort studies, case series) published in English between 1995 and February 2026. Editorials and letter-format papers were considered, provided they reported small-scale studies. Eligible studies focused on children and adolescents (<18 years) with primary ITP lasting ≥ 3 months. Studies including both paediatric and adult data were considered only if paediatric results were available separately. We excluded studies limited to adults, those on secondary ITP, case reports or case series with fewer than 3 participants, and studies that did not report efficacy or safety outcomes. All records were imported into the Rayyan review management platform and duplicates were removed by manual screening. Two reviewers independently screened titles and abstracts per predefined criteria, while blinded to each other's decisions. Disagreements were resolved by consensus and/or by discussion with a third reviewer.

Data extraction and analysis

The following data were extracted: a) study details (title, authors, year, design); b) study population (sample size, age, sex, country, previous treatments if any); c) treatment details and outcomes (intervention type, dosage, efficacy, adverse events); d) information relevant to risk-of-bias assessment.

Quality and risk-of-bias assessment

Study quality was assessed using the JBI critical appraisal tool. Each item was rated "Yes", "No" or "Unknown" (insufficiently reported). Quality was expressed as the percentage of "Yes" responses (items 11–13 omitted for RCTs) and categorized as high quality/low risk of bias ($\geq 80\%$), moderate quality/moderate risk of bias (50–79%) or low quality/high risk of bias ($<50\%$). "Not applicable" items were excluded. "No"

and "Unknown" were treated equivalently. Two reviewers independently performed the assessments, resolving discrepancies by discussion or consultation with a third reviewer.

Definitions

We defined complete remission (CR) as platelet count $\geq 100 \times 10^9/L$ and clinically relevant partial remission (PR) as platelet count $\geq 30 \times 10^9/L$. The 2009 International Working Group (IWG) criteria were used to classify ITP duration: persistent (3–12 months) and chronic (>12 months) (1). The precise definitions for each study are provided in Table 1.

Results

Our searches identified 7,644 articles. After removing duplicates and selection based on eligibility criteria, 500 articles were identified for full text reading. Finally, 94 studies were included (Figure 1). A detailed summary of the efficacy and safety outcomes for each therapy is provided in Table 2.

Thrombopoietin-receptor agonists (TPO-RAs)

TPO receptor agonists bind to the c-Mpl receptor on the megakaryocytes, which causes change of the receptor and thus activation of the JAK2/STAT pathway. This increases megakaryocyte proliferation and platelet production, countering immune-mediated peripheral destruction (12).

Our search identified 15 articles studying eltrombopag in 926 patients (5 to 143 per study): 2 RCTs, 11 cohorts and 2 case series (11, 13–26). Two additional articles compared eltrombopag with romiplostim (27,28). Three non-RCTs had a prospective design. We also found 10 studies on romiplostim in 472 patients (4 to 203 per study): 2 RCTs, 5 cohorts and 3 case series (11,29–37). Five of these non-RCTs were prospectively designed (32–35,37). One RCT and 2 retrospective cohort studies examined avatrombopag in 164 children (34 to 75 per study) (38,39,40). Additionally, one retrospective cohort studied hetrombopag in 30 patients with persistent or chronic ITP (41).

Eltrombopag significantly increased the platelet count with 62–75% of patients achieving $>50 \times 10^9/L$ at least once, compared to 3–32% of those on placebo (13,14). The response lasted >6 weeks in 40% of patients (14). Quality of life showed minor improvements, albeit not statistically significant nor clinically relevant (13). Real-world data confirmed overall response rates of 54–89% (CR in 10–45%) (11,15–26). Similarly, 71% of patients treated with romiplostim achieved platelet counts $>50 \times 10^9/L$ at least once versus 20% with placebo. A durable response (≥ 6 weeks) occurred in 52% (30). In the non-RCTs overall response rates were 65–100%, which was durable in 44–78% (31–37). A direct

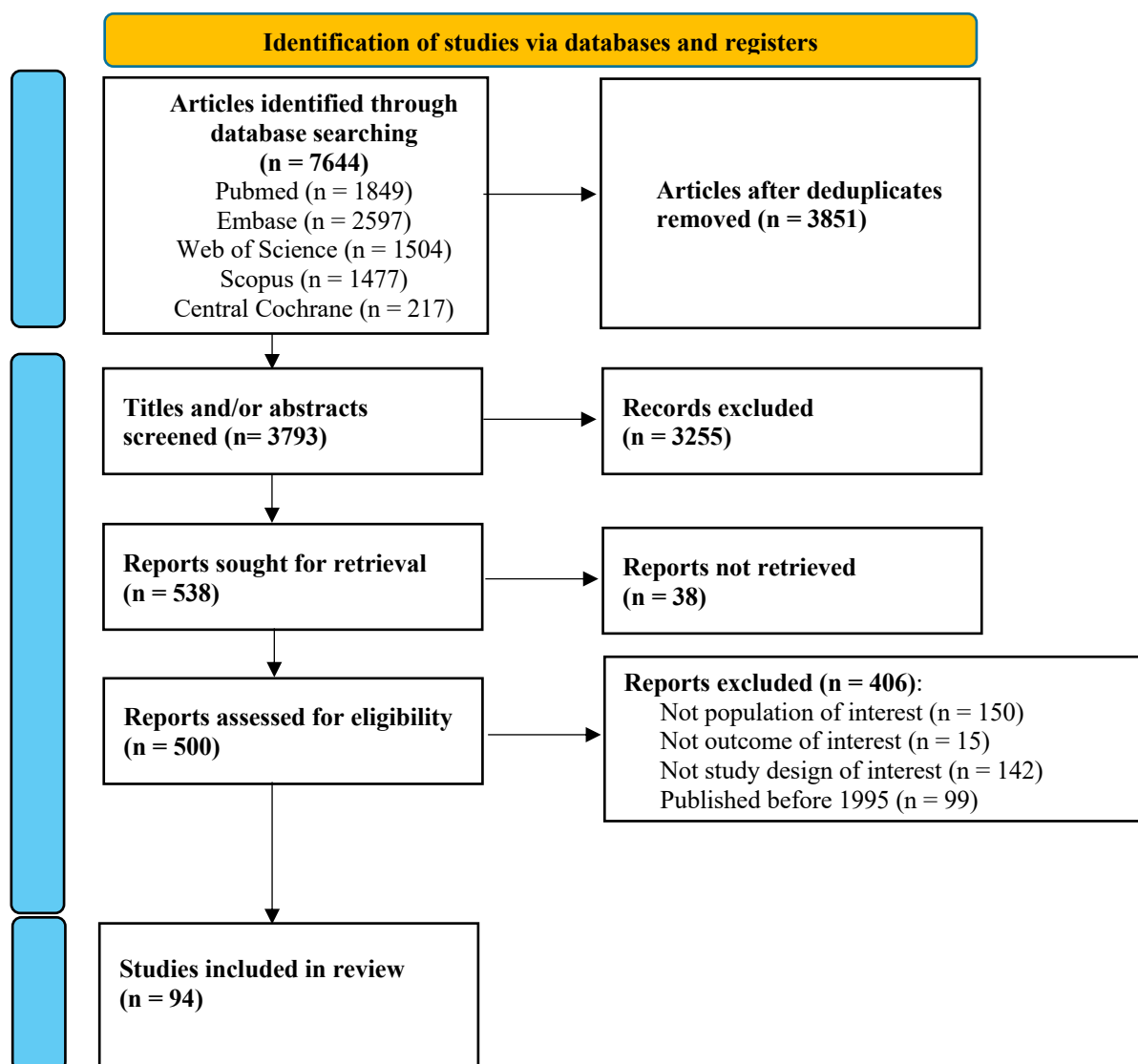


FIGURE 1: Selection process of articles following the Preferred Reporting Items for Systematic Meta-Analyses (PRISMA) flow diagram.

comparison between romiplostim and eltrombopag showed no statistical difference between both drugs (27,28). Avatrombopag led to an overall response of 61-88% which was sustained for 6 months in 33-55% (39,40). The RCT of Grace et al. demonstrated a durable platelet response in 28% of patients treated with avatrombopag, compared with 0% in the placebo group (38). Hetrombopag showed an overall response rate of 77%, including CR of 50%, and a durable overall response in 74% at 6 months (41).

The most common adverse events associated with eltrombopag were upper respiratory symptoms (20-30%) (13,14). Headache, gastrointestinal complaints and transient liver enzyme elevations were also reported (15-28). Most events were grade 1-2; grade 3-4 events occurred in 5% of patients on eltrombopag (13-18,20-26). For romiplostim, injection-site bruising (50%) and headache (43%) were most commonly reported, but also rash,

oropharyngeal pain and upper respiratory symptoms occurred (29-37). Thrombocytosis was noted both on eltrombopag and romiplostim but no thromboembolic events were reported. No malignancies were described. Avatrombopag was associated with upper respiratory and gastrointestinal symptoms, headache, fatigue, fever and oropharyngeal pain. No thromboembolic events were reported (38-40). The study on hetrombopag reported upper respiratory tract infection, thrombocytosis, diarrhea, headache, vomiting, abdominal pain, itchy and dry skin, and dizziness (41).

Recombinant human thrombopoietin (rhTPO)

Recombinant human thrombopoietin has similar functioning to endogenous thrombopoietin, which accounts for megakaryocyte proliferation, differentiation and maturation, as well as platelet production (42). We included 1 double-blind, placebo-controlled RCT on rhTPO in 56 children with chronic and persistent

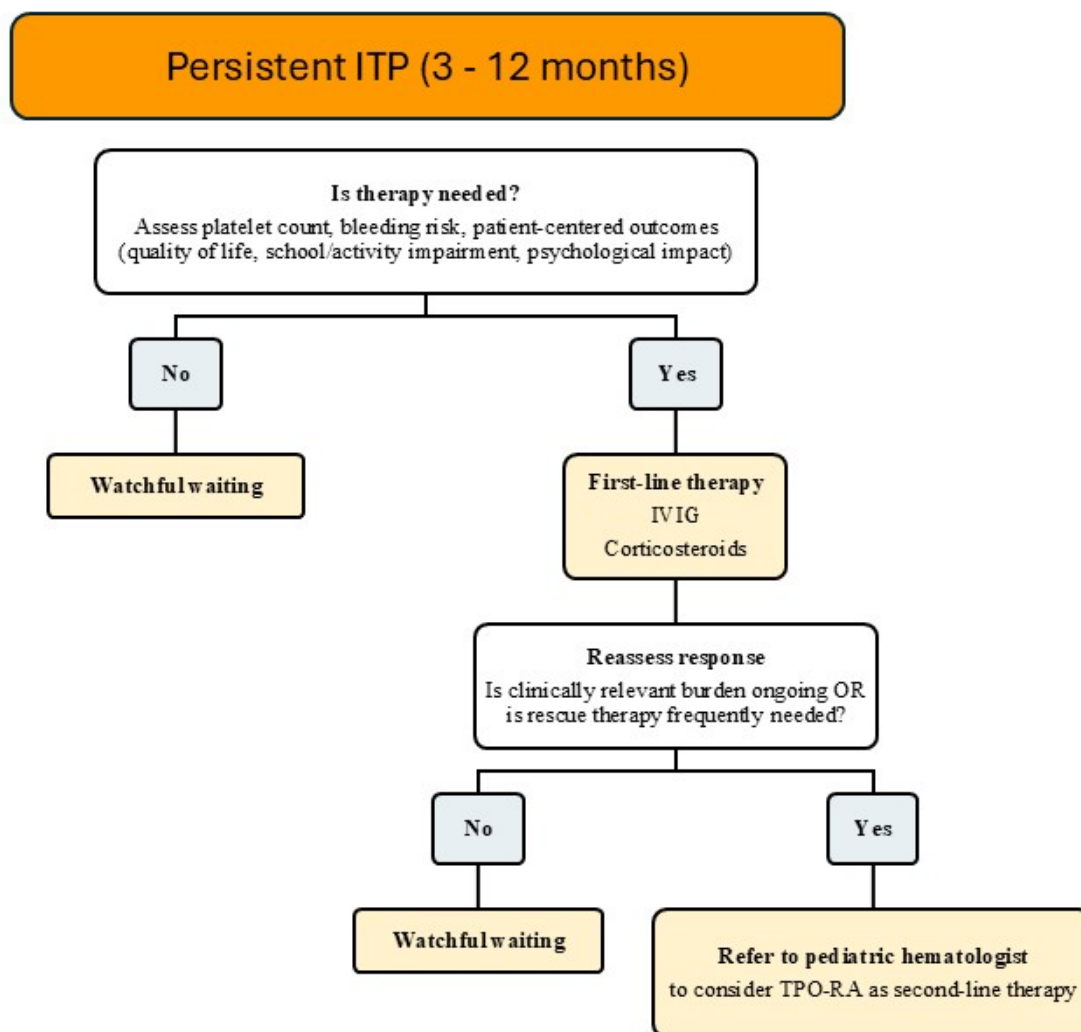


FIGURE 2: Proposed therapeutic algorithm for persistent immune thrombocytopenia. ITP: immune thrombocytopenia; IVIG: intravenous immunoglobulin; TPO-RA: thrombopoietin-receptor agonist.

ITP. An overall response rate of 59% was observed in the treatment group, compared to 13% in the placebo group. Epistaxis, cutaneous bleeding events and upper respiratory infection were most commonly reported adverse events (42).

Corticosteroids

Corticosteroids reduce autoantibody production, interfere with antibody binding and inhibit macrophage differentiation and phagocytosis (43). Ten studies evaluated corticosteroids in 164 patients (7 to 34 per study): 6 cohort studies and 4 case series (43–52). Most studies investigated high-dose dexamethasone whereas some used methylprednisolone or prednisone, or various types (43–52).

Dexamethasone increased platelet counts in most patients, but sustained responses were limited (43–48,50). Adams et al. reported that all 7 patients reached $\geq 30 \times 10^9/L$ above baseline, though counts eventually declined (50). Similarly, Chen et al. observed PR in 6 of 7 patients, with only 1 maintaining the

response after 12 months (45). Other studies reported responses during 6–12 months in 29–46% of patients, depending on the response criteria (43,46–48). Additionally, Ozer et al. evaluated monthly high-dose methylprednisolone (2 to 8 courses) and reported CR in 41%, maintaining counts of $20\text{--}100 \times 10^9/L$ without mucocutaneous bleeding in 18% for 12 months (49). Finally, 3 other groups reported CR in 21–34% up till 14 years, though responses were not stratified by corticosteroid type (44,51,52).

The most common adverse events of corticosteroids were fatigue, weight gain, mood changes and gastro-intestinal complaints (43,45–47,49–51). Hypertension was rare (48). No significant differences were observed between corticosteroid types (51).

Intravenous immunoglobulin (IVIG)

Intravenous immunoglobulins modulate Fc receptor expression or affinity, block Fc receptor-mediated platelet phagocytosis and regulate immunity by influencing the cytokine network (53). We retrieved 4

articles studying IVIG in 77 patients (5 to 37 per study): 2 RCTs comparing IVIG to anti-D and steroids, or to steroids, 1 prospective observational cohort study comparing IVIG plus steroids, steroids alone, and watchful waiting, and 1 retrospective case series (44,52,54,55).

IVIG was not superior to anti-D or steroids (54). However, IVIG gave higher short-term but lower long-term responses than dexamethasone: all patients ($n=8$) achieved PR by day 3, but only 1 maintained CR >3 months (55). Similarly, 1 out of 6 patients receiving IVIG plus steroids remained in CR after 3 months (44). Headache was a common side effect (70%) and led to discontinuation in 1 patient. Aseptic meningitis occurred in 1 of 15 patients (7%) (54,55).

Anti-Rhesus immunoglobulins (anti-D)

Anti-D immunoglobulin binds to red blood cells, resulting in direct competition for macrophage clearance of the coated red blood cells and autoantibody-coated platelets, which reduces platelet destruction and raises platelet counts (56). We included 4 prospective and 2 retrospective studies, evaluating anti-D in 124 patients (6 to 34 per study): 3 cohort studies, 2 case series and 1 randomized, non-blinded trial comparing anti-D to IVIG (11,52,53,56-58). In persistent ITP, the overall response rate was 83% (PR 50%, CR 33%), while in chronic ITP, PR ranged from 0% to 44% and CR from 0% to 17% (50,52,53,56,58). No next-line treatment was given in 17% of patients and all patients had a sufficient increase in platelet counts (defined as $\geq 20 \times 10^9/L$ if symptomatic and $\geq 10 \times 10^9/L$ if asymptomatic) to protect against severe bleeding (11,57). Intravascular haemolysis with haemoglobin drops of 0.1 to 3.6 g/dL was reported in 3 papers (53,56,57). Other side effects included fever, chills, skin rash and haemoglobinuria.

Immunosuppressive and immune-modulating agents

Cyclosporine A

Cyclosporine inhibits interleukin-2 production and suppresses T-cell activation, and thereby decreases immune-mediated platelet destruction (59). We included 1 RCT comparing cyclosporine to sirolimus, 1 prospective interventional cohort study, 1 prospective case series and 2 retrospective observational studies, comprising 124 children (4 to 61 per study) (11,59-62). PR ranged from 20-46% and CR varied between 7% and 53% (59-62). Responses were durable during a median of 42 months following cessation (62). Hirsutism was the most common side effect (37 to 60% of patients) (60,62). Other adverse effects included hypertrichosis, transient hyperbilirubinemia, oral mycosis, fungemia, tremor, gum hypertrophy, mild gastrointestinal complaints, neutropenia, hypertension and renal impairment (59,60,62).

Rituximab

Rituximab is a monoclonal antibody that reduces autoimmune activity of CD20-positive B cells by complement- and antibody-mediated cytotoxicity, inhibition of lymphocyte proliferation and induction of apoptosis (63,64). Eight studies evaluated the effect and safety of rituximab in 202 patients (6 to 62 per study): 5 case series (3 prospective interventional, 2 retrospective observational, 1 prospective cohort and 1 retrospective cohort study (11,63-67). One prospective interventional cohort study studied rituximab administration prior to eltrombopag treatment versus eltrombopag monotherapy (68). PR and CR ranged from 17% to 67% and 0% to 68%, respectively (52,63-67) and no next-line therapy was needed in more than 50% (11). The response lasted for a median of 12 to 33 months (65-67). In the study comparing rituximab prior to eltrombopag with eltrombopag monotherapy, more patients receiving monotherapy achieved platelet counts $\geq 30 \times 10^9/L$ and at least doubled their count at 1 month (85% vs 49%), whereas this difference was no longer observed at 12 months (88% vs 85%). CR was also more frequent in patients on monotherapy than those who received rituximab first (35% vs 9% at 1 month, 56% vs 48% at 12 months). Treatment cessation was achieved in 30% of the rituximab group versus none in the eltrombopag monotherapy group (68). Rituximab was generally well tolerated with mainly mild to moderate infusion reactions. Immunoglobulin levels could be reduced without major infections (64,66,68).

Sirolimus

Sirolimus is an mTOR-inhibitor and blocks cytokine-driven activation of lymphocytes (69). In a retrospective observational case series ($n=12$) on persistent ITP, PR was 8% and CR 75% (69). Additionally, an RCT comparing cyclosporine to sirolimus in 61 patients with chronic ITP reported a PR and CR of 50% after 6 months (60). No serious side effects were reported. One patient experienced haematuria, while several patients reported mild gastrointestinal complaints or upper respiratory symptoms (60,69).

Interferon alpha

Interferon alpha alters cytokine production, increases NK-cell activity and reduces secretion of autoantibodies (70,71). We identified 2 prospective case series, including 25 patients treated with interferon alpha (70,71). Hrstková et al. reported a PR of 27% and CR of 55%, for 18 to 30 months (70). In 82% of patients, a platelet count $>150 \times 10^9/L$ or an increase not reaching $150 \times 10^9/L$ was seen. However, counts returned to baseline shortly after interferon discontinuation (71). Most patients reported flu-like symptoms during two weeks. Additionally, severe neutropenia ($<1.0 \times 10^9/L$) was reported in one patient (71). Mildly elevated bilirubin and liver enzymes, without severe hepatotoxicity

occurred in another patient. No serious adverse effects were reported (70,71).

Mycophenolate mofetil

Mycophenolate mofetil is an inosine monophosphate dehydrogenase inhibitor, limiting de novo purine synthesis, necessary for lymphocyte proliferation, and antibody production (72). Only two studies investigated mycophenolate mofetil. A prospective case series (6 patients with persistent and chronic ITP) demonstrated that all responded to a combination of corticosteroids and mycophenolate mofetil (platelet counts $>100 \times 10^9/L$ within 1 month). Steroids were tapered over 42 days and the response was maintained up to 12 months after discontinuation (72). In addition, a retrospective cohort study reported that almost half of the children did not need next-line therapies after the start of mycophenolate mofetil (11).

Dapsone

Dapsone induces low grade haemolysis, which likely interferes with platelet clearance by the reticulo-endothelial system (73). We identified 5 retrospective observational cohort studies, evaluating dapsone in 171 patients (10 to 45 per study) (11,73–76). The PR varied between 9 and 48%, whereas CR ranged from 24–49%. Response after 6–12 months of therapy (with or without cessation of dapsone) showed considerable variation, ranging from 0–40% (75,76). Common side effects included haemolysis, anaemia, skin rashes/ulceration, hepatitis and methemoglobinemia (74,75).

Daratumumab

Daratumumab is a humanized anti-CD38 monoclonal antibody that targets CD38-positive plasma cells, which are responsible for producing autoantibodies against platelet (77). We included 1 prospective interventional and 1 retrospective case series comprising 31 children (78,79). A response was seen in 82–90%, which was a CR in 73%. Relapse occurred in 55% at 6 months but retreatment led to CR in most of them. Most common side effects were infusion-related reactions, upper respiratory tract infection, thrombocytosis and 1 patient with secondary hypogammaglobulinemia (78,79).

Hydroxychloroquine

Hydroxychloroquine, commonly known as an antimalarial drug, modulates immunity and interferes with metabolic pathways due to inhibition of lysosomal functioning (80). Liu et al. conducted a retrospective cohort study, including 191 patients with chronic ITP. An overall response rate of 57% was achieved at 3 months, and was sustained in 41% at 12 months. Adverse effects were observed in 14% of patients, predominantly involving retinopathy, elevated liver enzymes and alterations in skin pigmentation (80).

Splenectomy

Splenectomy removes the primary site of platelet destruction and autoantibody-producing B cell formation (81). All 12 studies evaluating splenectomy were retrospective observational cohorts (11,81–89) with the exception of 2 case series (52,90). Sample sizes ranged from 6 to 288 per study (1,157 patients). Overall response rates ranged from 73 to 95% (PR 6–75%; CR 45–85%) (11,52,81–90). However, follow-up periods differed widely (1 month – 16 years). Pincez et al. evaluated the failure-free survival (FFS), defined as the time from splenectomy to second-line treatment (excluding steroids or IVIG) or death, whichever occurred first. FFS was 88% at 1 year, 84% at 2 years and 77% at 5 years post-splenectomy (85). Infectious complications were common, with overwhelming sepsis being reported in 6 patients of whom 4 died (81,82,85,87,88). Additionally, severe intracerebral haemorrhage occurred in 3 patients of which 2 were fatal (81,87,88). Aronis et al. reported transient thrombocytosis in all patients (81).

Watchful waiting

We included 7 articles evaluating watchful waiting in 613 patients (25 to 230 per study). Except for one case series, all were retrospective observational cohort studies (82,83,89,91–94). Follow-up duration ranged between 6 months and 25 years (82,83,89,91–94). PR was reported in 38% (92) and 66%, while CR ranged from 14% to 76% (82,83,89,92,93).

Other therapies

H. pylori eradication

H. pylori possibly induces autoantibody production by chronic immune response or by molecular mimicry between platelet surface antigens and virulent surface factors of the bacterium (95). Eight prospective interventional studies on *H. pylori* eradication included 237 children (3 to 84 per study): 3 case series, 3 cohort studies and 2 RCTs (95–102). The RCTs reported CR in 14% and 60% (eradication group) versus 11% and 18% (control group) (101,102). Similarly, CR in the other studies ranged from 13–80% (84,95–98,100). The treatment was well tolerated with only mild and transient side effects, not further specified (98,101).

Herbal formulations

Japanese and Chinese herbal formulations are hypothesized to modulate immune homeostasis, promote blood cell production and enhance glucocorticoid effects (103–105). We identified 1 retrospective case series of 44 children treated with cepharanthin, 1 RCT on 42 children treated with Guishao Shengxue decoction and 1 RCT on 216 patients receiving Huaiqihuang granule (103,104,106). Patients treated with cepharanthin showed median platelet counts

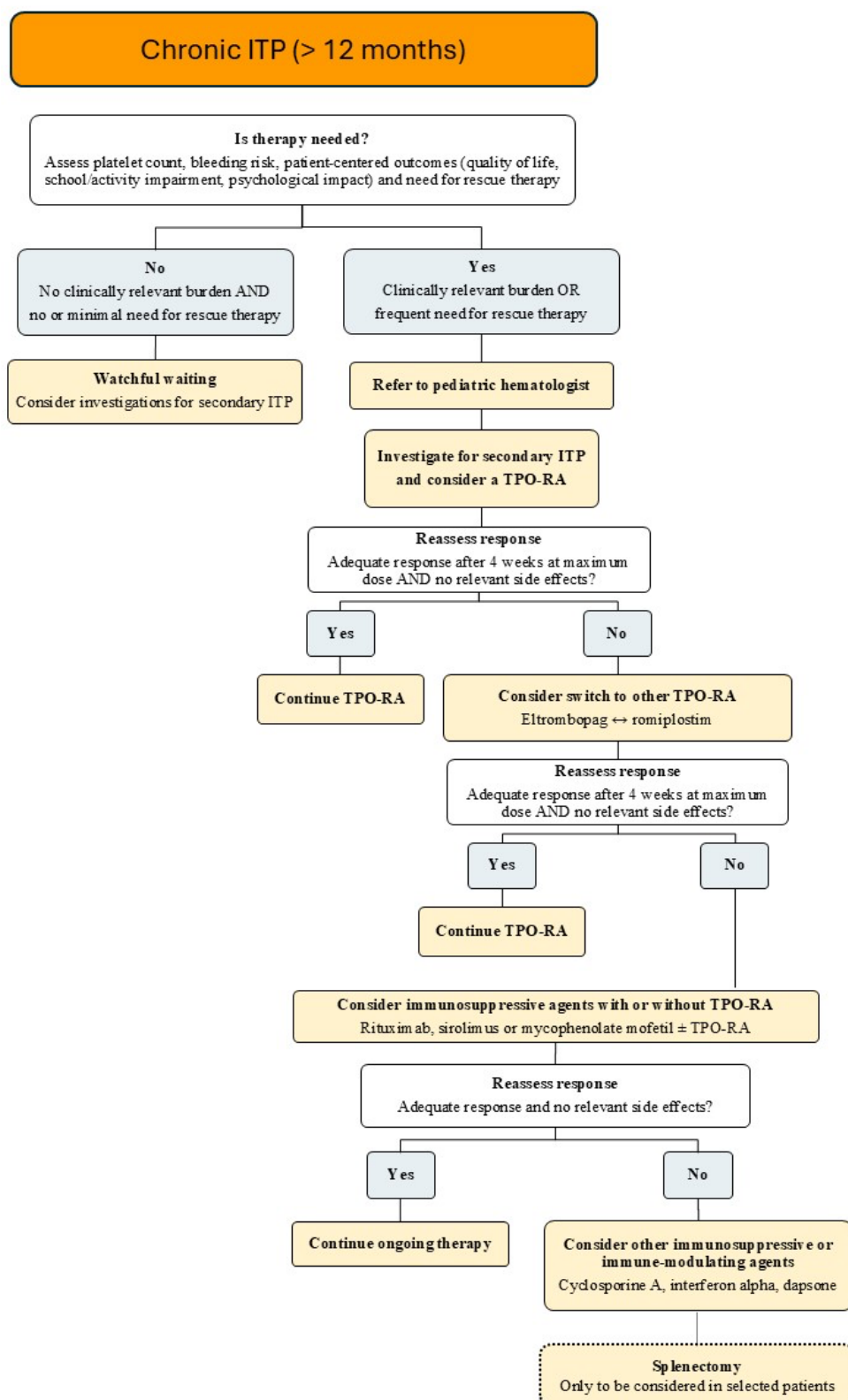


FIGURE 3: Proposed therapeutic algorithm for chronic immune thrombocytopenia.
ITP: immune thrombocytopenia; TPO-RA: thrombopoietin-receptor agonist.

increase from 21 to 59 x 10⁹/L at 12 months and to 69 x 10⁹/L at 24 months, with the greatest benefit in patients starting with platelet counts <20 x 10⁹/L. Bleeding symptoms improved in 71-78% and steroids could be weaned (106). For Guishao Shengxue decoction, overall response rates were 95% and 71% in the treatment and placebo groups, respectively.

Recurrence was reported in 4% of patients in the treatment arm versus 19% in the control arm (103). In the study on Huaqihuang granule, overall response rates were 72% in the treatment group and 46% in the placebo group (104). No serious adverse events occurred in the cepharantin and Guishao Shengxue decoction studies. One

patient treated with cepharanthin had transient hepatic dysfunction and Guishao Shengxue decoction was associated with nausea, fever and dizziness (though similar rates were reported in the control group) (103,106). Reported side effects in the Huaiqihuang granule study included diarrhoea, epistaxis, intracranial haemorrhage, gastrointestinal haemorrhage and gingival bleeding (104).

Escalating treatment strategy

Fu et al. retrospectively analysed 30 patients with chronic ITP who received stepwise treatment of high-dose dexamethasone, rituximab and eltrombopag (107). Nine patients received steroids alone, 4 received additional rituximab and 17 underwent triple therapy. Overall, 80% responded. The response persisted for ≥ 12 months in 37%. CR rates by treatment step were 33%, 75% and 29%, respectively (107).

Risk of bias and quality assessment

Detailed responses to each JBI checklist item are provided for each study type separately in Supplementary Tables 2-4. The methodological quality of the 27 case series was rated high for 21 (78%), moderate for 5 (18%) and low for 1 study (4%). Of the cohort studies ($n=53$), 9 were of high quality (17%), 38 of moderate (72%) and 6 of low quality (11%). Finally, 7 out of 14 RCTs (50%) had a high quality, 5 (36%) had a moderate and 2 (14%) had a low quality.

Discussion

Choosing the right treatment for a child with persistent or chronic ITP remains very challenging. By evaluating the efficacy and safety of the various options, this review aimed to support real-world clinical decision-making and provides an example of a therapeutic algorithm (Figure 2 and 3).

First of all, it is important to note that many patients with persistent ITP will recover and also a substantial proportion of patients achieve spontaneous remission more than 1 year after the initial diagnosis. Thus, the efficacy of therapies should be interpreted with caution, as it may be partially overestimated. Moreover, watchful waiting may be appropriate if significant bleeding is absent. If treatment is deemed necessary, first-line therapies (IVIG, corticosteroids, anti-D) are a reasonable option. However, as in acute ITP, these agents show short-term benefits, but relapse is common. Furthermore, the side effects and/or costs limit the long-term or repetitive usability.

This review reveals TPO-RAs (romiplostim, eltrombopag) as the second-line therapy with the most favourable balance between efficacy and safety, which is in line with the current treatment recommendations (108,109). Sustained responses were observed in over half of patients and these drugs are well tolerated.

However, long-term safety remains uncertain due to lack of existing data. Newer thrombopoietin receptor agonists, such as avatrombopag and hetrombopag, have further expanded the therapeutic landscape for ITP and demonstrate promising efficacy with favourable safety profiles. However, additional high-quality comparative studies and long-term follow-up data are needed to better define their relative positioning within second-line treatment strategies.

Alternative treatments, including rituximab, sirolimus, and MMF show promising efficacy but safety data are limited. On the other hand, cyclosporine A, dapsone, and interferon alpha demonstrate only modest or inconsistent efficacy with notable side effects, limiting their clinical use. Moreover, while splenectomy is effective in over 75% of patients, the risk of life-threatening infections and the irreversibility of the procedure urges us to consider splenectomy only as an option of last resort. Besides, although a link between *H. pylori* and chronic ITP has been suggested, response rates to eradication vary widely, reflecting differences in study populations and methodology. Screening may be considered in symptomatic patients, but is not recommended routinely in asymptomatic individuals. Finally, new therapeutic options are currently being studied: vitamin D as adjuvant treatment (NCT06073925), CAR-T cells (NCT06352281), obinutuzumab (NCT06094881), rilzabrutinib (NCT04562766) or efgartigimod (NCT07194850). Yet, we are awaiting the results of these emerging therapeutic strategies for children with chronic or persistent ITP.

Although this review provides a comprehensive overview of the currently available treatments for chronic and persistent paediatric ITP, several limitations should be considered. A key challenge is the inconsistent definitions for persistent and chronic ITP and treatment response, especially in studies conducted before the 2009 IWG consensus. This variability complicates direct comparisons. Besides, these IWG definitions do not fully reflect current patient-centred treatment goals, which emphasize quality of life and bleeding control rather than platelet count alone. Secondly, most included studies were retrospective cohort studies or case series, subject to inherent bias and only 3 of the included RCTs were considered high quality. Heterogeneity in study design further complicates comparisons and may explain variable response rates. This prompted us to a narrative synthesis, that guided the development of a therapeutic framework, which should be interpreted as a pragmatic synthesis of heterogeneous evidence rather than a definitive evidence-based pathway. Additionally, many studies lack long-term follow-up data, limiting assessment of response durability and long-term safety. Finally, given the limited number of studies on persistent ITP, lack of differentiation from chronic ITP and overlap between the former definition of chronic ITP (> 6 months) and current definition of persistent ITP (3-12 months), conclusions on the optimal treatment strategies for persistent ITP cannot be drawn.

Conclusion

The wide range of therapeutic options for persistent and chronic paediatric ITP makes selecting the most appropriate treatment challenging. Watchful waiting proves appropriate for many patients, whereas TPO-RAs appear to be the most favourable second-line treatment when pharmacological therapy is required. Future research should focus on monitoring of long-term safety and on comparing therapies while focusing on patient-centred outcomes.

Statements

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TABLE 1: Characteristics of included studies (Continued on next page)

Intervention	Study design	Year	N	Persistent or chronic	Definition of duration*	Definitions of efficacy*
Eltrombopag (13)	RCT	2015	67	Both		PLT >50x10 ⁹ /L at least once with no rescue therapy
Eltrombopag (14)	RCT	2015	92	Chronic		PLT >50x10 ⁹ /L with no rescue therapy for ≥ 6 weeks
Eltrombopag (15)	retrospective, observational cohort	2019	20	Chronic		
Eltrombopag (16)	retrospective cohort	2024	55	Both		PLT >30x10 ⁹ /L and more than a twofold increase compared to baseline and absence of bleeding events
Eltrombopag (17)	retrospective cohort	2020	71	Chronic		% of patients with PLT >30x10 ⁹ /L and >100x10 ⁹ /L at 1, 3, and 6 months of treatment
Eltrombopag (18)	retrospective, observational cohort	2020	60	Chronic		
Eltrombopag (19)	retrospective, observational cohort	2020	30	Chronic		
Eltrombopag (20)	prospective, observational cohort	2021	116	Both		
Eltrombopag (21)	retrospective, observational cohort	2023	56	Chronic		
Eltrombopag (22)	retrospective, observational cohort	2023	65	Chronic		
Eltrombopag (23)	retrospective, observational cohort	2023	143	Both		
Eltrombopag (24)	prospective, observational cohort	2023	30	Both		PLT >50x10 ⁹ /L for more than 75% of the tests
Eltrombopag (25)	prospective, interventional case series	2018	19	Both	Chronic if ≥ 6 months	
Eltrombopag (26)	retrospective case series	2024	13	Both	Not specified	complete: PLT >50x10 ⁹ /L with no rescue therapy for > 6 weeks; partial: response <6 weeks or requiring rescue therapy
Eltrombopag/romiplostim (27)	retrospective cohort	2014	33	Both	Chronic if ≥ 6 months	PLT >50x10 ⁹ /L for at least 2 consecutive weeks
Eltrombopag/romiplostim (28)	retrospective cohort	2024	33	Chronic		PLT >50x10 ⁹ /L
Romiplostim (29)	RCT	2011	18	Chronic		PLT >50x10 ⁹ /L
Romiplostim (30)	RCT	2016	62	Both	Chronic if ≥ 6 months	PLT >50x10 ⁹ /L with no rescue therapy in last 4 weeks
Romiplostim (31)	retrospective cohort	2014	7	Chronic	Not specified	PLT >30-50x10 ⁹ /L and low doses of romiplostim every 4-5 weeks
Romiplostim (32)	prospective, interventional cohort	2015	22	Chronic	Chronic if ≥ 6 months	PLT >50x10 ⁹ /L with no rescue therapy in last 4 weeks

TABLE 1: Characteristics of included studies (Continued on next page)

Romiplostim (33)	RCT	2019	66	Chronic	Chronic if ≥ 6 months	PLT $>50 \times 10^9/L$
Romiplostim (34)	prospective, interventional cohort	2022	40	Both		PLT $>50 \times 10^9/L$ with no rescue therapy
Romiplostim (35)	prospective, interventional case series	2012	7	Chronic		PLT $>50 \times 10^9/L$ with no rescue therapy
Romiplostim (36)	retrospective case series	2014	4	Both		PLT $>50 \times 10^9/L$ and more than twofold increase compared to baseline, with no rescue therapy in last 8 weeks
Romiplostim (37)	prospective, interventional case series	2023	203	Both		PLT $>50 \times 10^9/L$ with no rescue therapy in last 4 weeks
Avatrombopag (38)	RCT	2025	75	Both		Durable platelet response: at least 6 out of 8 weekly PLT $> 50 \times 10^9/L$ during the last 8 weeks of the 12-week treatment period, in the absence of rescue therapy
Avatrombopag (39)	retrospective cohort	2024	34	Both		
Avatrombopag (40)	retrospective cohort	2025	55	Both		
Hetrombopag (41)	retrospective cohort	2025	30	Both		
Recombinant human thrombopoietin (42)	RCT	2024	56	Both		
Steroids (43)	prospective, interventional case series	1997	11	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$ with no rescue therapy; partial: PLT $50\text{--}150 \times 10^9/L$ with no rescue therapy; none: PLT $<50 \times 10^9/L$ or requiring rescue therapy
Steroids (45)	prospective, interventional cohort	1997	7	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$; partial: PLT $50\text{--}150 \times 10^9/L$; none: PLT $<50 \times 10^9/L$
Steroids (46)	prospective, interventional cohort	1997	17	Chronic	Chronic if ≥ 6 months	normal PLT
Steroids (47)	prospective, interventional cohort	2002	13	Chronic	Not specified	complete: PLT $>150 \times 10^9/L$; partial: PLT $50\text{--}150 \times 10^9/L$; none: PLT $<50 \times 10^9/L$
Steroids (48)	prospective, interventional cohort	2010	13	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$; partial: PLT $50\text{--}150 \times 10^9/L$; minimal: PLT $20\text{--}30 \times 10^9/L$; none: unchanged PLT or increase but PLT $<20 \times 10^9/L$
Steroids (49)	prospective, interventional cohort	2000	22	Chronic	Chronic if ≥ 6 months	complete: PLT $>100 \times 10^9/L$; partial: PLT $20\text{--}100 \times 10^9/L$; none: PLT $<20 \times 10^9/L$
Steroids (50)	prospective, interventional case series	1996	7	Both	Chronic if ≥ 6 months	PLT $>30 \times 10^9/L$ above pretreatment value
Steroids (51)	retrospective case series	2005	29	Chronic	Chronic if ≥ 6 months	complete: PLT between $180\text{--}250 \times 10^9/L$; partial: PLT between $70\text{--}110 \times 10^9/L$
Steroids/IVIIG (44)	prospective, observational cohort	2006	12	Chronic	Chronic if ≥ 6 months	complete: PLT $>100 \times 10^9/L$ for >3 months off therapy and absence of abnormal bruising
Steroids/IVIIG (54)	RCT	2006	37	Chronic	Chronic if ≥ 6 months	complete: PLT $>100 \times 10^9/L$ or 3 months off therapy
Anti-D (56)	prospective, interventional cohort	2009	20	Both		

TABLE 1: Characteristics of included studies (Continued on next page)

Intervention	Study design	Year	N	Persistent or chronic	Definition of duration*	Definitions of efficacy*
Anti-D (57)	prospective, interventional cohort	2010	30	Chronic	Chronic if ≥ 6 months	PLT $>20 \times 10^9/L$ in symptomatic patients and $>10 \times 10^9/L$ in asymptomatic patients
Anti-D (58)	prospective, interventional case series	2013	9	Chronic		
IVIg/anti-D (53)	RCT	2006	34	Chronic	Chronic if ≥ 6 months	PLT $>50 \times 10^9/L$ or doubling of baseline PLT with absence of bleeding
Steroids/IVIg/anti-D (55)	RCT	2003	23	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$ with no rescue therapy; partial: PLT $>30 \times 10^9/L$ and above pretreatment value
Cyclosporin/sirolimus (60)	RCT	2020	61	Chronic		
Cyclosporin (59)	prospective, interventional case series	2002	14	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$; partial: PLT $50\text{--}150 \times 10^9/L$; none: unchanged PLT or $>50 \times 10^9/L$ with rescue therapy
Cyclosporin (61)	prospective, interventional cohort	2008	15	Chronic	Chronic if ≥ 6 months	complete: PLT $>100 \times 10^9/L$ for at least 2 months; partial: PLT $>50 \times 10^9/L$ and doubled; none: PLT $< 50 \times 10^9/L$
Cyclosporin (62)	retrospective cohort	2016	30	Both		
Rituximab (63)	prospective, interventional case series	2014	18	Chronic		complete: PLT $>100 \times 10^9/L$; partial: PLT $50\text{--}100 \times 10^9/L$; minimal: PLT $30\text{--}50 \times 10^9/L$; none: PLT $<30 \times 10^9/L$
Rituximab (64)	prospective, interventional cohort	2008	6	Chronic	Not specified	complete: PLT $>75 \times 10^9/L$; partial: PLT $30\text{--}75 \times 10^9/L$
Rituximab (65)	prospective, interventional case series	2011	12	Chronic		
Rituximab (66)	prospective, interventional case series	2005	24	Chronic	Chronic if ≥ 6 months	complete: peak PLT $>150 \times 10^9/L$; partial: PLT between $50\text{--}100 \times 10^9/L$; minimal: $>20 \times 10^9/L$ above pretreatment value but $<50 \times 10^9/L$; none: no increase
Rituximab (67)	retrospective case series	2006	19	Chronic	Chronic if ≥ 6 months	PLT $>50 \times 10^9/L$ for at least 7 days
Rituximab/eltrombopag (68)	prospective, interventional cohort	2025	55	Both		
Sirolimus (69)	retrospective case series	2017	12	Persistent		complete: PLT $>150 \times 10^9/L$ for 2 months with ability to taper steroids; partial: improvement in PLT by ≥ 1 CTCAE grade for ≥ 2 months with same dose of steroids or stable PLT while tapering steroids by at least 50%
Interferon alpha (70)	prospective, interventional case series	2002	11	Chronic	Chronic if ≥ 6 months	Poor: PLT $<30 \times 10^9/L$; fair: PLT $31\text{--}60 \times 10^9/L$; good: PLT $61\text{--}100 \times 10^9/L$; very good: PLT $>100 \times 10^9/L$
Interferon alpha (71)	prospective, interventional case series	2001	14	Chronic		complete: PLT $>150 \times 10^9/L$; partial: PLT increase but $< 150 \times 10^9/L$; none: no increase or PLT increase $<15\%$ more than pretreatment value
Mycophenolate mofetil (72)	prospective, interventional case series	2017	6	Both		initial: PLT $>100 \times 10^9/L$; complete: maintenance of initial response during >3 months while off steroids
Dapsone (73)	retrospective cohort	2020	29	Chronic		

TABLE 1: Characteristics of included studies (Continued on next page)

Dapsone (74)	retrospective cohort	2005	35	Chronic	Chronic if ≥ 6 months	complete: PLT $>100 \times 10^9/L$; partial: PLT 50-150 $\times 10^9/L$; none: PLT $<50 \times 10^9/L$
Dapsone (75)	retrospective cohort	2014	12	Both		
Dapsone (76)	retrospective cohort	2024	45	Chronic		
Daratumumab (78)	prospective interventional case series	2025	20	Both		PLT $>50 \times 10^9/L$ without using rescue medication or increasing the dose of concomitant therapy during the 8 weeks after the first dose
Daratumumab (79)	retrospective case series	2025	11	Chronic		
Hydroxychloroquine (80)	retrospective cohort	2025	191	Chronic		
Splenectomy/none (82)	retrospective cohort	1995	92	Chronic	Chronic if ≥ 6 months	recovery = absence of purpura or abnormal bruising together with persistently normal PLT
Splenectomy/none (83)	retrospective cohort	2006	230	Chronic	Chronic if ≥ 6 months	normalization of PLT
Splenectomy (81)	retrospective cohort	2004	33	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$; partial: PLT 50-150 $\times 10^9/L$
Splenectomy (84)	retrospective cohort	2006	90	Chronic	Chronic if ≥ 6 months	PLT $>50 \times 10^9/L$
Splenectomy (85)	retrospective cohort	2022	120	Chronic		Failure-free survival defined as time from splenectomy to second-line treatment or death
Splenectomy (86)	retrospective cohort	2003	112	Chronic	Chronic if ≥ 6 months	complete: PLT $>100 \times 10^9/L$ with no rescue therapy for >2 months; partial: PLT $>30 \times 10^9/L$ with no rescue therapy for >2 months; none: PLT $<30 \times 10^9/L$
Splenectomy (87)	retrospective cohort	2006	65	Chronic	Chronic if ≥ 6 months	complete: PLT $>100 \times 10^9/L$ with no rescue therapy; partial: PLT $>30 \times 10^9/L$ with no rescue therapy
Splenectomy (88)	retrospective cohort	2016	87	Both		
Splenectomy (90)	retrospective case series	2014	18	Chronic		
None (91)	retrospective case series	2004	62	Chronic	Chronic if ≥ 6 months	Complete: PLT $>100 \times 10^9/L$ for >3 months with no rescue therapy; partial: PLT $>50 \times 10^9/L$ for >3 months with no rescue therapy; none: PLT $<50 \times 10^9/L$
None (92)	retrospective cohort	2012	44	Chronic	Chronic if ≥ 6 months	PLT $>50 \times 10^9/L$
None (93)	retrospective cohort	2014	47	Chronic		group A: PLT $>100 \times 10^9/L$; group B: PLT 50-100 $\times 10^9/L$; group C: PLT $<50 \times 10^9/L$
None (94)	retrospective cohort	2016	72	Both		
HP eradication (96)	prospective, interventional case series	2007	3	Chronic		
HP eradication (97)	prospective, interventional case series	2009	5	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$; partial: PLT 50-150 $\times 10^9/L$
HP eradication (95)	prospective, interventional case series	2009	8	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$; partial: PLT $>50 \times 10^9/L$ above pretreatment values
HP eradication (98)	prospective, interventional cohort	2021	63	Chronic		complete: PLT $>150 \times 10^9/L$; partial: PLT 50-150 $\times 10^9/L$; none: PLT $<50 \times 10^9/L$ above pretreatment value
HP eradication (99)	prospective, interventional cohort	2011	37	Chronic		complete: PLT $>150 \times 10^9/L$; partial: PLT $>50 \times 10^9/L$ and $>30 \times 10^9/L$ above pretreatment values; none: PLT $<50 \times 10^9/L$ or $<30 \times 10^9/L$ above pretreatment value or need for rescue therapy

TABLE 1: Characteristics of included studies (End of table)

Intervention	Study design	Year	N	Persistent or chronic	Definition of duration*	Definitions of efficacy*
HP eradication (100)	prospective, interventional cohort	2021	55	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$; partial: improvement in PLT but $<150 \times 10^9/L$; none: no improvement in PLT
HP eradication (101)	RCT	2009	16	Chronic	Chronic if ≥ 6 months	PLT $>100 \times 10^9/L$ for >3 months
HP eradication (102)	RCT	2015	22	Chronic	Chronic if ≥ 6 months	complete: PLT $>150 \times 10^9/L$; partial: PLT $50\text{--}150 \times 10^9/L$ and $>20\text{--}30 \times 10^9/L$ above pretreatment values; none: PLT $<50 \times 10^9/L$ or $<20 \times 10^9/L$ above pretreatment value
Guishao Shengxue Decoction (103)	RCT	2025	42	Both		
Huaiqihuang Granule (104)	RCT	2025	216	Chronic		
Cepharantin (106)	retrospective case series	2017	44	Chronic	Chronic defined as self-perpetuating, PLT at subnormal levels even during clinical remission	Excellent: PLT $>100 \times 10^9/L$; good: increase of PLT, $50\text{--}100 \times 10^9/L$; fair: increase of PLT, $10\text{--}50 \times 10^9/L$; no change: less than $10 \times 10^9/L$ different from pretreatment value; progression: decrease of PLT by $>10 \times 10^9/L$
Escalating treatment regimen (107)	retrospective cohort	2021	30	Chronic		
Various drugs (11)	retrospective cohort	2020	392	Chronic		Complete: PLT $>100 \times 10^9/L$; partial: PLT $>30 \times 10^9/L$; none: PLT $<30 \times 10^9/L$
Various drugs (52)	retrospective case series	2016	60	Chronic	Chronic if ≥ 6 months	Complete: PLT $>150 \times 10^9/L$; partial: PLT $>50 \times 10^9/L$; none: PLT $<50 \times 10^9/L$
Various drugs (89)	retrospective cohort	2024	86	Chronic		
anti-D: anti-rhesus D immunoglobulins; HP: Helicobacter pylori; IVIG: intravenous immunoglobulins; N: number of patients; PLT: platelet count; RCT: randomized controlled trial; *Definitions consistent with International Working Group criteria when not explicitly stated						

TABLE 2: Overview of the efficacy and safety of the different treatment options (Continued on next page)

Intervention	Efficacy*	Safety
Eltrombopag (13)	response in 62% (eltrombopag) versus 32% (placebo)	headache, upper respiratory tract infection, diarrhoea
Eltrombopag (14)	response in 40% (eltrombopag) versus 3% (placebo)	headache, nasopharyngitis, pyrexia, upper respiratory tract infection, cough, diarrhoea, vomiting
Eltrombopag (15)	complete response 35%; partial response 40%	mild thrombocytosis, rash
Eltrombopag (16)	overall response 60% durable at 6 months in 45%	elevated aminotransferase levels, headache, vomiting, hair loss, rash, stomach pain
Eltrombopag (17)	complete response 44%; partial response 68% at 6 months durable >50x10 ⁹ /L for at least 12 weeks in 40%	headache, thrombocytosis, oral aphthous ulcers, allergic urticaria, microcytic anaemia, transient elevated liver enzymes
Eltrombopag (18)	complete response 30%; partial response 89% at 12 months	transient increase in transaminases
Eltrombopag (19)	complete response 37%; partial response 37% at 12 weeks	vomiting, transient elevated transaminases
Eltrombopag (20)	complete response 46%; partial response 31%	increased indirect bilirubin, increased transaminases, increased alkaline phosphatase, thrombocytosis
Eltrombopag (21)	PLT >50x10 ⁹ /L at >75% of assessments in 60% after 6 months	headache, thrombocytosis, iron deficiency anaemia, microcytosis without anaemia, liver enzyme elevation
Eltrombopag (22)	overall response 81%	liver dysfunction, rash
Eltrombopag (23)	Persistent ITP: complete response 46%; partial response 36% Chronic ITP: complete response 43%; partial response 24%	not reported
Eltrombopag (24)	response in 47%	thrombocytosis, elevated liver enzymes
Eltrombopag (25)	complete response 11%; partial response 47%	thrombocytosis
Eltrombopag (26)	complete response 46%; partial response 23%	cholestatic hepatitis with bacteraemia
Eltrombopag/romiplostim (27)	response in 82%	Eltrombopag: mild headache, thrombotic event (a provoked deep-vein thrombosis at the site of an ankle fracture) Romiplostim: rash, nausea, headache
Eltrombopag/romiplostim (28)	response in 94% durable >6 months: 58% (eltrombopag); 44% (romiplostim)	transient thrombocytosis, liver toxicity, haemolysis, headache
Romiplostim (29)	response in 83% (romiplostim) versus 0% (placebo)	rash
Romiplostim (30)	response in 71% (romiplostim) versus 20% (placebo) durable >6 weeks: 52% (romiplostim) versus 10% (placebo)	contusion, epistaxis, headache, upper respiratory tract infection, vomiting, oropharyngeal pain, diarrhoea, nausea, pyrexia
Romiplostim (31)	response in 43%	
Romiplostim (32)	response in 96%	headache, upper respiratory tract infection, pyrexia
Romiplostim (33)	response in 94% durable >24 weeks without therapy in 23%	headache, contusion, upper respiratory tract infection
Romiplostim (34)	response in 65%	headache, body aches, oropharyngeal pain

TABLE 2: Overview of the efficacy and safety of the different treatment options (Continued on next page)

Intervention	Efficacy*	Safety
Romiplostim (35)	overall response 57%	
Romiplostim (36)	response in 100% durable >6 weeks in 75%	rash, irritability, sleep disturbances and alopecia
Romiplostim (37)	response in 88% durable >24 weeks in 5%	epistaxis, headache, nasopharyngitis, pyrexia, cough, petechiae, vomiting, and hematoma
Avatrombopag (38)	durable platelet response 28% (avatrombopag) versus 0% (placebo)	petechiae, epistaxis, ecchymosis, headache, cough, pyrexia, oropharyngeal pain, upper respiratory tract infection, haematoma; no deaths, thromboembolic events, or grade 3 or higher bleeding events
Avatrombopag (39)	overall response 88% at 12 weeks and 55% at 24 weeks	not reported
Avatrombopag (40)	eltrombopag-switch group: complete response 61%, partial response 19%, durable response at 6 months 48% hetrombopag-switch group: complete response 44%, partial response 22%, durable response at 6 months 33%	gastrointestinal symptoms, headache, fatigue; no thromboembolic events
Hetrombopag (41)	overall response 77%; complete response 50% durable overall response 74% at 6 months	upper respiratory tract infection, thrombocytosis, diarrhoea, headache, vomiting, abdominal pain, itchy and dry skin, dizziness
Recombinant human thrombopoietin (42)	complete response 15%; partial response 44% (recombinant human thrombopoietin) versus complete response 0%; partial response 13% (placebo)	epistaxis, skin and mucosal bleeding, upper respiratory tract infection; no liver or kidney toxicity, no thromboembolic events
Steroids (43)	complete response 9%; partial response 27% after 6 months	fatigue, mood changes, facial flushing, headache, irritability, stomach aches, aggressiveness, weight gain
Steroids (45)	complete response 29%; partial response 57%	myalgia, bone pain, acne, fatigue, weight gain, drowsiness
Steroids (46)	response 1 month after the 6th cycle 35%; durable >1 year 29%; no response 24%	fatigue, irritability, anxiety, abdominal pain, striae, acne, weight gain
Steroids (47)	complete response 23%; partial response 23% at 12 and 24 months	bloating, nausea, vomiting, insomnia, anxiety and depression, transient glucosuria
Steroids (48)	complete response 67%; partial response 17% after 1 cycle durable overall response after 4 cycles in 33%	hypertension
Steroids (49)	complete response 41%; partial response 18% at 12 months	weight gain, anxiety
Steroids (50)	response 100% but relapse in all patients; duration of response variable	fatigue, epigastric pain
Steroids (51)	complete response 34%; partial response 28%; failure 38%	
Steroids/IVIG (44)	steroids: complete response 25-29% IVIG: complete response 29-38% anti-D: complete response 38%	Steroids: hypertension, hyperglycaemia IVIG: aseptic meningitis Dapsone: not reported
Steroids/IVIG (54)	steroids: complete response 25% steroids + IVIG: complete response 8% no intervention: complete response 8%	not reported
Anti-D (56)	Persistent ITP: complete response 33%; partial response 50% Chronic ITP: complete response 12%; partial response 38%	low grade fever, haemolysis with drop in haemoglobin

TABLE 2: Overview of the efficacy and safety of the different treatment options (Continued on next page)

Anti-D (57)	response to provide prevention of hemorrhage in 100%	haemoglobin drop, haemoglobinuria, chills
Anti-D (58)	complete response 0%; partial response 44% at day 5 but 11% after 37 weeks	
IVIg/anti-D (53)	response 38% (IVIg) versus 39% (anti-D) on day 28	IVIg: aseptic meningitis with generalized seizures, headache, mild fever, rash anti-D: haemolysis with Hb drop, low-grade fever, rash
Steroids/IVIg/anti-D (55)	steroids: complete response 27% at day 3 (>6 months 18%); partial response 45% at day 3 (>6 months in 36%) IVIg: complete response 57% at day 3 (>6 months 14%); partial response 43% at day 3 (>6 months in 14%)	Steroids: moodiness, irritability, aggressiveness, altered mental state, depressive feelings, concentration difficulties, hyperactivity, sleeping disturbance, fatigue, increased appetite, dyspepsia, headache, facial flush, signs of Cushing syndrome, myalgia, and fever IVIg: headache
Cyclosporin/sirolimus (60)	cyclosporine: complete response 52%; partial response 45% at 6 months sirolimus: complete response 50%; partial response 50% at 6 months	cyclosporin: gum hypertrophy, hirsutism, GI symptoms sirolimus: respiratory infection, nausea, abdominal discomfort
Cyclosporin (59)	complete response 29%; partial response 21%	hypertrichosis, transient hyperbilirubinemia, oral mycosis, C. albicans fungemia
Cyclosporin (61)	complete response 7%; partial response 20%	not reported
Cyclosporin (62)	complete response 37%; partial response 20% durable in 23%	hirsutism, tremor, hypertension, impaired renal function, gum hypertrophy, neutropenia
Rituximab (63)	complete response 33%; partial response 11%; minimal response 6% at 4 weeks complete response 22%; partial response 17%; minimal response 6% at 6 months complete response 22%; partial response 17%; minimal response 17% at 36 months	not reported
Rituximab (64)	complete response 50%; partial response 33%	not reported
Rituximab (65)	complete response 63%; partial response 8%; minimal response 8%	infusion reactions (pruritus, urticaria, throat tightness), serum sickness leading to discontinuation in 2 patients, decreased immunoglobulin levels
Rituximab (66)	response 68%; durable in 37%	urticaria, fever and chills
Rituximab (67)	complete response 0%; partial response 67%	cough, rash, muscle cramps, headache, angioedema
Rituximab/eltrombopag (68)	rituximab plus eltrombopag: overall response 49%; durable response at 12 months 85%; successful treatment cessation in 30% with PLT remaining >30x10 ⁹ /L for at least 3 months eltrombopag alone: overall response at 1 month 85%; durable response at 12 months 88%; no successful treatment cessation	rituximab plus eltrombopag: infusion-related reactions, neutropenia, anaemia; no persistent hypogammaglobulinemia eltrombopag alone: thrombocytosis, elevated bilirubin
Sirolimus (69)	complete response 75%; partial response 8%	haematuria
Interferon alpha (70)	very good response 46%; good response 9%; fair response 9%; poor response 36% at 3 months very good response 55%; good response 0%; fair response 27%; poor response 18% at 18-30 months	fever, flu-like symptoms, mildly elevated bilirubin and liver enzymes
Interferon alpha (71)	complete response 43% (>3 months 29%); partial response 43% (>6 weeks 0%); no response 7%; worsening PLT below pretreatment values in 7% after one course	flu-like symptoms, neutropenia
Mycophenolate mofetil (72)	complete response 100% (6/6)	not reported

TABLE 2: Overview of the efficacy and safety of the different treatment options (Continued on next page)

Intervention	Efficacy*	Safety
Dapsone (73)	complete response 24%; partial response 48%	methemoglobinemia, skin ulceration
Dapsone (74)	complete response 49% (>6 months: 31%); partial response 17%	haemolysis, rash
Dapsone (75)	complete response 46%; partial response 9%; no response 46% durable >6 months: 0%	skin rash, hepatitis, anaemia
Dapsone (76)	complete response 40%; partial response 24% at 12 months	methaemoglobinemia
Daratumumab (78)	overall response 90%	infusion-related reactions, upper respiratory tract infection
Daratumumab (79)	complete response 73%; partial response 9% at week 1 durable response 91% at 3 months, 55% at 6 months	infusion-related reactions, thrombocytosis, secondary hypogammaglobulinemia
Hydroxychloroquine (80)	overall response 57% at 3 months durable response 41% at 12 months	retinopathy, elevated liver enzymes, changes in skin pigmentation
Splenectomy/none (82)	recovery post-splenectomy 78% compared to 61% after 15 years if no intervention	death due to OPSI
Splenectomy/none (83)	response post-splenectomy 73% compared to 27% after 0.5-10 years if no intervention	not reported
Splenectomy (81)	complete response 85%; partial response 6%; durable in 75% at 6 months to 4 years	death due to OPSI, transient thrombocytosis
Splenectomy (84)	response 75%	infectious episodes and death
Splenectomy (85)	failure-free survival: 1 year in 88%; 2 years in 84%; 5 years in 77%	severe bacterial infections, thrombosis, death
Splenectomy (86)	complete response 45%; partial response 30% after 5-16 years	OPSI
Splenectomy (87)	complete response 62%; partial response 15%; no response 9% at 6 months; relapse 14%	subphrenic effusion, death due to OPSI
Splenectomy (88)	overall response 93%; durable in 72% at 54 months	infection including OPSI, thrombosis
Splenectomy (90)	complete response 78%; partial response 17% durable in 50% after 82 months	not reported
None (91)	complete response 45%; PLT > 50x10 ⁹ /L in 11%	not reported
None (92)	response 46% (39% if non-splenectomized; 75% if splenectomized)	not reported
None (93)	PLT >100x10 ⁹ /L in 45% PLT 50-100x10 ⁹ /L in 21% PLT <50x10 ⁹ /L in 34%	not reported
None (94)	complete remission at 2 years 50%; at 5 years 76%	
HP eradication (96)	complete response 75%; partial response 25%	not reported
HP eradication (97)	complete response 67%; partial response 33% after 3 months	not reported
HP eradication (95)	partial response 100%; relapse 20%	not reported
HP eradication (98)	complete response 63%; partial response 42%	not reported

TABLE 2: Overview of the efficacy and safety of the different treatment options (End of table)

HP eradication (99)	complete response 21%; partial response 18%	not reported
HP eradication (100)	complete response 13%; partial response 53%	not reported
HP eradication (101)	response 14% (HP eradication) versus 11% (no intervention)	not reported
HP eradication (102)	complete response 60% (HP eradication) versus 18% (no intervention)	not reported
Guishao Shengxue Decoction (103)	overall response 95% (Guishao Shengxue Decoction) versus 71% (placebo)	nausea, fever, dizziness
Huaiqihuang Granule (104)	overall response 72 % (Huaiqihuang granule) versus 46% (placebo) at 24 weeks	diarrhoea, epistaxis, intracranial haemorrhage, gastrointestinal haemorrhage, gingival bleeding
Cepharantin (106)	median PLT increase to $58.5 \times 10^9/L$ after 12 months and to $69 \times 10^9/L$ after 24 months; PLT increase by $>10 \times 10^9/L$ in 54%	hepatic dysfunction
Escalating treatment regimen (107)	dexamethasone alone: complete response 33% dexamethasone plus rituximab: complete response 50% dexamethasone plus rituximab and eltrombopag: complete response 29%	not reported
Various drugs (11)	no intervention: response in 61% hydroxychloroquine: response in 54% rituximab: response in 52% azathioprine: response in 55% mycophenolate mofetil: response in 47% vinblastine: response in 25% anti-D: response in 17% vincristine: response in 0% dapson: response in 20% colchicine: response in 47% romiplostim: response in 54% eltrombopag: response in 40% splenectomy: response in 84%	not reported
Various drugs (52)	steroids: complete response 21%; partial response 44% IVIg: complete response 20%; partial response 0% anti-D: complete response 17%; partial response 0% 6-mercaptopurine: complete response 0%; partial response 8% rituximab: complete response 0%; partial response 50% splenectomy: complete response 83%; partial response 0%	not reported
Various drugs (89)	no intervention: response in 29% splenectomy: complete response in 70% after 3 years rituximab, dapson, danazole, vincristine: no response rate reported	
anti-D: anti-rhesus immunoglobulins; HP: Helicobacter pylori; ITP: immune thrombocytopenia; IVIG: intravenous immunoglobulins; OPSI = overwhelming post-splenectomy sepsis; PLT = platelet counts; *response reported according to the definition in the respective publication		

Pubmed

("purpura, thrombocytopenic, idiopathic"[Mesh])
OR ("idiopathic thrombocytopenia"[tiab] OR "immune
thrombocytopenia"[tiab] OR "autoimmune thrombocyto-
penia"[tiab] OR werlhof*[tiab] OR ITP[tiab])

AND

("child"[Mesh] OR "adolescent"[Mesh] OR "pediat-
rics"[Mesh]) OR (child*[tiab] OR adolescen*[tiab]
OR juvenile[tiab] OR youth*[tiab] OR teen*[tiab] OR
paediatric*[tiab] OR pediatric*[tiab] OR minor*[tiab]
OR infan*[tiab])

AND

(chronic[tiab] OR persistent[tiab] OR refractory[tiab])

AND

("safety" [Mesh:NoExp] OR "adverse effects"
[Mesh:NoExp] OR "watchful waiting" [Mesh] OR "rituxi-
mab" [Mesh] OR "thrombopoietin" [Mesh] OR "splene-
ctomy" [Mesh] OR "tyrosine kinase inhibitors" [Mesh] OR
"immunoglobulins, intravenous" [Mesh] OR "steroids"
[Mesh] OR "vincristine" [Mesh] OR "vinblastine" [Mesh]
OR "mycophenolic acid" [Mesh] OR "immunosuppres-
sive agents" [Mesh]) OR (efficacy[tiab] OR safety[tiab]
OR adverse*[tiab] OR side*[tiab] OR treatment[tiab]
OR therapy[tiab] OR "second-line"[tiab] OR "watchful
waiting"[tiab] OR observation*[tiab] OR rituximab
[tiab] OR thrombopoietin*[tiab] OR TPO[tiab] OR TPO-
RA*[tiab] OR romiplostim[tiab] OR eltrombopag[tiab]
OR avatrombopag [tiab] OR lusutrombopag[tiab] OR
splenectomy[tiab] OR immune*[tiab] OR cyclophos-
phamide[tiab] OR cyclofosfamide[tiab] OR cyclo-
sporine[tiab] OR azathioprine[tiab] OR dapsone[tiab]
OR "protein tyrosine kinase inhibitor*[tiab] OR "ty-
rosine protein kinase inhibitor*[tiab] OR TKI[tiab] OR
"tyrosine kinase inhibitor*[tiab] OR "intravenous an-
tibod*[tiab] OR immunoglobulin*[tiab] OR "intrave-
nous IG"[tiab] OR IVIG[tiab] OR anti-D[tiab] OR "anti
rh"[tiab] OR rhesus*[tiab] OR steroid*[tiab] OR corti-
co*[tiab] OR vincristine[tiab] OR vinblastine[tiab] OR
danazol[tiab] OR mycophenol*[tiab] OR cellcept[tiab]
OR immunosuppress*[tiab] OR "immuno suppress*"
[tiab] OR immunodepress*[tiab])

Embase

'idiopathic thrombocytopenic purpura'/exp OR 'auto-
immune thrombocytopenia'/de OR ('idiopathic throm-
bocytopenia' OR 'autoimmune thrombocytopenia' OR 'im-
mune thrombocytopenia' OR 'werlhof*' OR 'ITP'):ti,ab,kw

AND

'child'/de OR 'infant'/de OR 'adolescent'/de OR 'juve-
nile'/de OR 'minor (person)'/exp OR ('child*' OR 'infant*'
OR 'adolescent*' OR 'juvenile' OR 'youth*' OR 'teen*'

OR 'pediatric*' OR 'paediatric*' OR 'minor*'):ti,ab,kw

AND

('chronic' OR 'persistent' OR 'refractory'):ti,ab,kw

AND

'safety'/de OR 'adverse event'/de OR 'side effect'/de
OR 'watchful waiting'/exp OR 'second-line treatment'/
exp OR 'rituximab'/exp OR 'thrombopoietin'/exp OR
'thrombopoietin receptor'/exp OR 'romiplostim'/exp
OR 'eltrombopag'/exp OR 'avatrombopag'/exp OR
'lusutrombopag'/exp OR 'splenectomy'/exp OR 'cyclo-
phosphamide'/exp OR 'cyclosporine'/exp OR 'azathio-
prine'/exp OR 'protein tyrosine kinase inhibitor'/de OR
'immunoglobulin'/de OR 'rhesus D antibody'/exp OR
'steroid'/de OR 'corticosteroid'/de OR 'vincristine'/exp
OR 'vinblastine'/exp OR 'danazol'/exp OR 'mycophen-
olate mofetil'/exp OR 'immunosuppressive agent'/de
OR ('efficacy' OR 'safety' OR 'adverse*' OR 'side*' OR
'treatment' OR 'therapy' OR 'second-line' OR 'watch-
ful waiting' OR 'observation' OR 'rituximab' OR 'throm-
bopoietin*' OR 'TPO' OR 'TPO-RA*' OR 'romiplostim'
OR 'eltrombopag' OR 'avatrombopag' OR 'lusutrom-
bopag' OR 'splenectomy' OR 'immune*' OR 'cyclofos-
famide' OR 'cyclophosphamide' OR 'cyclosporine' OR
'azathioprine' OR 'dapsone' OR 'protein tyrosine ki-
nase inhibitor*' OR 'tyrosine protein kinase inhibitor*'
OR 'TKI' OR 'tyrosine kinase inhibitor*' OR 'immuno-
globulin*' OR 'intravenous antibody*' OR 'intravenous
IG' OR 'IVIG' OR 'anti-D' OR 'anti rh' OR 'rhesus*' OR
'cortico*' OR 'steroid*' OR 'vincristine' OR 'vinblas-
tine' OR 'danazol' OR 'mycophenol*' OR 'cellcept'
OR 'immunosuppress*' OR 'immuno suppress*' OR
'immunodepress*'):ti,ab,kw

Web of science

TS=("idiopathic thrombocytopenia" OR "immune throm-
bocytopenia" OR "autoimmune thrombocytopenia" OR
"werlhof*" OR "ITP")

AND

TS=("child*" OR "adolescent*" OR "juvenile" OR
"youth*" OR "teen*" OR "paediatric*" OR "pediatric*"
OR "minor*" OR "infan*")

AND

TS=("chronic" OR "persistent" OR "refractory")

AND

TS=("efficacy" OR "safety" OR "adverse*" OR "side*"
OR "treatment" OR "therapy" OR "second-line" OR
"watchful waiting" OR "observation*" OR "rituxi-
mab" OR "thrombopoietin*" OR "TPO" OR "TPO-
RA*" OR "romiplostim" OR "eltrombopag" OR "ava-
trombopag" OR "lusutrombopag" OR "splenectomy"

OR "immune*" OR "cyclophosphamide" OR "cyclofosfamide" OR "cyclosporine" OR "azathioprine" OR "dapson" OR "protein tyrosine kinase inhibitor*" OR "tyrosine protein kinase inhibitor*" OR "TKI" OR "tyrosine kinase inhibitor*" OR "intravenous antibody*" OR "immunoglobulin*" OR "intravenous IG" OR "IVIG" OR "anti-D" OR "anti rh" OR "rhesus*" OR "steroid*" OR "cortico*" OR "vincristine" OR "vinblastine" OR "danazol" OR "mycophenol*" OR "cellcept" OR "immunosuppress*" OR "immuno suppress*" OR "immunodepress*")

Scopus

TITLE-ABS(("idiopathic thrombocytopenic*" OR "immune thrombocytopenic*" OR "autoimmune thrombocytopenic*" OR "werlhof*" OR "ITP") OR AUTHKEY(("idiopathic thrombocytopenic*" OR "immune thrombocytopenic*" OR "autoimmune thrombocytopenic*" OR "werlhof*" OR "ITP"))

AND

TITLE-ABS(("child*" OR "adolescen*" OR "juvenile" OR "youth*" OR "teen*" OR "paediatric*" OR "pediatric*" OR "minor*" OR "infan*") OR AUTHKEY(("child*" OR "adolescen*" OR "juvenile" OR "youth*" OR "teen*" OR "paediatric*" OR "pediatric*" OR "minor*" OR "infan*"))

AND

TITLE-ABS(("chronic" OR "persistent" OR "refractory") OR AUTHKEY(("chronic" OR "persistent" OR "refractory"))

AND

TITLE-ABS(("efficacy" OR "safety" OR "adverse*" OR "side*" OR "treatment" OR "therapy" OR "second-line" OR "watchful waiting" OR "observation*" OR "rituximab" OR "thrombopoietin*" OR "TPO" OR "TPO-RA*" OR "romiplostim" OR "eltrombopag" OR "avatrombopag" OR "lusutrombopag" OR "splenectomy" OR "immune*" OR "cyclophosphamide" OR "cyclofosfamide" OR "cyclosporine" OR "azathioprine" OR "dapson" OR "protein tyrosine kinase inhibitor*" OR "tyrosine protein kinase inhibitor*" OR "TKI" OR "tyrosine kinase inhibitor*" OR "intravenous antibody*" OR "immunoglobulin*" OR "intravenous IG" OR "IVIG" OR "anti-D" OR "anti rh*" OR "rhesus*" OR "steroid*" OR "cortico*" OR "vincristine" OR "vinblastine" OR "danazol" OR "mycophenol*" OR "cellcept" OR "immunosuppress*" OR "immuno suppress*" OR "immunodepress*") OR AUTHKEY(("efficacy" OR "safety" OR "adverse*" OR "side*" OR "treatment" OR "therapy" OR "second-line" OR "watchful waiting" OR "observation*" OR "rituximab" OR "thrombopoietin*" OR "TPO" OR "TPO-RA*" OR "romiplostim" OR "eltrombopag" OR "avatrombopag" OR "lusutrombopag" OR "splenectomy" OR "immune*" OR "cyclophosphamide" OR "cyclofosfamide" OR "cyclosporine" OR "azathioprine"

OR "dapson" OR "protein tyrosine kinase inhibitor*" OR "tyrosine protein kinase inhibitor*" OR "TKI" OR "tyrosine kinase inhibitor*" OR "intravenous antibody*" OR "immunoglobulin*" OR "intravenous IG" OR "IVIG" OR "anti-D" OR "anti rh" OR "rhesus*" OR "steroid*" OR "cortico*" OR "vincristine" OR "vinblastine" OR "danazol" OR "mycophenol*" OR "cellcept" OR "immunosuppress*" OR "immuno suppress*" OR "immunodepress*")

Central (cochrane)

#1 [mh "purpura, thrombocytopenic, idiopathic"]
#2 (("idiopathic" NEXT thrombocytopenic*) OR ("immune" NEXT thrombocytopenic*) OR ("autoimmune" NEXT thrombocytopenic*) OR (werlhof*) OR "ITP"):ti,ab,kw

#3 = #1 OR #2

#4 [mh "child"] OR [mh "adolescent"] OR [mh "pediatrics"]

#5 ((child*) OR (adolescen*) OR "juvenile" OR (youth*) OR (teen*) OR (paediatric*) OR (pediatric*) OR (minor*) OR (infan*)):ti,ab,kw

#6 = #4 OR #5

#7 ("chronic" OR "persistent" OR "refractory"):ti,ab,kw
#8 [mh ^"safety"] OR [mh ^"adverse effects"] OR [mh "watchful waiting"] OR [mh "rituximab"] OR [mh "thrombopoietin"] OR [mh "splenectomy"] OR [mh "tyrosine kinase inhibitors"] OR [mh "immunoglobulins, intravenous"] OR [mh "steroids"] OR [mh "vincristine"] OR [mh "vinblastine"] OR [mh "mycophenolic acid"] OR [mh "immunosuppressive agents"]

#9 ("efficacy" OR "safety" OR (adverse*) OR (side*) OR "treatment" OR "therapy" OR "second-line" OR "watchful waiting" OR (observation*) OR "rituximab" OR (thrombopoietin*) OR "TPO" OR (TPO-RA*) OR "romiplostim" OR "eltrombopag" OR "avatrombopag" OR "lusutrombopag" OR "splenectomy" OR (immune*) OR "cyclophosphamide" OR "cyclofosfamide" OR "cyclosporine" OR "azathioprine" OR "dapson" OR ("protein tyrosine kinase" NEXT inhibitor*) OR ("tyrosine protein kinase" NEXT inhibitor*) OR "TKI" OR ("tyrosine kinase" NEXT inhibitor*) OR (intravenous NEXT antibody*) OR (immunoglobulin*) OR "intravenous IG" OR "IVIG" OR "anti-D" OR "anti rh" OR (rhesus*) OR (steroid*) OR (cortico*) OR "vincristine" OR "vinblastine" OR "danazol" OR (mycophenol*) OR "cellcept" OR (immunosuppress*) OR (immuno NEXT suppress*) OR (immunodepress*)):ti,ab,kw

#10 = #8 OR #9

#11 = #3 AND #6 AND #7 AND #10

Supplementary TABLE 2: JBI Critical Appraisal checklist for case series

	Clear criteria for inclusion?	Condition measured in a standard, reliable way?	Valid methods for identification of condition?	Consecutive inclusion of participants?	Complete inclusion of participants?	Clear reporting of demographics?	Clear reporting of clinical information?	Outcomes or follow-up results clearly reported?	Presenting site(s)/clinic(s)/ demographic information clearly reported?	Appropriate statistical analysis?
Leblebisatan et al. (25)	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
Lopes et al. (26)	N	Y	Y	U	U	Y	Y	Y	Y	Y
Mokhtar et al. (35)	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA
Marquez-Alonzo et al. (36)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Grainger et al. (37)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kuhne et al. (43)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Adams et al. (50)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Ferrara et al. (51)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Sabhan et al. (52)	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Sirachainan et al. (58)	Y	Y	Y	N	U	Y	Y	Y	Y	Y
Perrotta et al. (59)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Ansari et al. (63)	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Citak et al. (65)	Y	Y	Y	U	Y	Y	Y	Y	N	NA
Wang et al. (66)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Parodi et al. (67)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Jasinski et al. (69)	Y	Y	Y	U	U	Y	Y	Y	Y	N
Hrstkova et al. (70)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Donato et al. (75)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Panigrahi et al. (72)	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Sun et al. (78)	Y	Y	Y	Y	Y	N	Y	Y	N	NA
Hu et al. (79)	Y	Y	Y	Y	Y	Y	Y	Y	N	NA
Ramenghi et al. (84)	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Jayabose et al. (91)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ferrara et al. (95)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Neefjes et al. (96)	Y	Y	Y	N	N	N	N	Y	N	N
Maghbool et al. (97)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yamazaki et al. (106)	Y	Y	Y	N	U	Y	Y	U	Y	Y
Y = yes; N = no; U = unclear; NA = not applicable										

Supplementary TABLE 3: JBI Critical Appraisal checklist for cohort studies (Continued on next page)

	Groups similar and recruited from same population?	Exposure measured similarly for exposed and unexposed groups?	Exposure measured in a valid and reliable way?	Confounding factors identified?	Strategies to deal with confounding factors stated?	Participants free of outcome at start of study (or at the moment of exposure)?	Outcomes measured in a valid and reliable way?	Follow up time reported and long enough for outcomes to occur?	Follow up complete, and if not, reasons to loss to follow up described and explored?	Strategies to address incomplete follow up utilized?	Appropriate statistical analysis?
Ducassou et al. (11)	NA	NA	N	N	N	Y	Y	Y	Y	NA	Y
Cheng et al. (15)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Yang et al. (16)	NA	NA	Y	N	NA	Y	Y	Y	N	N	Y
Giordano et al. (17)	NA	NA	Y	Y	N	Y	Y	Y	Y	Y	Y
Richert-Przygonska et al. (18)	NA	NA	Y	N	N	Y	Y	Y	Y	Y	Y
Chen et al. (19)	NA	NA	Y	U	N	Y	Y	Y	Y	N	Y
Cheng et al. (20)	NA	NA	Y	Y	Y	Y	Y	N	Y	Y	Y
Giordano et al. (21)	NA	NA	Y	N	N	Y	Y	Y	Y	Y	Y
Wang et al. (22)	NA	NA	Y	N	NA	Y	Y	Y	Y	N	Y
Wang et al. (23)	NA	NA	Y	N	N	Y	Y	Y	Y	Y	Y
Dong et al. (24)	NA	NA	Y	Y	Y	Y	Y	N	Y	Y	Y
Ramaswamy et al. (27)	NA	NA	Y	Y	N	Y	Y	Y	Y	Y	Y
Obrisca et al. (28)	NA	NA	Y	Y	N	Y	Y	N	Y	N	Y
Seidel et al. (31)	NA	NA	Y	Y	N	Y	Y	Y	Y	N	Y
Bussel et al. (32)	Y	Y	Y	N	U	Y	Y	Y	Y	Y	Y
Tarantino et al. (33)	NA	NA	Y	N	N	Y	Y	Y	Y	NA	NA
Mareddy et al. (34)	NA	NA	Y	N	NA	Y	Y	Y	N	N	Y
Wang et al. (39)	NA	Y	Y	U	N	Y	Y	Y	Y	NA	Y
Hu et al. (40)	Y	Y	Y	N	N	Y	Y	Y	Y	NA	Y
Wang et al. (41)	NA	NA	Y	N	N	Y	Y	Y	Y	NA	Y
Ruggiero et al. (44)	NA	NA	N	N	N	Y	Y	Y	Y	NA	Y
Chen et al. (45)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Borgna-Pignatti et al. (46)	NA	NA	Y	N	N	Y	U	N	N	N	Y
Wali et al. (47)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Yadav et al. (48)	NA	NA	Y	N	N	Y	Y	N	N	N	N
Özer et al. (49)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Naithani et al. (56)	NA	NA	Y	N	N	Y	Y	U	Y	NA	Y
Yetgin et al. (57)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Choudhary et al. (61)	NA	NA	Y	N	N	Y	Y	N	Y	NA	Y
Liu et al. (62)	NA	NA	Y	N	NA	Y	Y	Y	Y	N	Y
Rao et al. (64)	NA	NA	Y	N	N	Y	Y	Y	U	U	Y
Ma et al. (68)	N	Y	Y	N	N	Y	Y	Y	N	N	Y
Khera et al. (73)	NA	NA	Y	N	N	Y	Y	Y	N	N	Y
Damodar et al. (74)	NA	NA	Y	Y	Y	Y	Y	N	U	N	Y
Patel et al. (75)	NA	NA	Y	N	NA	Y	Y	Y	N	N	Y

Supplementary TABLE 3: JBI Critical Appraisal checklist for cohort studies (End of table)

	Groups similar and recruited from same population?	Exposure measured similarly for exposed and unexposed groups?	Exposure measured in a valid and reliable way?	Confounding factors identified?	Strategies to deal with confounding factors stated?	Participants free of outcome at start of study (or at the moment of exposure)?	Outcomes measured in a valid and reliable way?	Follow up time reported and long enough for outcomes to occur?	Follow up complete, and if not, reasons to loss to follow up described and explored?	Strategies to address incomplete follow up utilized?	Appropriate statistical analysis?
Bharadwaj et al. (76)	NA	NA	Y	N	N	Y	Y	Y	N	N	Y
Liu et al. (80)	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Aronis et al. (81)	NA	NA	NA	Y	Y	Y	Y	Y	N	N	U
Reid et al. (82)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Donato et al. (83)	NA	NA	NA	Y	Y	Y	U	Y	N	N	U
Pincez et al. (85)	NA	NA	NA	Y	Y	Y	Y	Y	N	N	Y
El-Alfy et al. (86)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wang et al. (87)	NA	NA	NA	N	N	Y	Y	Y	N	N	N
Ahmed et al. (88)	NA	NA	NA	N	N	Y	Y	N	N	N	Y
Koc et al. (89)	Y	Y	Y	N	N	Y	Y	Y	NA	NA	Y
Kim et al. (90)	NA	NA	NA	N	N	Y	Y	N	U	U	Y
Kato et al. (92)	NA	NA	NA	N	N	Y	Y	Y	Y	NA	Y
Shim et al. (93)	NA	NA	Y	N	N	Y	Y	Y	U	U	Y
Kim et al. (94)	NA	NA	NA	Y	Y	Y	Y	Y	U	N	Y
Hodeib et al. (98)	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Russo et al. (99)	NA	NA	Y	N	N	Y	Y	Y	Y	Y	Y
Ahmed et al. (100)	Y	Y	Y	N	N	Y	Y	Y	Y	U	Y
Fu et al. (107)	NA	NA	Y	N	NA	Y	Y	N	Y	NA	Y
Y = yes; N = no; U = unclear; NA = not applicable											

Supplementary TABLE 4: JBI Critical Appraisal checklist for randomized controlled trials

	True randomization for assignment of participants?	Allocation to treatment groups concealed?	Treatment groups similar at baseline?	Participants blind to treatment assignment?	Those delivering treatment blind to treatment assignment?	Treatment groups treated identically other than the intervention of interest?	Outcome assessors blind to treatment assignment?	Outcomes measured in the same way for groups?	Outcomes measured in a reliable way?	Follow-up complete and if not, differences adequately described and analysed?	Participants analysed in the groups to which they were randomized?	Appropriate statistical analysis?	Trial design appropriate and any deviations accounted for?
Bussel et al. (13)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Grainger et al. (14)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Elalfy et al. (29)	U	N	Y	U	U	Y	U	Y	Y	Y	Y	Y	U
Tarantino et al. (30)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Grace et al. (38)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Ma et al. (42)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
El Alfy et al. (53)	N	N	U	N	N	U	N	Y	Y	U	U	Y	N
El Alfy et al. (54)	U	U	Y	U	U	Y	U	Y	Y	U	Y	U	N
Hedlund-Treutiger et al. (55)	Y	N	Y	N	N	Y	N	Y	Y	N	Y	Y	Y
Mousavi-Hasanzadeh et al. (60)	Y	U	Y	U	U	N	U	Y	Y	Y	Y	Y	Y
Treepongkaruna et al. (101)	Y	N	Y	N	N	Y	N	Y	Y	U	Y	Y	Y
Brito et al. (102)	Y	U	Y	N	N	Y	U	Y	Y	Y	Y	Y	Y
Wang et al. (103)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Han et al. (104)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y = yes; N = no; U = unclear; NA = not applicable													

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