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ABSTRACT

Introduction: Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low platelet count (<100 × 10^9/L) with an increased risk of bleeding. Recent (2019) guidelines from the International Consensus Report (ICR) expert panel and the American Society of Hematology (ASH) provide updated recommendations for the diagnosis and management of ITP.

Areas covered: The 2019 ICR and ASH guidelines are reviewed, and differences and similarities highlighted. Clinical approaches to the treatment of ITP are discussed, including the role of fostamatinib which is an approved treatment option in adult patients who are refractory to other treatments.

Expert opinion: The 2019 ICR and ASH guidelines reflect recent changes in the management of ITP. Current treatment approaches for ITP are more rational and evidence-based than in the past. Patients should be treated based on their needs rather than on disease stage, and patient-specific outcomes, (e.g. quality of life) should be considered. Whilst corticosteroids are the mainstay of initial ITP treatment their use should be limited. For subsequent treatment, the use of thrombopoietin receptor agonist (TPO-RA) agents, fostamatinib and rituximab in adults is supported by robust evidence. Rituximab and recently approved fostamatinib offer viable alternatives to splenectomy.

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1. Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low platelet count (<100 × 10^9/L) with a variably increased risk of bleeding. These definitions and standard terminology for ITP were developed by an International Working Group of expert clinicians who also defined different phases of the disease: newly diagnosed being within 3 months from diagnosis, persistent ITP from 3 to 12 months from diagnosis, and chronic ITP lasting for more than 12 months [1].Table 1

Secondary ITP is a broad term which includes all forms of immune-mediated thrombocytopenia that are due to an underlying disease or drug exposure. Secondary ITP is associated with diseases including systemic lupus erythematosus, antiphospholipid syndrome, immunodeficiency states (IgA deficiency and common variable immunodeficiency), lymphoproliferative disorders (chronic lymphocytic leukemia, large granular lymphocytic leukemia, lymphoma, and autoimmune lymphoproliferative syndrome), infection with human immunodeficiency virus (HIV) H Pylori, CMV, and hepatitis C virus (HCV); and can also develop following therapy with drugs such as heparin and quinidine [2].

Published data on the epidemiology of ITP among adults are limited. Studies report an incidence of ITP among European adults ranging from 1.6 to 3.9 per 100,000 persons per year [3–5], and a prevalence ranging from 9.5 to 23.6 per 100,000 persons [5]. Incidence was higher among women than men but reversed in older patients [5].

ITP is a disease of increased peripheral platelet destruction and/or reduced or inadequate platelet production. Although most patients are identified to have antibodies to specific platelet membrane glycoproteins, the trigger for production of autoantibodies against platelets is currently unknown. Furthermore, megakaryocytes, the precursors of platelets in the bone marrow, may suffer damage by platelet autoantibodies which limits their production of platelets. Studies show that most patients have inadequately low levels of platelet production [6–10].

Patients with chronic ITP have an increased risk of bruising and spontaneous bleeding events, and especially may have an increased risk of serious bleeding events with platelet counts <30 × 10^9/L. Life-threatening bleeding is rare in patients with platelet counts >10 × 10^9/L [1,2,11–15].

Fatigue is common among patients with ITP, although its causes are not well understood [16–18] and it has a major impact on patients' health-related quality of life (HRQoL) [19]. Surveys of ITP patients in the UK and US found a prevalence of fatigue of 39% and 22%, respectively, which was higher than in normal subjects ($p < 0.0001$ for both) [17]. The recent ITP World Impact Survey (iWISh) found that 50% of patients (n = 1507) reported fatigue both at initiation of their ITP and at survey completion 5 years later whilst physicians (n = 472) believed that 38% of their patients experienced fatigue [18]. Fatigue in ITP may correlate with thrombocytopenia but may not improve with an increase in platelet numbers [16,17].

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Article highlights

- The 2019 guidelines from the International Consensus Report (ICR) expert panel and the American Society of Hematology (ASH) for primary immune thrombocytopenia (ITP) reflect recent changes in the management of ITP in clinical practice.
- Corticosteroids are the mainstay of initial treatment of ITP but their use should be shortened to the first 3 months of treatment. IVIg and IV anti-D are also used in severe cases and in patients unresponsive to corticosteroids.
- For subsequent therapy, the use of thrombopoietin receptor agonist (TPO-RA) agents, fostamatinib, and rituximab in adults is supported by robust evidence.

2. Methods

The goal of this article was to review recent (2019) guidelines from the International Consensus Report (ICR) expert panel and the American Society of Hematology (ASH) which provide updated recommendations for the diagnosis and management of ITP. We sought to specifically examine the evidence provided by new therapeutic options and their potential role in ITP relative to traditional treatment recommendations. The review is based upon presentations at two Expert-based symposia held in 2020:

- ISTH Virtual Congress July 2020 Update on immune thrombocytopenia: clinical perspectives
- BSH Virtual Congress December 2020: Practical Experience with a New Treatment for Chronic ITP

This was augmented with peer-reviewed papers identified by a search of PubMed as well as papers known to authors of this review.

3. Overview of ITP diagnosis and treatment

ITP is one of the most common causes of acquired thrombocytopenia in otherwise asymptomatic adults. Major diagnostic concerns include distinguishing ITP from other causes of thrombocytopenia (systemic disease, infection, drugs, and primary hematologic disorders) which often have a similar presentation but may require different management approaches; and the lack of a sensitive or specific diagnostic test for ITP [10]. There are many other potential causes of thrombocytopenia, and some may be overlooked, e.g. myelodysplastic syndrome, drug-induced thrombocytopenia, hereditary thrombocytopenia, and cyclical thrombocytopenia [10,20–22].

Diagnosis of ITP is one of exclusion [1,2]. The initial basic diagnostic evaluation includes patient and family histories, physical examination, complete blood and reticulocyte counts, peripheral blood film, quantitative immunoglobulin measurement, blood group (Rhesus), direct antiglobulin test, *Helicobacter pylori* stool antigen, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) status, bone marrow biopsy in selected patients, and laboratory investigation of hemolysis (Box 1) [23].

The misdiagnosis rate of primary ITP was assessed in 614 consecutive patients with thrombocytopenia (platelet count $<150 \times 10^9$/L) in the prospective, longitudinal McMaster ITP Registry. A total of 295 patients were initially diagnosed with primary ITP, of whom 36 (12.2%) were reclassified during follow-up. A further 319 patients were initially diagnosed with another thrombocytopenic condition, of whom 10 (3.1%) were reclassified as having primary ITP. Misdiagnosed patients (n = 46) were more often male, had milder thrombocytopenia, and fewer grade 2 bleeds than patients correctly diagnosed with primary ITP (n = 259) [24]. ITP is most common in the elderly among whom it is seen more in males.

The goals of ITP therapy are to prevent severe bleeding episodes, maintain a target platelet count of at least $20–30 \times 10^9$/L, minimize toxicity of treatments, and optimize HRQoL. The timing and selection of treatment is dependent on the nature of the disease and patient-specific variables such as age, sex, occupation/activities, comorbidities and medication for their treatment, and pregnancy. As reviewed below, data from randomized controlled trials (RCTs) are now available for several ITP treatments (e.g. romiplostim, eltrombopag, fostamatinib, avatrombopag), but all these trials compare active medication with placebo or standard of care. There are currently no comparative studies of second-line/subsequent treatments for ITP.

Box 1. Diagnosis of ITP in children and adults. Adapted from Provan et al. 2019 [23].

Basic evaluation	Assays of Potential Value	Tests of unproven/uncertain benefit
Patient history	Direct platelet glycoprotein-specific antibodies	Thrombopoietin (TPO)
Family history	Antiphospholipid antibodies[c]	Reticulated platelets/immature platelet fraction
Physical examination	Antithyroid antibodies and thyroid function	Bleeding time
Complete blood count	Pregnancy test[d]	Serum complement
Reticulocyte count	Antinuclear antibodies	
Peripheral blood film	Viral polymerase chain reaction (PCR) for Epstein-Barr virus (EBV), parvovirus and cytomegalovirus (CMV)	
Quantitative immunoglobulins[a]	Bone marrow biopsy[e]	
Blood group (Rhesus)	Direct antiglobulin test	
Human immunodeficiency virus (HIV)[b]	Helicobacter pylori[b]	
Hepatitis C virus (HCV)[b]		
Hepatitis B virus (HBV)		

[a]Considered in children with ITP and recommended in children with persistent or chronic ITP for reassessment evaluation. [b] In the appropriate geographical setting. [c] Including anticardiolipin and lupus anticoagulant. [d] In women of childbearing potential. [e] In selected patients, including patients who have other abnormalities identified on their blood smear, such as white cell dysplasia or anemia that cannot be explained by bleeding or iron deficiency

The mainstay of treatment for ITP has been corticosteroids which have been used in clinical practice for around 70 years. Intravenous immunoglobulin (IVIg) or anti-D immunoglobulin have also been frequent early options. Failure of these classical first-line options was usually followed by splenectomy, which has been undertaken for nearly 100 years, but its use worldwide has been declining. For refractory ITP which occurs in 25–30% of patients, a mix of immunosuppressive therapy, immunomodulatory drugs – danazol and dapsone, chemotherapeutic agents and *H. pylori* eradication have been used but these treatments are evidence-based only in single-arm studies [10]. These treatment options have been superseded by recent guidelines from the ICR expert panel [23] and ASH [25] which are discussed below.

3.1. Pregnancy

ITP is often seen in otherwise healthy women of childbearing age, many of whom may have their first platelet count during pregnancy. Thrombocytopenia occurs in about 7% of pregnant women and a UK study estimated the incidence of severe ITP (platelet count $<50 \times 10^9$/L) in pregnancy as 0.83 per 10,000. Platelet antibodies are a potential threat to newborns as they can cross the placenta causing neonatal thrombocytopenia. Pregnancy is also associated with other causes of thrombocytopenia including gestational thrombocytopenia and pregnancy-associated microangiopathic syndromes [26,27].

2019 ICR guidelines for ITP in pregnancy are outlined in Box 2 [23]. Thrombopoietin receptor agonist (TPO-RA) therapy is an option in late pregnancy (>30 weeks gestation), and if used, romiplostim may be preferred due to its fewer adverse events (AEs), including lack of hepatic toxicity and iron chelation.

4. Updated guidelines for ITP

The 2019 ICR guidelines provide consensus recommendations on the diagnosis and management of ITP in adults, during pregnancy and in children, and pays particular attention to improving the patient's quality of life (QoL). Guidelines emphasize that patients should be treated based on their needs rather than on their disease phase – newly diagnosed, persistent, or chronic ITP [23]. The 2019 evidence-based ASH guidelines formulated 21 recommendations on the management of ITP in adults and children with newly diagnosed, persistent, and chronic disease refractory to first-line therapy, and with non-life-threatening bleeding [25]. Both sets of guidelines update previous ICR and ASH guidelines published in 2010 and 2011, respectively [10,28]. The 2019 ICR guidelines divide treatment options into initial and subsequent treatment, rather than first-line, second-line, etc. [23]. It is important to recognize that there were only two strong recommendations for adults with ITP in the ASH guidelines but none that were well supported by evidence.

4.1. Initial treatment for newly diagnosed patients

There are no widely adapted or standardized care paths for the treatment of ITP, as few randomized studies comparing different approaches have been conducted for this relatively rare disease. Guidelines indicate that initial treatment options for newly diagnosed adults are corticosteroids, IVIg and anti-D [10,23,25,28].

Although the initial corticosteroid treatment response rate is 50–90%, only 10–30% sustain remission [29]. In addition to the lack of long-term responsiveness, tolerability reduces with repeated dosing. AEs include weight gain, anxiety, insomnia, infections and diabetes [10] which are a concern for most patients, but seemingly less so for clinicians.

Box 2. Outline of 2019 ICR guidelines for ITP in pregnancy, emergency treatment, and patients failing multiple therapies [23].

ITP in pregnancy	Emergency treatment	Patients failing multiple therapies
Initial treatment is with oral corticosteroids or IVIg	Combination of initial treatments including IV corticosteroids & IVIg (usually), where there is an urgent need to increase platelet count; platelet transfusions	Accessory splenectomy
IV anti-D in Rh(D)-positive non-splenectomized women can be well tolerated and effective, but potentially can cause maternal or fetal hemolysis	TPO-RAs should be considered in a patient receiving corticosteroids with life-threatening bleeding and absence of a significant response to IVIg and platelet transfusion	Alemtuzumab
Combination therapy (prednisone + IVIg and/or IV anti-D) can be effective in patients' refractory to single agents alone		Combination of initial and subsequent therapies
Rituximab can be considered for very severe cases, but potential complications are perinatal and neonatal immunosuppression and subsequent infection		Combination chemotherapy
TPO-RAs and recombinant human TPO (only available in China) may be considered in late pregnancy when other treatments have failed, but limited data available.		Enrollment in a clinical trial
		HSCT
		Splenectomy (if not already performed) with pre-splenectomy predictive tests
		Supportive care

HSCT, human stem cell transplant; IVIg, intravenous immunoglobulin; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist

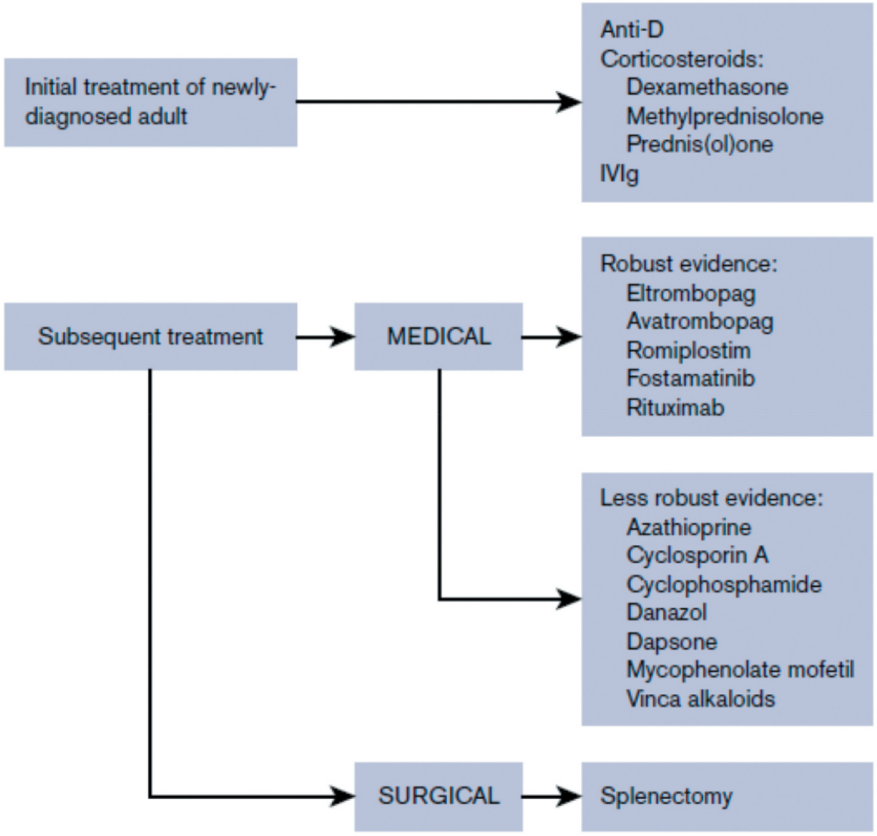

Figure 1. Overview of therapies for the treatment of adult ITP. Reproduced from [23] with permission from Elsevier.

The 2019 ICR guidelines recommend initial treatment with prednisone/prednisolone (1.0 mg/kg daily; maximum dose 80 mg, even for patients weighing >80 kg) for 2 weeks (maximum of 3 weeks) or dexamethasone (40 mg/day for 4 days) repeated up to 3 times. For responsive patients, e.g. platelet count >50 × 10^9/L the prednis(ol)one dose should be tapered, with the aim of stopping treatment by 6 weeks (maximum 8 weeks) even if the platelet count drops during dose tapering. For patients who are non-responsive to the initial dose within 2 weeks, prednis(ol)one should be tapered rapidly over 1 week and stopped. IVIg (1 g/kg) on one or two consecutive days (or 0.4 g/kg/day for 5 days) or IV anti-D immunoglobulin (50–75 µg/kg) where available, can be used to increase the platelet count quickly in patients who are bleeding or have a high risk of bleeding, although these agents are not used routinely. TPO-RAs and rituximab are not considered to be initial therapies [23].

The 2019 ASH guidelines for initial treatment are broadly similar to the new ICR guidelines. Corticosteroids (rather than observation) are recommended in newly diagnosed adults with a platelet count <30 × 10^9/L who are asymptomatic or have minor mucocutaneous bleeding. In patients who are asymptomatic or have minor mucocutaneous bleeding and a platelet count ≥30 × 10^9/L, observation (rather than corticosteroids) is recommended. Hospital admission is advocated for patients with a platelet count <20 × 10^9/L. Guidelines recommend a short course (≤6 weeks) of corticosteroids including treatment and tapering: either dexamethasone (40 mg/day for 4 days) or prednisone (0.5–2.0 mg/kg/day) as initial therapy, but dexamethasone may be preferred if a rapid response is essential. Finally, corticosteroids alone rather than in combination with rituximab should be given for initial therapy [25].

There is no consensus at this point regarding a preference for dexamethasone or prednisone. The initial reason to use dexamethasone (increased rate of cure) has not eventuated so different practitioners choose one or the other according to their preferences and those of their patients.

In summary, both ICR and ASH guidelines recommend a short course of corticosteroids for initial therapy. Although corticosteroids can be used as a rescue medication they should not be used for multiple cycles or their dose increased if the platelet count falls during tapering [23,25].

4.2. Subsequent treatment

Both the 2019 ICR and ASH guidelines have updated recommendations for the use of TPO-RAs (romiplostim, eltrombopag, avatrombopag), and rituximab in subsequent treatment courses, following publication of data from recent clinical trials and observational studies [23,25]. The 2019 ICR guidelines also include fostamatinib [23].

Figure 1 summarizes the initial and subsequent treatment options for adult ITP according to the 2019 ICR guidelines. These guidelines include the addition of two new

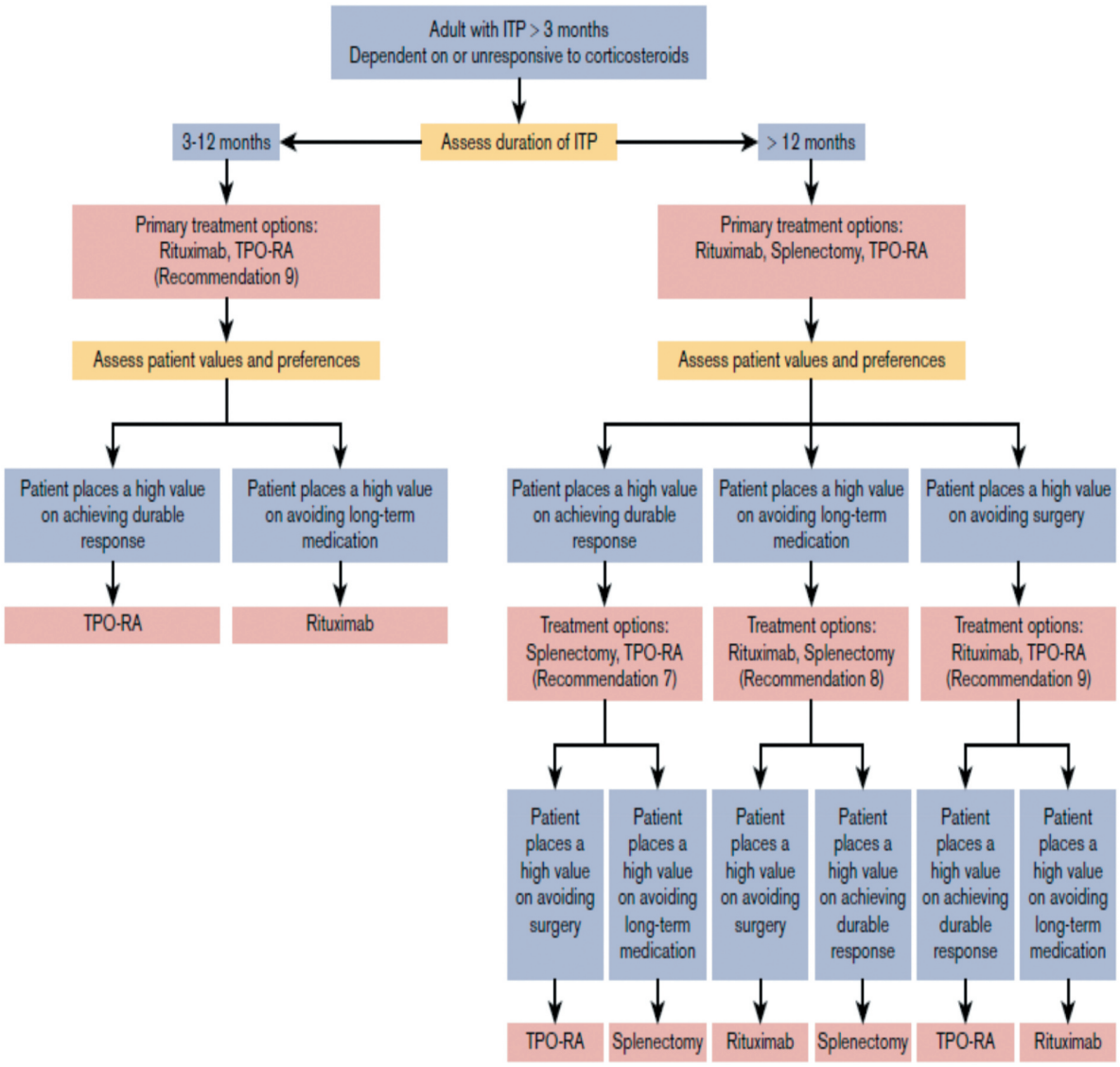

Figure 2. 2019 ASH guidelines: treatment algorithm for selecting second-line therapy in adults with ITP [25].

agents: avatrombopag (a TPO-RA) and fostamatinib. It is worth noting that the ASH Guidelines stopped reviewing any new data published after 2017 so that the licensure of fostamatinib and publication of its trial results were not included; the same is true for avatrombopag. There is robust evidence supporting the use of TPO-RAs, fostamatinib and rituximab as second-line treatment options. TPO-RAs are recommended for both splenectomized and non-splenectomized patients and may be used as emergency treatment (see below). Splenectomy is only recommended after failure of medical (pharmacological) therapy with recommendations that splenectomy not be performed until after ≥1 year from ITP diagnosis. Switching from one TPO-RA to another and sequential therapy has been shown to positively affect response rates in some cases and reduce AEs [30–32]. In the elderly, a recent real-world study demonstrated that eltrombopag and romiplostim were effective with no fatal hemorrhages and a sustained off-therapy response rate of 13.8% [33].

Guidelines indicate that newly diagnosed children requiring treatment, perhaps 20% of the total, should be treated more aggressively, and that TPO-RAs are recommended for all children with persistent/chronic ITP with platelet counts $<30 \times 10^9$/L and either a history of bleeds or impaired QoL. Fostamatinib is not approved for use in children because of potential bone and cartilage growth issues.

There is less robust evidence for the use of immunosuppressive agents including mycophenolate mofetil (MMF), cyclosporin A, and azathioprine, and the 'corticosteroid-sparing' agents, danazol and dapsone [23]. These have, however, been widely used in single arm and anecdotal fashion. To a much lesser extent, they have also been used in combination with other agents.

The 2019 ASH guidelines, for further treatment options in adult patients who are unresponsive to corticosteroids or are corticosteroid-dependent and for whom TPO-RAs are considered as a treatment option, suggest treatment with romiplostim

or eltrombopag, with patient preference for daily oral medication (eltrombopag) or weekly subcutaneous injections (romiplostim) being an important consideration. In adults with ITP lasting ≥3 months who are unresponsive to corticosteroids or are corticosteroid-dependent, guidelines suggest either splenectomy or TPO-RA therapy, with patient preference being a major determinant. Guidelines indicate that in these patients, TPO-RAs are preferred to rituximab, and rituximab is preferred to splenectomy; both of these recommendations are weak with a very low strength of evidence (very low degree of confidence). A treatment algorithm for selecting second-line therapy in adults with ITP, according to ASH guidelines, is shown in Figure 2 [25]. The 2019 ICR guidelines for surgical intervention in subsequent therapy recommend that splenectomy should only be considered after discontinuation of TPO-RA or other medical therapies and conducted not earlier than 12–24 months from diagnosis. Increasing age (≥60 years) is associated with a lower response rate and increased postoperative complications. Indium-labeled autologous platelet scanning (where available) prior to splenectomy is suggested to show that the spleen is the main site of platelet sequestration [23].

Recent ICR guidelines for ITP in emergency treatment, patients failing multiple therapies as well as pregnancy are outlined in Box 2 [23]. For emergency treatment, TPO-RAs should be considered in a patient receiving corticosteroids with life-threatening bleeding and absence of a significant response to IVIg and platelet transfusion. Although there are many options for patients failing several therapies, there is very little reliable data in pregnancy. Furthermore, toxicity to the fetus is understood and is low. Azathioprine, cyclosporin and rituximab are all thought to be relatively safe for the fetus although rituximab may induce late (after 3 months from birth) hypogammaglobulinemia in the infant. Supportive care is an important option using tranexamic acid for patients who are bleeding.

5. Clinical approaches to treatment of ITP

5.1. Corticosteroids: prednisone/prednisolone vs dexamethasone

Corticosteroids are the first-line treatment option for adults with symptomatic ITP, with guidelines recommending prednisone/prednisolone or dexamethasone [23,25]. Dexamethasone has less mineralocorticoid activity than prednisone and is active against plasma cells. A randomized controlled trial compared dexamethasone (40 mg/day for 4 days; n = 95) with prednisone (1.0 mg/kg daily for 4 weeks; n = 97) which was tapered from 4 to 6 weeks. Non-responders (platelet count <30 × 10^9/L or bleeding by day 10) to dexamethasone therapy received an additional 4-day course (40 mg/day). Dexamethasone produced a higher initial complete response (platelet count ≥100 × 10^9/L and absence of bleeding) rate (50.5% *vs*. 26.8%; p = 0.001) and a shorter median time to response (3 *vs*. 6 days, p < 0.001) compared with prednisone, but sustained complete response at 6 months was comparable in both treatment groups (40.0% *vs*. 41.2%). In general, dexamethasone was tolerated better, with AEs such as Cushingoid appearance (13.4% vs. 0%) and weight gain (10.3% vs. 0%) more common with prednisone [34]. A meta-analysis of nine randomized trials (n = 1138) confirmed that the initial platelet count response (at 14 days) was higher with dexamethasone than prednisone (79% vs. 59%, relative risk [RR] 1.22, 95% Confidence Interval [CI] 1.00–1.49; p = 0.048), but that responses at 6 months were similar (54% vs. 43%, RR 1.16, 95% CI 0.79–1 · 71; p = 0.44). Dexamethasone had fewer reported toxicities than prednisone [35].

5.2. Thrombopoietin receptor agonists (TPO-RAs)

The thrombopoietin-mimetics romiplostim, eltrombopag, and avatrombopag are now well established as effective treatments for relapsed, refractory ITP [36–40].

In the RAISE study, 6 months treatment with eltrombopag significantly improved the response rate (platelet count >50 × 10^9/L) compared with placebo (79% *vs*. 28%), with an odds ratio of 8.2 (99% CI: 3.59–18.73; p < 0.0001). Although cessation of eltrombopag treatment resulted in a loss of response, several patients maintained a response suggesting that TPO-RAs can induce treatment-free remission [41].

Treatment-free remission was investigated in a phase 2 study of romiplostim, which was administered for ≤12 months and then dose tapered until discontinuation. In these newly diagnosed patients, romiplostim induced a high response rate (>90%) during treatment and following tapering remission (platelet count ≥50 × 10^9/L for 24 consecutive weeks) was observed in 32% of patients (24/75) [42]. In the phase 2 GIMEMA study, eltrombopag administered for 24 weeks produced an overall response rate of 67% (34/51). Following tapering, the rate of treatment-free remission with eltrombopag was 25% (13/51) [43]. Results from both studies support the use of short-to-medium length treatment with TPO-RAs for patients with early-stage ITP.

Demonstration of the long-term efficacy of TPO-RAs was shown in the EXTEND study of eltrombopag in adults with ITP [44,45] and in studies of romiplostim which showed maintenance of platelet counts for ≥2 years in adults and children [46,47].

In patients refractory to corticosteroids and IVIg, the use of TPO-RAs to increase platelet counts prior to splenectomy was investigated in the retrospective, observational GIMEMA study. Treatment with romiplostim (n = 24) or eltrombopag (n = 7) increased median platelet counts from 11 × 10^9/L to 114 × 10^9/L, with a response rate of 77%. Splenectomy was performed in 29 patients with a complete response rate of 70% [48].

The choice of daily oral eltrombopag or weekly subcutaneous (sc) romiplostim should be made according to patient preference, drug availability, and physician experience. The bioavailability of eltrombopag is altered by food intake (it must be taken on an empty stomach and at least 2 hours before food) and may not be suitable for patients with eating disorders or who need to eat frequent meals. Whilst many patients self-administer romiplostim, some may require help; e.g. hospital or clinic for drug delivery.

Cost is an additional consideration for the choice of a TPO-RA, although cost-effectiveness studies comparing eltrombopag with romiplostim have produced equivocal results. A study of chronic ITP patients in England and Wales found that eltrombopag was more cost-effective than romiplostim in both

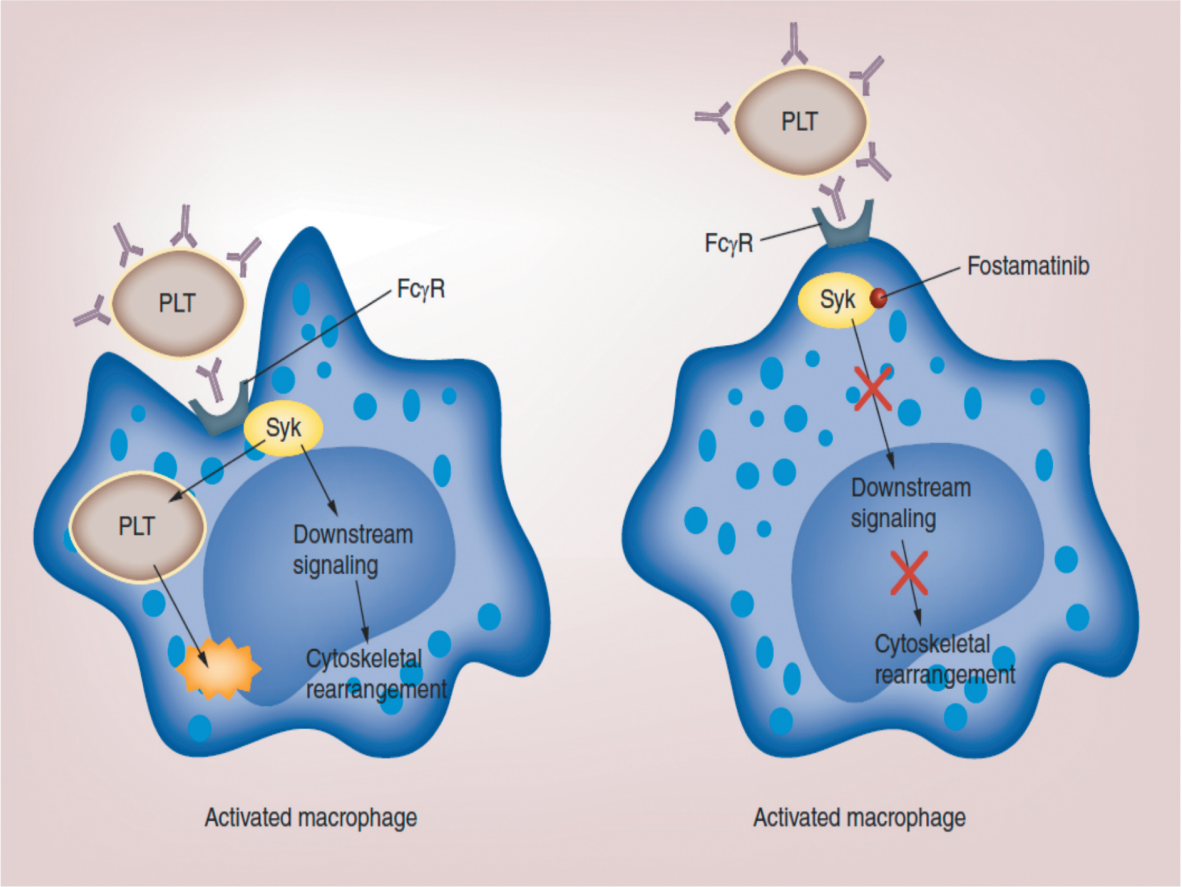

Figure 3. Proposed mechanism of action of fostamatinib in ITP [From 68, with permission from Future Medicine].
FcγR, IgG receptor; PLT, platelet; Syk, spleen tyrosine kinase

splenectomized and non-splenectomized patients [49]. In contrast, analysis of US data for adults with chronic ITP found that romiplostim had lower costs per response than eltrombopag, while both TPO-RAs had lower costs than a watch and rescue strategy [50]. A second US study reported that total costs of eltrombopag treatment were lower than those of romiplostim (total estimated lifetime costs $1.58 *vs* $2.13 million), primarily because of lower drug costs [51].

Preliminary findings from temporary off-label use of a TPO-RA (eltrombopag, n = 8; or romiplostim, n = 7) for severe and/or refractory ITP during pregnancy suggested that both agents appeared to be safe for mother and neonate. With the exception of neonatal thrombocytosis in one neonate, no other TPO-RA-related fetal or neonatal complications nor maternal thromboembolic events were found [52]. This confirms a previous Chinese study of 31 women with 33 pregnancies using a TPO agent licensed in China but not in Europe.

5.3. Rituximab

Rituximab is an anti-CD20 monoclonal antibody which has been widely utilized in patients with ITP, but is not currently approved for this indication. In a systematic review of adults with ITP (n = 313), rituximab therapy produced complete (platelet count >150 × 10^9/L) and overall response (platelet count >50 × 10^9/L) rates of 43.6% (95% CI: 29.5–57.7) and 62.5% (95% CI: 52.6–72.5), respectively [53]. Long-term response rates are 20–40% [54–56].

Age, gender, and duration of the interval from diagnosis to treatment have been reported as predictors of response to rituximab in adult ITP patients [57–65]. Chart review of 67 ITP patients showed that combination therapy of rituximab plus three cycles of dexamethasone produced an overall long-term response of 44%. Long-term remission rates were higher in women compared with men (61% *vs*. 17%) and in patients with a diagnosis with ITP <2 years compared with >2 years (59% *vs*. 19%). These response rates are comparable to those reported for splenectomy [65]. A retrospective analysis of rituximab in ITP (n = 103) reported response and complete response rates of 55% and 36%, respectively. Younger patients (aged <40 years) had a higher probability to achieve a complete response (p = 0.025), and younger women were significantly more likely to achieve a response (p = 0.039) or complete response (p = 0.009). Furthermore, a better long-term response was associated with female sex (p = 0.033) and younger age (p = 0.021) [66].

The standard dose of rituximab is 375 mg/m^2 weekly for 4 weeks, but studies to examine a lower dose which may improve the safety profile and substantially lower expense were inconclusive. A study investigating the activity of lower

dose rituximab (100 mg/weekly for 4 weeks) when compared with standard rituximab in routine clinical practice, produced a lower short-term response rate (61% *vs*. 73%), a higher relapse rate (57% *vs*. 44%) and a lower sustained response (27% *vs*. 40%) [64, Zaja F, unpublished]. In contrast, a retrospective review using data from the UK ITP Registry reported that low-dose rituximab was as effective as the standard dose in improving platelet counts for up to 6 months and achieving 6-month partial remission (34% *vs*. 27%) in ITP patients (n = 301) [67].

5.4. Fostamatinib

Fostamatinib is an inhibitor of spleen tyrosine kinase (Syk), which is involved in the Fc receptor (FcR) and B-cell antigen receptor (BCR) signaling pathways. In macrophages, Syk inhibition impairs the phagocytosis of autoantibody-coated platelets which bind to cell surface FcRs. Among ITP therapeutic agents, fostamatinib has a novel mechanism of action: inhibiting platelet phagocytosis by macrophages, and possibly reducing B cell activation [68–70] (Figure 3). Fostamatinib is an oral medication that can be taken with or without food. The FIT program included two phase 3, randomized trials (FIT-1, FIT-2) and a long-term extension study that included patients with persistent and chronic ITP. Responses (platelet count ≥50 × 10^9/L) were achieved by 54% of patients treated with fostamatinib (n = 146), with 43% of patients responding within 12 weeks and a median time to response of 15 days [70–72]. Responses were maintained for up to 52 months, and the median duration of response was >28 months with a median platelet count of 89 ×10^9/L.

Post hoc analysis of phase 3 study data in 32 patients who received fostamatinib as second-line therapy showed that a higher proportion of these patients achieved an overall response compared with those receiving fostamatinib as later line therapy (78% *vs*. 47%). Responses were maintained for a median of 83% and 86% of treatment days in patients receiving fostamatinib as second-line and later line therapy, respectively. Additionally, a higher proportion of patients with persistent ITP (90%) responded compared with earlier stage (1–2 years), chronic ITP (57%) or later stage chronic ITP (50%). These results suggest that higher response rates may be seen with fostamatinib used as second-line therapy and in persistent ITP patients [73].

Analysis of the occurrence of thromboembolic events (TEEs) in patients treated with fostamatinib for up to 5 years in the phase 3 studies, showed a single event (0.7%), a transient ischemic attack, which resolved spontaneously in a patient with preexisting atherosclerosis [74]. For comparison, the rate of TEEs reported in ITP patients receiving TPO-RAs in multiple studies of up to 8 years duration ranged from 0% to 9% [37,41,45,74–80].

5.5. Splenectomy

A European retrospective analysis of 233 patients with a minimum follow-up of 10 years who received splenectomy as a curative treatment for ITP reported a complete response rate of 77% (platelet count 100 × 10^9/L) and a response rate of 11% (platelet count 30–100 × 10^9/L and ≥2-fold increase from baseline). However, a third of responsive patients relapsed, with a median time from first response to relapse of 15 (range 1–255) months. Overall, the long-term stable response rate following splenectomy was 59%. Long-term complications of surgery were infections (31%) mainly in the lung (18%) including two fatal cases of sepsis (1%), hemorrhage (25%) including 3 fatal cases of intracranial hemorrhage (1.2%), and thrombosis (8%) including 4 fatal cases (2%) due to stroke (n = 2) or acute myocardial infarction (n = 2) [81].

Splenectomy rates in the UK, Europe and the US have declined in recent years [82]. The availability of new treatments such as TPO-RAs, fostamatinib and rituximab, but also patient preference, has contributed to the decline in splenectomy rates [23,82–84]. Recent data from the UK ITP registry showed an overall response (OR) rate for splenectomy of 48% at 24 months (n = 351), with lower response rates in older patients: ORs at 12 months in patients <65 years and ≥65 years were 54.5% and 38.8%, respectively. Median duration of response (DOR) in these groups was 3.3 and 0.8 years, respectively. DOR was reduced with an increase in the number of treatment lines: 2.7 years after second-line and 1.5 years after sixth-line treatment. Complications included infections (12.9%), thromboses (15.2%) and mortality (3.5%) with 1 of 12 patients who died being attributable to surgery [84]. Awareness of these data through patient registries enables patients to make informed decisions about splenectomy.

Improved selection of patients for splenectomy should reduce the risk of short- and long-term complications. As well as younger age, autologous indium^{111}-labeled platelet sequestration is an adjunctive method for clinical prediction of response to splenectomy [85]. Patients with purely or predominantly splenic sequestration have better responses to splenectomy than those with hepatic or mixed sequestration [85–87]. The use of indium^{111}-labeled platelets is recommended by the 2019 ICR guidelines [23].

6. Conclusion

Recommendations from the 2019 ICR and ASH guidelines reflect changes in the management of ITP in recent years following increasing use of TPO-RAs and newer agents over the last 10 years in both adults and children. In addition to TPO-RAs, approved fostamatinib and off-label rituximab offer viable alternatives to splenectomy which is declining in its application.

7. Expert opinion

Current treatment approaches for ITP are more rational and evidence-based than in the past. Patients should be treated based on their needs rather than on the disease stage, i.e. newly diagnosed, persistent or chronic ITP. The publication of new international consensus and ASH ITP guidelines reflect changes in the management of the disease in recent years, with increased use of TPO-RAs and the approval of fostamatinib among the key changes in therapeutic options for ITP. The areas covered by current [23,25] and previous (2010 ICR, 2011 ASH) [10,28] guidelines illustrate that the 2019 ICR guidelines

have a wider scope for TPO-RA treatment than the recent ASH guidelines [23,25].

The main points from the 2019 ICR guidelines are:

- treatment should have a patient-specific focus
- corticosteroids remain as first-line therapy, but their use is restricted (see above)
- further treatment options are divided into medical and surgical (Figure 1) – splenectomy is no longer considered to be a second-line treatment option, and predictive studies using radio-labeled platelets should be used to assess its likely efficacy
- earlier use of TPO-RAs
- fostamatinib and rituximab along with TPO-RAs have robust evidence supporting their use
- newer experimental treatments should only be used in the context of clinical trials.

Table 1. Comparison of 2019 International Consensus Report (ICR) and American Society of Hematology (ASH) guidelines for ITP: main similarities and differences.

	International Consensus Report (ICR) 2019 guidelines [23]	American Society of Hematology (ASH) 2019 guidelines [25]
Diagnosis	Little change	Little change
Corticosteroids	Limit corticosteroid exposure	Limit corticosteroid exposure; dexamethasone or prednisone
Subsequent treatment	Robust evidence for TPO-RAs, rituximab and fostamatinib as viable options	Second-line TPO-RAs
	Earlier use of TPO-RAs	Earlier use of TPO-RAs
Splenectomy	Consider only after failure of medical (pharmacological) therapies	Patient preference
Pediatrics	More aggressive treatment	
Patient-specific	QoL plays a role in decision-making	

There is little change in the 2019 ICR guidelines from the previous 2010 version regarding diagnosis – guidelines are expanded for the differential diagnosis of ITP and hepatitis B virus (HBV) infection, and bone marrow examination/biopsy is no longer necessary for diagnosis. In adult ITP, recent guidelines reflect increasing data with robust evidence available for TPO-RAs and fostamatinib, and recommend that splenectomy should be performed only after failure of medical (pharmacological) therapies. In pregnancy, cyclosporin A (CsA), TPO-RAs, and recombinant human (rh)-TPO (only available in China) are recommended and, in children, more aggressive treatment of newly diagnosed cases is recommended with early use of TPO-RAs for non-responders. Finally, there is a new QoL section for adults and children [23].

The main recommendations from the 2019 ASH guidelines are:

- Limiting the use of corticosteroids to a maximum of 6 weeks regardless of response

Table 2. New agents for immune thrombocytopenia (ITP).

	Mode of action	Study	Main efficacy outcome	Reference
Rilzabrutinib	Bruton Tyrosine Kinase (BTK) inhibition	Open-label Phase 1/2 (n = 47)	43% of patients achieved primary endpoint (≥ 2 consecutive platelet counts ≥ 50 x 10^9/L)	[88]
		Placebo-controlled Phase 3	Ongoing	[NCT04562766]
Rozanolixizumab	Neonatal Fc receptor (FcRn) inhibition	Open-label Phase 2 (n = 66)	66.7% and 54.5% patients treated with single-dose 15 and 20 mg/kg rozanolixizumab, respectively achieved Day 8 platelet count ≥ 50 x 10^9/L	[89]
		Placebo-controlled Phase 3	Ongoing	[NCT04200456]
Efgartigimod	Neonatal FcRn inhibition	Placebo-controlled Phase 2 (n = 38)	Efgartigimod vs. placebo: 46% vs. 25% achieved platelet count ≥50 × 10^9/L on ≥2 occasions; 38% vs. 0% achieved ≥50 × 10^9/L for ≥10 cumulative days	[90]
		Open-label Phase 3	Planned	[NCT04812925]
Oseltamivir	Reduction of platelet glycoprotein desialylation [91]	Randomized, Phase 2: oseltamivir + DXM vs. DXM (n = 90)	Oseltamivir + DXM vs. DXM: day-14 initial response (platelet count ≥30 x10^9/L, ≥2-fold increase from baseline, no bleeding), 86% vs. 66% (p = 0.030), 6-month sustained response, 53% vs. 30% (p = 0 · 032)	[92]
		Placebo-controlled Phase 3	Ongoing	[NCT03520049]
Sutimlimab (BIVV009)	Complement subcomponent C1 (C1s) inhibition [93]	Phase 1 (n = 12)	42% achieved a durable response (platelet counts ≥50 x 10^9/L & >2-fold increase from baseline on 2 consecutive occasions) at 21 weeks	[94]
Bortezomib	Proteosome inhibition	Case report	Bortezomib increased platelet counts resulting in hospital discharge	[95]
Daratumumab	Anti-CD38	Case report	Sustained complete remission in refractory ITP	[96]
Belimumab	B-cell activating factor (BAFF) inhibition	Open label Phase 2 (n = 15)	Combination belimumab + rituximab: 80% overall response rate (platelet count >30 x10^9/L & ≥2-fold increase from baseline) & 67% complete response (platelet count >100x10^9/L) at 1 year	[97]
All-Trans Retinoid Acid (ATRA)	Regulation of complement-IL-1β loop & TNFAIP3/NF-κB/SMAD7 signaling pathway [99,100]	Open-label, randomized, Phase 2: ATRA + danazol vs. danazol (n = 93)	ATRA + danazol vs. danazol: 1-year sustained response (platelet count ≥30 x10^9/L & ≥2-fold increase from baseline) 62% vs. 25% (p = 0 · 00037)	[98]
		Open-label, randomized, Phase 2: ATRA + HD-DXM vs. HD-DXM (n = 300)	ATRA + HD-DXM vs. HD-DXM: 6-month sustained response (platelet count > 50 × 10^9/L) 61% vs. 37% (p = 0.009)	[101]

DXM, dexamethasone; HD-DXM, high-dose dexamethasone

- TPO-RAs (romiplostim or eltrombopag) are recommended as second-line treatment option immediately after corticosteroids
- Recommended for adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids
- Preferable to splenectomy and rituximab
- Rituximab rather than splenectomy in ITP lasting ≥3 months if corticosteroid-dependent or have no response
- Inclusion of patient-reported outcomes helps ensure that the information provided relates closely to benefits that matter most to patients [25]

Note that the 2019 ASH guidelines were based on treatments available in 2017, prior to the approval of fostamatinib or avatrombopag, and for this reason, they are not included in the ASH recommendations [25].

The main similarities and differences between 2019 ICR and ASH guidelines for ITP are summarized in Table 1. There is little change from previous ICR and ASH guidelines [10,28] in diagnostic procedures and both current guidelines recommend limiting corticosteroid exposure. Both 2019 guidelines recommend use of TPO-RAs in early-stage disease and ICR guidelines recommend rituximab and fostamatinib as treatment options with robust evidence supporting their use. As the 2019 ASH guidelines do not address emergent treatment after May 2017, there are no guidelines for fostamatinib or avatrombopag therapy [23,25]. Fostamatinib provides a novel treatment pathway for ITP. Recent results have shown that fostamatinib is well tolerated in the majority of patients, and fostamatinib produces responses in ITP patients including those who are refractory to multiple treatments. When given earlier in the disease pathway for ITP, response rates were better (78%) [73], although larger clinical series are needed. Fostamatinib may have additional benefits in patients with Evans syndrome, and in those with increased risks or rates of thrombosisTable 1.

Both ICR and ASH guidelines recommend that splenectomy should be performed after failure of medical (pharmacological) therapies in the chronic phase of ITP, and at least 12 months from diagnosis. ICR guidelines also recognize the effect of age on splenectomy outcome as increased relapse rates and complications arise in patients aged >60 years; and recommend the use of In-^{111} labeled platelets, laparoscopic splenectomy performed by an expert surgeon and postoperative thromboprophylaxis in patients with platelet counts of 30–50 × 10^9/L [23,25]. In contrast, the recent ASH guidelines reiterate the 2011 guidelines which recommend that both laparoscopic and open splenectomy have equal efficacy [25,28]. Recent ICR guidelines recommend pneumococcal, *H. influenzae* type B and meningococcal vaccination pre-splenectomy, and 6 months before rituximab treatment if possible; and antibiotic prophylaxis given according to national guidelines [23], whilst 2019 ASH guidelines recommend appropriate vaccinations before splenectomy and that patients receive counseling about antibiotics following splenectomy [25].

The development of new agents will enhance the therapeutic landscape for ITP. Emerging agents with ongoing or planned phase 3 trials following promising phase 2 trial results include the Bruton Tyrosine Kinase (BTK) inhibitor, rilzabrutinib; the neonatal Fc receptor (FcRn) inhibitors, rozanolixizumab and efgartigimod; and the antiviral agent, oseltamivir which reduces platelet glycoprotein desialylation. Encouraging results from phase 2 trials have also been reported for belimumab (anti-BAFF), and All-Trans Retinoid Acid (ATRA) (regulatory of complement and other pathways) (Table 2) [88–101]. In addition, more data are needed on existing therapeutic agents. These include the sustained post-treatment effects of TPO-RAs, identification of predictors of response, and the optimal dose for rituximab, and use of fostamatinib in newly diagnosed and persistent disease and in combination therapy Table 2.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113(11): 2386–2393.
   - **International Working Group standardization of terminology, definitions and outcome criteria in immune thrombocytopenia**

2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med. 2002;346(13):995–1008.
3. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood. 1999;94(3):909–913.
4. Neylon AJ, Saunders PWG, Howard MR, et al. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. Br J Haematol. 2003;122(6):966–974.
5. Abrahamson PE, Hall SA, Feudjo-Tepie M, et al. The incidence of idiopathic thrombocytopenic purpura among adults: a population-based study and literature review. Eur J Haematol. 2009;83(2):83–89.
6. Kaushansky K. Thrombopoietin. N Engl J Med. 1998;339(11):746–754.
7. Gernsheimer T, Stratton J, Ballem PJ, et al. Mechanisms of response to treatment in autoimmune thrombocytopenic purpura. N Engl J Med. 1989;320(15):974–980.
8. Kuter DJ, and Gernsheimer TB. Thrombopoietin and platelet production in chronic immune thrombocytopenia. Hematol Oncol Clin North Am. 2009;23(6):1193–1211.
9. McMillan R, Wang L, Tomer A, et al. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. Blood. 2004;103(4):1364–1369.
10. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168–186.
11. Lacey JV, Penner JA. Management of idiopathic thrombocytopenic purpura in the adult. Semin Thromb Hemost. 1977;3(3):160–174.
12. Cortelazzo S, Finazzi G, Buelli M, et al. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. Blood. 1991;77(1):31–33.
13. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, et al. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med. 2000;160(11):1630–1638.
14. Sarpatwari A, Bennett D, Logie JW, et al. Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom general practice research database. Haematologica. 2010;95(7):1167–1175.
15. Warrier R, and Chauhan A. Management of immune thrombocytopenic purpura: an update. Ochsner J. 2012;12(3):221–227.
16. Hill QA, Newland AC. Fatigue in immune thrombocytopenia. Br J Haematol. 2015;170(2):141–149.
17. Newton JL, Reese JA, Watson SI, et al. Fatigue in adult patients with primary immune thrombocytopenia. Eur J Haematol. 2011;86(5):420–429.
18. Cooper N, Kruse A, Kruse C, et al. Immune thrombocytopenia (ITP) world impact survey (I-WISh): patient and physician perceptions of diagnosis, signs and symptoms, and treatment. Am J Hematol. 2021a;96:188–198.
19. Cooper N, Kruse A, Kruse C, et al. Immune thrombocytopenia (ITP) world impact Survey (I-WISh): impact of ITP on health-related quality of life. Am J Hematol. 2021b;96(2):199–207.
20. Bakchoul T, Irene Marini I. Drug-associated thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2018;2018(1):576–583.
21. Almazni I, Stapley R, Morgan NV, et al. Inherited thrombocytopenia: update on genes and genetic variants which may be associated with bleeding. Front Cardiovasc Med. 2019;6:80.
22. Go RS. Idiopathic cyclic thrombocytopenia. Blood Rev. 2005;19(1):53–59.
23. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780–3817.

•• **Updated International Consensus Report (ICR) guidelines for immune thrombocytopenia**

24. Arnold DM, Nazy I, Clare R, et al. Misdiagnosis of primary immune thrombocytopenia and frequency of bleeding: lessons from the McMaster ITP registry. Blood Adv. 2017;1(25):2414–2420.
25. Neunert C, Terrell DR, Arnold DM, et al. American society of hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23): 3829–3866.

•• **Updated American Society of Hematology (ASH) guidelines for immune thrombocytopenia**

26. Care A, Pavord S, Knight M, et al. Severe primary autoimmune thrombocytopenia in pregnancy: a national cohort study. BJOG. 2018;125(5):604–612.
27. Kalaycı H, Durdağ GD, Baran SY, et al. Pregnancy of patients with idiopathic thrombocytopenic purpura: maternal and neonatal outcomes. J Turk Ger Gynecol Assoc. 2020;21(2):97–101.
28. Neunert C, Lim W, Crowther M, et al. The American society of hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190–4207.
29. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). Blood. 2005;106(7):2244–2251.
30. Khellaf M, Viallard JF, Hamidou M, et al. A retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia. Haematologica. 2013;98:881–887.
31. Kuter DJ, Macahilig C, Grotzinger KM, et al. Treatment patterns and clinical outcomes in patients with chronic immune thrombocytopenia (ITP) switched to eltrombopag or romiplostim. Int J Hematol. 2015;101(3):255–263.
32. Lakhwani S, Perera M, Fernández-Fuertes F, et al. Thrombopoietin receptor agonist switch in adult primary immune thrombocytopenia patients: a retrospective collaborative survey involving 4 Spanish centres. Eur J Haematol. 2017;99(4):372–377.
33. Palandri F, Rossi E, Bartoletti D, et al. Real-world use of thrombopoietin receptor agonists in elderly patients with primary immune thrombocytopenia. Blood. 2021 Apr 22:blood.2021010735. DOI:10.1182/blood.2021010735.
34. Wei Y, Ji XB, Wang YW, et al. High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. Blood. 2016;127(3):296–302.
35. Mithoowani S, Gregory-Miller K, Goy J, et al. High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis. Lancet Haematol. 2016;3(10):e489–e496.
36. Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. N Engl J Med. 2006;355(16):1672–1681.
37. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet. 2008;371(9610):395–403.
38. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med. 2007;357(22):2237–2247.
39. Bussel JB, Kuter DJ, Aledort LM, et al. A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia. Blood. 2014;123(25):3887–3894.
40. Cheloff AZ, Al-Samkari H. Avatrombopag for the treatment of immune thrombocytopenia and thrombocytopenia of chronic liver disease. J Blood Med. 2019;10:313–321.
41. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet. 2011;377(9763):393–402.
42. Newland A, Godeau B, Priego V, et al. Remission and platelet responses with romiplostim in primary immune thrombocytopenia: final results from a phase 2 study. Br J Haematol. 2016;172(2):262–273.
43. Lucchini E, Palandri F, and Volpetti S, et al. Eltrombopag as second line therapy in adult patients with primary immune thrombocytopenia (ITP) in attempt to treatment-free remission. Updated Results of a Phase II Prospective Study by GIMEMA Group. Presented at the 24th European Hematology Association (EHA) Congress; 2019; Amsterdam, The Netherlands; PF695. Updated Results of a Phase II Prospective Study by GIMEMA Group https://library.ehaweb.org/eha/2019/24th/266494/elisa.lucchini.eltrombopag.as.second.line.therapy.in.adult.patients.with.html?f=listing%3D3%2Abrowseby%3D8%2Asortby%3D1%2Amedia%3D1 Accessed 22 October 2021

44. Saleh MN, Bussel JB, Cheng G, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood. 2013;121(3):537–545.
45. Wong RSM, Mansoor N, Saleh MN, et al. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood. 2017;130(23):2527–2536.
46. Khellaf M, Michel M, Quittet P, et al. Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a romiplostim compassionate-use program. Blood. 2011;118(16):4338–4345.
47. Bussel JB, Hsieh L, Buchanan GR, et al. Long-term use of the thrombopoietin-mimetic romiplostim in children with severe chronic immune thrombocytopenia (ITP). Pediatr Blood Cancer. 2015;62(2):208–213.
48. Zaja F, Barcellini W, Cantoni S, et al. Thrombopoietin receptor agonists for preparing adult patients with immune thrombocytopenia to splenectomy: results of a retrospective, observational GIMEMA study. Am J Hematol. 2016;91(5):E293–E295.
49. Allen R, Bryden P, Grotzinger KM, et al. Cost-effectiveness of eltrombopag versus romiplostim for the treatment of chronic immune thrombocytopenia in England and Wales. Value Health. 2016;19(5):614–622.
50. Fust K, Parthan A, Li X, et al. Cost per response analysis of strategies for chronic immune thrombocytopenia. Am J Manag Care. 2018;24((8 Spec No.):SP294–SP302.
51. Tremblay G, Dolph M, Roy AN, et al. The cost-effectiveness of eltrombopag for the treatment of immune thrombocytopenia in the United States. Clin Ther. 2020;42(5):860–872. e8.
52. Michel M, Ruggeri M, Gonzalez-Lopez TJ, et al. Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicenter study. Blood. 2020 Aug 19: blood.2020007594. DOI:10.1182/blood.2020007594.
53. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med. 2007;146(1):25–33.
54. Patel VL, Mahévas M, Lee SY, et al. Outcomes 5 years after response to rituximab therapy in children and adults with immune thrombocytopenia. Blood. 2012;119(25):5989–5995.
55. Zaja F, Volpetti S, Chiozzotto M, et al. Long-term follow-up analysis after rituximab salvage therapy in adult patients with immune thrombocytopenia. Am J Hematol. 2012;87(9):886–889.
56. Khellaf M, Anaïs Charles-Nelson A, Fain O, et al. Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients. Blood. 2014;124(22):3228–3236.
57. Cooper N, Stasi R, Cunningham-Rundles S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. Br J Haematol. 2004;125(2):232–239.
58. Braendstrup P, Bjerrum OW, Nielsen OJ, et al. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adult refractory idiopathic thrombocytopenic purpura. Am J Hematol. 2005;78(4):275–280.
59. Peñalver FJ, Jiménez-Yuste V, Almagro M, et al. Rituximab in the management of chronic immune thrombocytopenic purpura: an effective and safe therapeutic alternative in refractory patients. Ann Hematol. 2006;85(8):400–406.
60. Zaja F, Vianelli N, Battista M, et al. Earlier administration of rituximab allows higher rate of long-lasting response in adult patients with autoimmune thrombocytopenia. Exp Hematol. 2006;34(5):571–572.
61. Garcia-Chavez J, Majluf-Cruz A, Montiel-Cervanteset L, et al. Rituximab therapy for chronic and refractory immune thrombocytopenic purpura: a long-term follow-up analysis. Ann Hematol. 2007;86(12):871–877.
62. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. Blood. 2008;112(4):999–1004.
63. Medeot M, Zaja F, Vianelli N, et al. Rituximab therapy in adult patients with relapsed or refractory immune thrombocytopenic purpura: long-term follow-up results. Eur J Haematol. 2008;81(3):165–169.
64. Zaja F, Vianelli N, Volpetti S, et al. Low-dose rituximab in adult patients with primary immune thrombocytopenia. Eur J Haematol. 2010;85(4):329–334.
65. Bussel JB, Lee CS, Seery C, et al. Rituximab and three dexamethasone cycles provide responses similar to splenectomy in women and those with immune thrombocytopenia of less than two years duration. Haematologica. 2014;99(7):1264–1271.
66. Marangon M, Vianelli N, and Palandri F, et al. Rituximab in immune thrombocytopenia: gender, age, and response as predictors of long-term response. Eur J Haematol. 2017;98(4):371–377 Accessed 22 October 2021.
67. Gracie C, Zaidi A, and Doobaree U, et al. Comparison of standard- and low-dose rituximab in primary immune thrombocytopenia (ITP): data from the UK ITP registry. Presented at European Hematology Association (EHA) Stockholm 2018. Available from: https://library.ehaweb.org/eha/2018/stockholm/214599/caitlin.gracie.comparison.of.standard-.and.low-dose.rituximab.in.primary.html?f=menu=6*ce_id=1346*ot_id=19068*media=3*marker=170 Accessed 22 October 2021.
68. Newland A, Lee EJ, McDonald V, et al. Fostamatinib for persistent/chronic adult immune thrombocytopenia. Immunotherapy. 2018;10(1):9–25.
69. Cooper N, Ghanima W. Immune thrombocytopenia. N Engl J Med. 2019;381(10):945–955.
70. Newland A, McDonald V. Fostamatinib: a review of its clinical efficacy and safety in the management of chronic adult immune thrombocytopenia. Immunotherapy. 2020;12(18):1325–1340.
71. Bussel J, Arnold DM, Grossbard E, et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. Am J Hematol. 2018;93(7): 921–930.

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72. Bussel J, Arnold DM, Duliege AM, et al. Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program. Am J Hematol. 2019;94(5):546–553.
73. Boccia R, Cooper N, Ghanima W, et al. Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia. Br J Haematol. 2020;190(6):933–938.
74. Cooper N, Altomare I, Thomas MR, et al. Assessment of thrombotic risk during long-term treatment of immune thrombocytopenia with fostamatinib. Ther Adv Hematol. 2021;12:20406207211010875.
75. Gernsheimer TB, George JN, Aledort LM, et al. Evaluation of bleeding and thrombotic events during long-term use of romiplostim in patients with chronic immune thrombocytopenia (ITP). J Thromb Haemost. 2010;8(6):1372–1382.
76. Gernsheimer TB, Kuter DJ, Cines DB, et al. Analysis of mortality rates during romiplostim clinical studies of patients (Pts) with immune thrombocytopenia (ITP). Blood. 2010;116(21):3701.
77. Janssens A, Rodeghiero F, Anderson D, et al. Changes in bone marrow morphology in adults receiving romiplostim for the treatment of thrombocytopenia associated with primary immune thrombocytopenia. Ann Hematol. 2016;95(7):1077–1087.
78. Jurczak W, Chojnowski K, Mayer J, et al. Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol. 2018;183(3):479–490.
79. Kuter DJ, Bussel JB, Newland A, et al. Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. Br J Haematol. 2013;161(3):411–423.

80. Altomere I, Markovtsov VV, Todd L, et al. Potential anti-thrombotic effect without accompanying hemorrhage with fostamatinib use in patients with immune thrombocytopenia. Blood. 2019;134 (Suppl_1):4889.
81. Vianelli N, Palandri F, Polverelli N, et al. Splenectomy as a curative treatment for immune thrombocytopenia: a retrospective analysis of 233 patients with a minimum follow up of 10 years. Haematologica. 2013;98(6):875–880.
82. Boyle S, White RH, Brunson A, et al. Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia. Blood. 2013;121(23):4782–4790.
83. Provan D, Newland AC. Current management of primary immune thrombocytopenia. Adv Ther. 2015;32(10):875–887.
84. Todd S, Sardo Infirri S, Miah H, et al. Splenectomy in immune thrombocytopenia: do changing treatment patterns for ITP affect outcome? data from the UK ITP registry. Br J Haematol. 2020;189 (S1):11–12.
85. Sarpatwari A, Provan D, Erqou S, et al. Autologous 111 in-labelled platelet sequestration studies in patients with primary immune thrombocytopenia (ITP) prior to splenectomy: a report from the United Kingdom ITP registry. Br J Haematol. 2010;151(5):477–487.
86. Cuker A, and Cines DB. Evidence-based mini-review: is indium-labeled autologous platelet scanning predictive of response to splenectomy in patients with chronic immune thrombocytopenia? Hematology Am Soc Hematol Educ Program. 2010;2010:385–386.
87. Kazi S, Mckiddie F, Anderson J, et al. Autologous 111 in-labelled platelet scan as a predictor of splenectomy outcome in ITP. Br J Haematol. 2019;184(6):1043–1045.
88. Kuter D, Efraim M, Mayer J, et al. Phase I/II, open-label, ongoing study of PRN1008 (Rilzabrutinib), an oral Bruton tyrosine kinase inhibitor, in patients with heavily pretreated immune thrombocytopenia (ITP). Res Pract Thromb Haemost. 2020;4(Suppl 1):PB1318. Available from: https://abstracts.isth.org/abstract/phase-i-ii-open-label-ongoing-study-of-prn1008-rilzabrutinib-an-oral-bruton-tyrosine-kinase-inhibitor-in-patients-with-heavily-pretreated-immune-thrombocytopenia-itp/. Accessed August 21, 2020.
89. Robak T, Kaźmierczak M, Jarque I, et al. Phase 2 multiple-dose study of an FcRn inhibitor, rozanolixizumab, in patients with primary immune thrombocytopenia. Blood Adv. 2020;4(17):4136–4146.
90. Newland AC, Sánchez-González B, Rejtő L, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. Am J Hematol. 2020;95 (2):178–187.
91. Shao L, Wu Y, Zhou H, et al. Successful treatment with oseltamivir phosphate in a patient with chronic immune thrombocytopenia positive for anti-GPIb/IX autoantibody. Platelets. 2015;26(5):495–497.
92. Sun L, Liu X, Zhou H, et al. High-dose dexamethasone (HD-DXM) plus oseltamivir versus high-dose dexamethasone for treatment of adult primary immune thrombocytopenia: interim analysis of a prospective, multicenter, randomized, controlled trial. Blood. 2019;134(Suppl_1):900.
93. Nikitin PA, Rose EL, Byun TS, et al. C1s inhibition by BIVV009 (Sutimlimab) prevents complement-enhanced activation of autoimmune Human B Cells in vitro. J Immunol. 2019;202(4):1200–1209.
94. Broome CM, Röth A, Kuter DJ, et al. Long-term safety and efficacy of sutimlimab in patients with chronic immune thrombocytopenia. Blood. 2020;136(Suppl_1):14–15.
95. Beckman JD, Rollins-Raval MA, Raval JS, et al. Bortezomib for refractory immune-mediated thrombocytopenia purpura (ITP). Am J Ther. 2018;25(2):e270–e272.
96. Migdady Y, Ediriwickrema A, Jackson RP, et al. Successful treatment of thrombocytopenia with daratumumab after allogeneic transplant: a case report and literature review. Blood Adv. 2020;4(5):815–818.
97. Mahévas M, Azzaoui I, Crickx E, et al. Efficacy, safety and immunological profile of combining rituximab with belimumab for adults with persistent or chronic immune thrombocytopenia: results from a prospective phase 2b trial. Haematologica. 2020. DOI:10.3324/haematol.2020.259481.
98. Zhu X, Wang Y, Jiang Q, et al. All- trans retinoic acid protects mesenchymal stem cells from immune thrombocytopenia by regulating the complement-interleukin-1β loop. Haematologica. 2019;104(8):1661–1675.
99. He Y, Xu -L-L, Feng F-E, et al. Mesenchymal stem cell deficiency influences megakaryocytopoiesis through the TNFAIP3/NF-κB/SMAD pathway in patients with immune thrombocytopenia. Br J Haematol. 2018;180(3):395–411.
100. Feng F-E, Feng R, Wang M, et al. Oral all-trans retinoic acid plus danazol versus danazol as second-line treatment in adults with primary immune thrombocytopenia: a multicentre, randomised, open-label, phase 2 trial. Lancet Haematol. 2017;4(10):e487–e496.
101. Huang Q-S, Liu Y, Wang J-B, et al. Combination of ATRA and high-dose dexamethasone as first-line treatment in adult immune thrombocytopenia: a randomized, phase 2, open-label trial. Blood. 2019;134(Suppl_1):899.