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Immune thrombocytopenia: Modern management, knowledge gaps, and future perspectives

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Abstract:

Immune thrombocytopenia (ITP) is an autoimmune disorder with increased risk of bleeding due to a low number of platelets. The pathophysiology is complex and not fully understood, but platelet autoantibodies and/or CD8+ T-cells are responsible, via diverse mechanisms, for disrupting platelet production and enhancing platelet destruction. The symptomatology of ITP seems to be more complex than has traditionally been perceived as thrombocytopenia and bleeding as the disease often has impact on the health-related quality of life and daily functions. The management thus requires a holistic approach and patient involvement at every stage. Corticosteroids still represent the cornerstone of the first-line treatment. Treatment with corticosteroid should not exceed 6–8 weeks. Patients who fail to achieve remission with a short course of corticosteroids may require a second-line therapy. Most guidelines recommend starting with a thrombopoietin receptor agonist (TPO-RA), rituximab, or fostamatinib since these agents have been investigated in randomized trials and have well-characterized efficacy and safety profiles. Patient involvement to reach a shared decision regarding choice of therapy is essential as these treatments have different modes of administration and mechanisms of action. Less than 10% of adults ITP patients will fail to respond to and/or be intolerant of multiple second-line therapies and would thus require a third-line therapeutic option. Such patients may respond well to a combination of TPO-RA and an immunomodulatory agent. Splenectomy or a continuation with nontherapeutic agents that has different mechanism of action may be an alternative approach.

Keywords:

Immune thrombocytopenia, management, pathophysiology

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Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease, characterized by an immune-mediated platelet destruction and suboptimal platelet production. ITP is diagnosed in 3–5/100,000 persons annually with a slight preponderance of female sex. The incidence of adult ITP has two peaks, the first occurs around the age of 20–30 years and the second after the age of 60 years. ITP is divided into primary, or secondary when it is triggered by another condition as it is the case in 20%. The disease is classified according to the time from diagnosis, into newly diagnosed (0–3 months), persistent (3–12 months) or chronic (>12 months); however, this classification has limited clinical value in the management of the disease.[1]

Immune Thrombocytopenia Symptomatology – More Complex than Traditionally Perceived

Patients with ITP most commonly experience nonfatal bleeding events. Around 60% of the patients would have bleeding manifestations at diagnosis. Most of these are mucocutaneous bleeds,

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whereas < 10% would have serious bleeding including CNS bleeding that occurs in 1%–2%. A platelet threshold of <20 × 10^9/L has been identified to be associated with bleeding at the diagnosis.[2] Other factors include use of use of anticoagulant and patients' comorbidities.

In addition to bleeding, around 60% of ITP patients suffer from fatigue.[3] The etiology of fatigue is multifactorial and may be related the pathophysiology of the disease itself or its clinical manifestations, for example, anemia, associated disorders such as hypothyroidism, or the treatment. Of note fatigue is not always related to the platelet count.

The disease has been shown to affect the several aspects of patients' daily living including work, the ability to concentrate, exercise or undertake tasks, study, and sleep.[3]

As a result of the physical, psychological, and social impact of the disease, as well as the burden of treatment, health-related quality of life (HRQoL) is negatively impacted in ITP. Treatment often, but not always, improves the HRQoL of ITP patients.[4]

A Complex and Multifactorial Pathophysiology

The pathophysiology of ITP is still not fully understood. A loss of immune tolerance, reflected by a reduced number and function of immunosuppressive cells such as CD4+ T regulatory cells, dendritic cells, and myeloid-derived suppressor cells, enables targeting of megakaryocytes in the bone marrow and platelets in the spleen, liver, and circulation through the action of platelet glycoprotein (GP)-specific immunoglobulin G autoantibodies (e.g., anti-GPIIb/IIIa, anti-GPV, and anti-GPIb/IX) and/or CD8+ cytotoxic T-cells.[5] This can occur through diverse mechanisms, including via Fcγ receptor-mediated platelet-phagocytosis via the splenic and hepatic macrophages, complement activation, through affecting apoptosis, induction of desialylation of platelets which results in their clearance via the hepatic Ashwell-Morell receptor, and through a direct cytotoxic effect of CD8+ T-cells.[5] These pathophysiological pathways result in an impaired platelet production and an increased platelet destruction, translating to the development of thrombocytopenia [Figure 1]. It is worth noting that not all biological mechanisms occur universally in all patients, indicating heterogeneity in ITP patients which may impact therapeutic efficacy. Interestingly, platelets themselves may not only be the end targets in ITP, but they may also actively contribute to their own fate.[6]

Immunethrombocytopenia – Still a Diagnosis of Exclusion

ITP is diagnosed by the presence of isolated thrombocytopenia (platelet count <100 × 10^9/L) in the absence of other conditions mimicking ITP such as, myelodysplastic syndrome, hereditary thrombocytopenia and hypoplastic conditions, and absence of secondary ITPs, for example, drug-induced ITP and ITP secondary to infections (cytomegalovirus, human immune deficiency virus, and hepatitis C virus) or autoimmune diseases (systemic lupus erythematosus [SLE] and rheumatoid arthritis). The diagnostic process should include a thorough medical history including family, bleeding, infection, medication and vaccination history, presence of comorbidities, and a clinical examination to exclude lymphadenopathy and splenomegaly. Table 1 shows the main diagnostic tests that should be performed to reach a diagnosis.[7]

Table 1: Main diagnostic investigation for immune thrombocytopenia

Investigation	Purpose
In all patients	
Complete blood count and blood film	To confirm the presence of isolated thrombocytopenia and exclude any abnormalities in peripheral blood cell count or morphology
General biochemistry	To exclude other comorbid conditions that may cause thrombocytopenia e.g. liver disease
Viral serology (HCV, HIV, CMV)	To exclude ITP secondary to viral infections
Hemolysis tests	To exclude conditions associated with ITP like Evans syndrome
Immunoglobulin quantification	To exclude immune deficiency in particular common variable immune deficiency which is associated with ITP
Thyroid function test	Thyroid disorders are occasionally associated with ITP and require treatment
In selected patients	
Bone marrow examination	Is indicated in the presence of any abnormalities in peripheral blood cell count or morphology or in the presence of multi-refractory ITP
Helicobacter pylori	Can be assessed with the urea breath test or stool antigen test in patients with gastrointestinal symptoms
Optional tests	
APA	APA is commonly associated with ITP and be associated with an increased risk of thrombosis
ANA	Frequently associated with ITP and may predict chronicity but could indicate the presence of SLE
Antiplatelet GP antibodies	Positive test would rule in the presence of ITP

APA=Antiphospholipid antibodies, ANA=Antinuclear antibodies, HCV=Hepatitis C virus, HIV=Human immunodeficiency virus, CMV=Cytomegalovirus, ITP=Immune thrombocytopenia, SLE=Systemic lupus erythematosus, GP=Glycoprotein

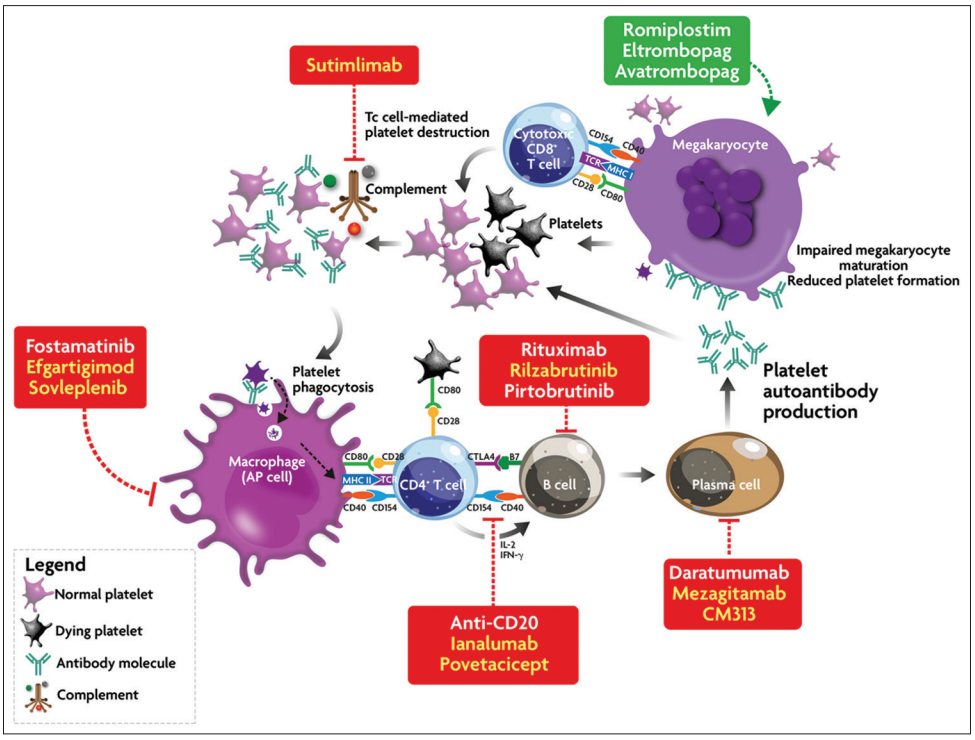

Figure 1: Pathophysiological mechanisms involved in immune thrombocytopenia (ITP) and drugs targeting these mechanisms. Schematic representation of the pathophysiology of ITP showing the various compartments involved. These include autoantibody production by pathological plasma cells, autoreactive cytotoxic CD8+ T cells, and complement. The sites of action of agents used in ITP treatment are shown; red represents inhibition and green is stimulation. Agents in white are licensed for ITP or other indications; Investigational agents in yellow

The Modern Management of Immune Thrombocytopenia

The modern management of ITP should adopt a holistic, patient-centered approach. The physician should evaluate the physical, psychological, and social impact of the disease and should involve other disciplines whenever needed.[8]

The management of ITP starts by defining treatment goals. The main goals are to prevent severe bleeding by achieving and maintaining a hemostatically safe count using treatments with minimal toxicity, to improve HRQoL, and, whenever possible, to induce lasting treatment-free remission. Current guidelines emphasize the need for patient involvement and shared decision-making – a process that requires patient education and dialog to reach a common understanding of patients' expectations and treatment options.[9,10]

The key approaches for treating ITP involve immunomodulation, stimulation of thrombopoiesis or splenectomy. Table 2 summarizes the characteristics of the main drugs used in the various lines of therapy. Because of the lack of reliable biomarkers to facilitate a personalized approach to treatment, current strategies are still based on sequential administration of single agents based on the factors such as the urgency for elevating the platelet count (rapidly acting agents are needed in case of bleeding) and toxicity profile (thrombopoietin receptor agonist [TPO-RA] should be avoided in patients with high risk of thrombosis), availability of drugs, and very importantly patient's preference. Switching to the next drug or line of treatment is indicated in cases of suboptimal response, intolerance or inconvenience. Although the term "lines" is commonly used in ITP, there is no consensus on how to define "a line," or what medications to include in each line.[1]

The standard platelet count threshold for starting therapy is 30×10^9/L. Occasionally, treatment at higher platelet counts (50×10^9/L) is indicated in patients at high risk of bleeding (e.g. those on anticoagulation or having recurrent bleeding). This threshold maybe increased or decreased during the course of disease based on the bleeding risk, effect of, and tolerance to, available therapies.[16] Generally, patients with platelet count >30×10^9/L do not require therapy in the absence of bleeding and can be managed by watch and wait policy.[17]

First-line therapies

For initial treatment, guidelines recommend a short course of prednisolone not exceeding 6–8 weeks or up to three cycles of dexamethasone, 4-day courses of dexamethasone [Figure 2].[9,10,17] Dexamethasone provides

Table 2: Characteristics of first- and second-line drugs

Agent	Indication	Administration	Response rates	Main side effects
Prednisolone	Initial therapy	Oral, short course of up to 8 weeks	Durable response rates 30%–35%	Weight gain, insomnia, glucose intolerance, mood changes, gastritis, osteoporosis
Dexamethasone	Initial therapy	Oral, 20–40 mg daily for 4 days. Can be repeated for up to 3 cycles	Responses at 6 months of 35%–40%	
IVIG	Initial therapy and later phases as rescue	IV, 1–5 days, can be repeated if needed	Transient response achieved in 80%	Headache, aseptic meningitis, thromboembolism
Romiplostim (thrombopoietic agent)	Second line and beyond	Weekly subcutaneous administration of 1–10 ug/kg* as maintenance therapy	Durable response rates of 38% in splenectomy-ized patients and 56% in nonsplenectom-ized[11]§	Key special warnings and precautions for use for all TPO-Ras include: Increased thromboembolic complications
Eltrombopag (thrombopoietic agent)	Second line and beyond	Oral, daily administration of 25–75 mg*, as maintenance therapy	Durable response rates on treatment of 60%–70%[12]§	Increased bone marrow reticulin; eltrombopag can cause hepatotoxicity
Avatrombopag (thrombopoietic agent)	Second line and beyond	Oral, daily administration of 20–40 mg* as maintenance therapy	Durable response rates of 34%[13]§	
Rituximab (B-cell depleting agent)	Second line and beyond	2 IV infusions of 1000 mg 2 weeks apart or 4 weekly IV infusions of 375 mg/m^2. Lower doses have shown effect in studies; remission inducing therapy	Durable response rate at 6 months 39%,[9] and at 5 years of 29%[14]	Infusion related reactions, immunosuppression and slight increase in the risk of bacterial infections; reactivation of HBV; Serum sickness disease. Secondary hypogammaglobulinemia
Fostamatinib spleen tyrosine kinase inhibitor	Second line and beyond	Oral, daily administration of 100–150 mg × 2, as maintenance therapy	Durable response rates of 18%[15]§	Hypertension, diarrhea, hepatotoxicity, neutropenia

*Occasionally lower doses are needed, §In pivotal phase three trials, all agents demonstrated significantly greater durable platelet response rates versus placebo at 6 months, however, definitions of durable platelet response rate differed slightly, making direct cross-study comparisons difficult. IVIG=Intravenous immunoglobulin, TPO=Thrombopoietin, HBV=Hepatitis B virus

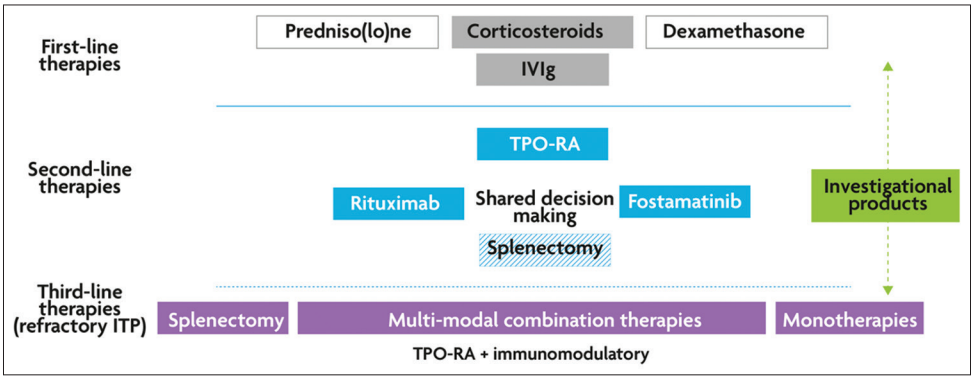

Figure 2: Current therapeutic approach for adults with immune thrombocytopenia (ITP). Used for patients with active serious bleeding or high risk of bleeding; Rituximab can be used prior to thrombopoietin receptor agonist (TPO-RA) if the patient places a high value on limiting the duration of therapy, or if TPO-RA is not advised because of the risk of thromboembolism; fostamatinib can be used off-label prior to TPO-RA if TPO-RA is not advised because of the risk of thromboembolism; Dapsone and Danazol can be used in countries where alternative treatment is not available; investigational products should be considered in all stages, not only for refractory ITP; many combination therapies have shown promising results in the first-and second-line but are currently not considered as standard treatment. Splenectomy is still an option that can be considered among second line treatments although it is recommended to delay it until at least 1 year after ITP onset. ITP: Immune thrombocytopenia, IVIg: Intravenous immunoglobulin

quicker and more rapid response than prednisolone, but there is no difference with regard to long-term remissions.[18] There is unlikely to be any advantage from prolonging treatment with corticosteroids beyond 2 months or 3 cycles of dexamethasone in patients who are refractory to corticosteroids, who relapse after initial response, or become dependent on large doses of corticosteroids, apart from exposing the patients to more side effects.

Patients who present with serious bleeding, or are at high risk of bleeding due to severe thrombocytopenia, require rapid elevation of the platelet count. For these, a combination of corticosteroids and intravenous immunoglobulin (IVIg) is recommended. High-dose TPO-RA can be utilized as an add-on therapy in patients with life-threatening bleeding not responding well to standard treatment.[17]

Several studies have evaluated the role of combining immunomodulatory agents with corticosteroids to improve durable response rates that persist after the discontinuation of therapy, including rituximab, mycophenolate mofetil, TPO-RAs, All-trans retinoic acid (ATRA), and oseltamivir with corticosteroids. All these combinations performed substantially better than corticosteroids alone. A recent meta-analysis showed that compared with corticosteroids alone, combination regimens demonstrated better early (80% vs. 69%; odds ratio [OR] = 1.8, 95% confidence interval [CI]: 1.1–3.0) and sustained responses (60% vs. 37%; OR = 2.6, 95% CI 1.9–3.4).[19] However, despite higher durable response rates, guidelines still recommend corticosteroid monotherapy as the first-line treatment. The reluctance toward adopting combination therapies may be attributable to concerns related to toxicities, and cost. currently the combination of dexamethasone with 12 weeks of romiplostim or eltrombopag as upfront therapy is being investigated.[16] This combination may change the current practice if it proves to be safe and effective in increasing remission rates.[16]

Second-line therapies

Around 70% of adult ITP patients fail to respond, relapse after, or become dependent on large doses of corticosteroids to maintain a response and thus require subsequent therapy.[20]

The second line includes either drugs that are licensed for ITP, like TPO-RA and fostamatinib, or agents that have been evaluated in randomized controlled trials (RCT) and are frequently used, such as rituximab [Figure 2]. Although splenectomy has traditionally been considered as a second-line therapy, it is rarely performed at this stage, and it is recommended to be deferred for at least 1 year after diagnosis. There are no trials directly comparing the efficacy and safety of various second-line agents although TPO-RAs seem to be the most effective ones when compared indirectly.[9] However, since these agents have different modes of administration and properties, it is important to make a shared decision based on patient's preference.

Most guidelines recommend starting with a TPO-RA as a first choice in the second-line.[9,10,17] Romiplostim, eltrombopag, and avatrombopag are thrombopoietic agents licensed for ITP in the different parts of the world. TPO-RAs are effective and well-tolerated,[21] providing durable response rates in 34%–60% of treated patients.[11-13] They act by stimulating thrombopoiesis and can be given either as weekly subcutaneous (sc) injections (romiplostim) or orally (eltrombopag and avatrombopag). Unlike eltrombopag, avatrombopag has no interaction with dairy products or cations and causes no liver toxicity. The dose of TPO-RA should be adjusted to maintain a platelet count between 50 and 100×10^9/L.[20]

Although most patients would require continuous therapy, some patients can discontinue TPO-RA without losing response. Several studies have shown that tapering of TPO-RAs after 2–12 months of stable response would result in 30% achieving a sustained response off-therapy (SROT).[22,23] The chances for achieving SROT are higher (50%) in those who maintain a platelet response >100×10^9/L for >2 months.[23]

Patients who do not respond initially to a TPO-RA or lose response usually benefit from switching to another agent.[24] Patients who fail to respond/lose response to 2 or 3 TPO-RAs, or do not tolerate TPO-RAs, may switch to rituximab or fostamatinib.[20]

Thromboembolism is a potential side effect associated with the use of TPO-RAs. Although meta-analyses have failed to show a significant increase in the rate of thromboembolic events (TEE), all have shown a trend toward higher TEE rate in the TPO-RA arms. The most recent meta-analysis found an OR of 1.76, with a 95% CI: 0.78–4.00, P = 0.18,[25] in line with the real-world studies suggesting an increased risk of thrombosis with TPO-RA.[26]

Elderly patients with multiple risk factors for thromboembolism, patients with previous TEE not receiving anticoagulation, and patients with SLE, antiphospholipid syndrome or strong antiphospholipid antibody positivity may be at increased risk of developing TEE on TPO-RA and should thus be considered for other treatments such as rituximab, mycophenolate mofetil or fostamatinib.[16]

Rituximab, a B-cell depleting agent, provides response in 45%–60% at 6 months. However, half of responding patients will lose response within 2–5 years.[14] Rituximab is indicated in patients who prefer a limited treatment period or has a high thromboembolic risk. Although not confirmed in prospective trials, rituximab might be an appropriate choice for younger patients since current literature indicates better and more prolonged response.[27]

Fostamatinib is an oral spleen tyrosine kinase inhibitor. In the RCT, the durable response rate of fostamatinib was 18%.[15] Recently published real world data showed that responses were maintained in around 65% of the patients at 6 months.[28] Fostamatinib may be a good alternative treatment if there is a contraindication to a TPO-RA, high risk of thromboembolism, or lack of response/relapse after TPO-RA/rituximab.[16] An effect is expected within 2 weeks in most responding patients. This might be an

advantage over rituximab in the choice of treatment since the response to rituximab may take 6–12 weeks. The main side effects include diarrhea and hypertension.[15]

Several studies have investigated the efficacy of combination therapies at this stage too.[16] ATRA in combination with low-dose rituximab or with danazol versus rituximab or danazol monotherapy. Once again, the combinations were superior to monotherapy, but still none of these is implemented for routine use.[16]

Third-line therapeutic options

Less than 10% fail to respond to several second-line options, hence labeled as refractory. At this stage it is imperative to reassess the diagnosis to ensure that we are dealing with ITP, as well as to reassess treatment goals. Patients who have platelet count between 20 and 30×10^9/L or even less, with low risk of bleeding may benefit from watch-and-wait rather than expose the patient to the toxic effects of more therapies.

The main approaches to treating refractory ITP involve either a combination approach, continuation with sequential monotherapies, preferably with drugs having different mechanisms of action than previous ones, for example, like mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, danazol or decitabine, etc., or splenectomy [Figure 2].[16]

Combining drugs with different mechanisms of action is our preferred approach for treating multi-refractory patients. Several reports indicate that the combination of TPO-RA and an immunomodulatory agent is more effective than monotherapy.[29] In one study of 39 multi-refractory patients, 77% responded to a combination of TPO-RA and immunosuppressant agents like mycophenolate mofetil, cyclosporine, or azathioprine.[30] The combination seems to be effective whatever immunomodulatory (mycophenolate mofetil, cyclosporin, and fostamatinib) or TPO-RA is used. A recently reported series of 18 patients receiving avatrombopag and fostamatinib showed a 78% response rate.[31] Fostamatinib in combination with TPO-RA might be an attractive combination because of its relatively rapid response compared to other immunosuppressants.[16] Following the achievement of a stable response, one can start tapering one of the two agents to maintain the lowest possible adequate platelet count.

Splenectomy remains a valid option in this population. Its main advantage is that if response is achieved, which is the case in 60%–70%, no other ITP therapy is needed. What is unknown is the actual response rates to splenectomy when it is performed in multi-refractory patients. This issue remains debatable in the absence of good evidence. A French retrospective study of 185 patients splenectomized between 2011 and 2020, 65% achieved sustained response. Among patients who received at least one TPO-RA or rituximab before splenectomy, 61% had a sustained response, whereas of those with lacked response to both, 46% had a sustained response to splenectomy.[32] Conversely a recent report based on the UK Adult ITP registry showed substantially inferior effectiveness in those splenectomized after being treated with >2 previous therapies versus <2.[33]

Immune Thrombocytopenia and Thrombosis – A Mechanistic Enigma and Therapeutic Dilemma

The risks of venous thrombosis, and to a lesser extent arterial thrombosis, are increased in ITP patients compared to the general population. The underlying pathophysiological changes leading to increase thrombotic risk include, increased activated platelets, increased number and procoagulant activity of extracellular vesicles, and enhanced thrombin generation,[34] endothelial cell activation and neutrophil extracellular traps,[35] and increased plasminogen activator inhibitor-1 (PAI-1).[36]

As mentioned, TPO-RAs further increase that risk but the mechanisms for this is not fully understood. It has been shown that TPO-RA treatment is associated with an increase in soluble P-selectin levels indicating an increase in platelet activation, enhanced phospholipid-dependent procoagulant activity of microvesicles leading to increased thrombin generation,[37] and further increase in PAI-1 probably leading to impaired fibrinolysis.[38]

If thrombosis is encountered, adequate anticoagulation/antiplatelet and/or interventional procedures should be undertaken without delay if the platelet count permits. Generally, it is safe to administer anticoagulation when the platelet count is $>50 \times 10^9$/L and antiplatelet therapy when platelet count is $>30 \times 10^9$/L. However, if the platelet count is below the recommended limit, IVIG and/or platelet transfusion should be considered to raise the platelet count for appropriate intervention. The decision on treatment often requires a multidisciplinary approach. It is important not to discontinue TPO-RA in the event of an acute thrombosis as this would lead to rapid fall in platelet count that may prevent proper therapy. A decision to change ITP treatment can be delayed until the condition is stabilized. We would recommend changing the TPO-RA in case of stroke but not necessarily after venous or cardiac thrombotic events.[39]

New Drugs on the Horizon

Several drugs are currently being investigated in ITP. Both the neonatal Fc receptor inhibitor, efgartigimod, and Bruton tyrosine kinase inhibitor, rilzabrutinib, have completed phase 3 studies. Efgartigimod administered as weekly iv injection has been shown to be superior to placebo in inducing durable response rates (21% vs. 5%).[40]

Rilzabrutinib is administered orally. The phase 3 study compared its superiority compared to placebo (durable response rates 23% vs. 0%), reduction of fatigue, bleeding and improvement of HRQoL (In press).

Other currently evaluated agents including those inhibiting the BAFF and APRIL receptors like Ianalumab (anti-BAFF/B-cell depletion) and povetacicept (anti-BAFF and APRIL) and anti CD38 depleting agents such as daratumumab and mezagitimab [Figure 1].[41]

Knowledge Gaps and Unmet Needs in Immune Thrombocytopenia

One of the major unmet needs in ITP involves the absence of biomarkers that can allow for the proper selection of therapies based on probability to achieve response and/or expected toxicity. The need for such markers or tools will be greater as more therapies are being introduced. Recent studies using immunological markers and machine learning methodology provided promising results and hope for the development of tools that can help in individualizing therapy.[42] Other unmet needs include the lack of diagnostic test, tools that assist in predicting bleeding, thrombosis, and chronicity.

Conclusion

In conclusion, the management of ITP is continuously evolving due to the development of new therapies, improved understanding of pathophysiology, and expanding knowledge of HRQoL and disease burden. Modern management of ITP involves a holistic, patient-centered approach. While most patients would respond to the first- and second-line therapies, a few fail to respond and require a third line; these may benefit from combination therapies. A better understanding of the ITP pathophysiology is needed to better understand the relevant biological mechanisms and to identify diagnostic and prognostic biomarkers.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ghanima W, Hill QA, Kuter DJ. ITP definitions: Time for an update. Br J Haematol 2023;201:1005-6.
2. Piel-Julian ML, Mahévas M, Germain J, Languille L, Comont T, Lapeyre-Mestre M, *et al.* Risk factors for bleeding, including platelet count threshold, in newly diagnosed immune thrombocytopenia adults. J Thromb Haemost 2018;16:1830-42.
3. Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, *et al.* Immune thrombocytopenia (ITP) World Impact Survey (I-WISh): Impact of ITP on health-related quality of life. Am J Hematol 2021;96:199-207.
4. Kuter DJ, Ghanima W, Cooper N, Liebman HA, Zhang L, Hu Y, *et al*. Safety and efficacy of rilzabrutinib versus placebo in adults with immune thrombocytopenia: The phase 3 LUNA3 study. Blood 2025. [doi: 10.1182/blood.2024027336].
5. Schoenaker JM, Nelson VS, Henderickx JG, Terveer EM, Jansen AJ, Porcelijn L, *et al*. The intestinal flora: The key to unraveling heterogeneity in immune thrombocytopenia? Blood Rev 2025;69:101252.
6. Nelson VS, Jolink AC, Amini SN, Zwaginga JJ, Netelenbos T, Semple JW, *et al*. Platelets in ITP: Victims in charge of their own fate? Cells 2021;10:3235. [doi: 10.3390/cells10113235].
7. Cooper N, Ghanima W. Immune thrombocytopenia. N Engl J Med 2019;381:945-55.
8. Maitland H, Lambert C, Ghanima W. Patient-centric care in primary immune thrombocytopenia (ITP): Shared decision-making and assessment of health-related quality of life. Hematology 2024;29:1-11.
9. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, *et al.* American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019;3:3829-66.
10. Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, *et al.* Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv 2019;3:3780-817.
11. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, *et al.* Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: A double-blind randomised controlled trial. Lancet 2008;371:395-403.
12. Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, *et al*. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): A 6-month, randomised, phase 3 study. Lancet 2011;377:393-402.

13. Jurczak W, Chojnowski K, Mayer J, Krawczyk K, Jamieson BD, Tian W, *et al.* Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol 2018;183:479-90.
14. Deshayes S, Khellaf M, Zarour A, Layese R, Fain O, Terriou L, *et al.* Long-term safety and efficacy of rituximab in 248 adults with immune thrombocytopenia: Results at 5 years from the French prospective registry ITP-ritux. Am J Hematol 2019;94:1314-24.
15. Bussel J, Arnold DM, Grossbard E, Mayer J, Treliński J, Homenda W, *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;93:921-30.
16. Ghanima W, Cuker A, Michel M. Insights on treatment of adult ITP: Algorithm for management and role of multimodal therapy. Hematology Am Soc Hematol Educ Program 2024;2024:678-84.
17. Matzdorff A, Alesci SR, Gebhart J, Holzhauer S, Hütter-Krönke ML, Kühne T, *et al.* Expert report on immune thrombocytopenia: Current diagnostics and treatment – Recommendations from an expert group from Austria, Germany, and Switzerland. Oncol Res Treat 2023;46 Suppl 2:5-44.
18. Mithoowani S, Gregory-Miller K, Goy J, Miller MC, Wang G, Noroozi N, *et al.* High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: A systematic review and meta-analysis. Lancet Haematol 2016;3:e489-96.
19. Wang Y, Sheng L, Han F, Guo Q, Zhang Z, Hou Y, *et al.* Efficacy and safety of treatments in newly diagnosed adult primary immune thrombocytopenia: A systematic review and network meta-analysis. EClinicalMedicine 2023;56:101777.
20. Ghanima W, Gernsheimer T, Kuter DJ. How I treat primary ITP in adult patients who are unresponsive to or dependent on corticosteroid treatment. Blood 2021;137:2736-44.
21. Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: Ten years later. Haematologica 2019;104:1112-23.
22. Cooper N, Ghanima W, Vianelli N, Valcárcel D, Yavaşoğlu İ, Melikyan A, *et al.* Sustained response off-treatment in eltrombopag-treated adult patients with ITP who are refractory or relapsed after first-line steroids: Primary, final, and ad-hoc analyses of the phase II TAPER trial. Am J Hematol 2024;99:57-67.
23. Guillet S, Crickx E, Azzaoui I, Chappert P, Boutin E, Viallard JF, *et al.* Prolonged response after TPO-RA discontinuation in primary ITP: Results of a prospective multicenter study. Blood 2023;141:2867-77.
24. Al-Samkari H, Jiang D, Gernsheimer T, Liebman H, Lee S, Wojdyla M, *et al.* Adults with immune thrombocytopenia who switched to avatrombopag following prior treatment with eltrombopag or romiplostim: A multicentre US study. Br J Haematol 2022;197:359-66.
25. Shen N, Qiao J, Jiang Y, Yan J, Wu R, Yin H, *et al.* Thrombopoietin receptor agonists use and risk of thrombotic events in patients with immune thrombocytopenic purpura: A systematic review and meta-analysis of randomized controlled trials. Biomed Rep 2024;20:44.
26. Goncalves I, Lewis C, Grainger B, Dring R, Lee N, Pasricha SR, *et al.* Thrombosis in patients with immune thrombocytopenia: Incidence, risk, and clinical outcomes. Res Pract Thromb Haemost 2024;8:102342.
27. Marangon M, Vianelli N, Palandri F, Mazzucconi MG, Santoro C, Barcellini W, *et al.* Rituximab in immune thrombocytopenia: Gender, age, and response as predictors of long-term response. Eur J Haematol 2017;98:371-7.
28. González-López TJ, Bermejo-Vega N, Cardesa-Cabrera R, Martínez-Robles V, Aguilar-Monserrate G, Pérez-Segura G, *et al.* Fostamatinib effectiveness and safety for immune thrombocytopenia in clinical practice. Blood 2024;144:646-56.
29. Mahévas M, Gerfaud-Valentin M, Moulis G, Terriou L, Audia S, Guenin S, *et al.* Characteristics, outcome, and response to therapy of multirefractory chronic immune thrombocytopenia. Blood 2016;128:1625-30.
30. Crickx E, Ebbo M, Rivière E, Souchaud-Debouverie O, Terriou L, Audia S, *et al.* Combining thrombopoietin receptor agonists with immunosuppressive drugs in adult patients with multirefractory immune thrombocytopenia, an update on the French experience. Br J Haematol 2023;202:883-9.
31. Mingot-Castellano ME, Bastida JM, Ghanima W, Ruiz Sainz E, Nuñez Vazquez R, Pedrote Amador B, *et al.* Avatrombopag plus fostamatinib combination as treatment in patients with multirefractory immune thrombocytopenia. Br J Haematol 2024;205:1551-5.
32. Mageau A, Terriou L, Ebbo M, Souchaud-Debouverie O, Orvain C, Graveleau J, *et al.* Splenectomy for primary immune thrombocytopenia revisited in the era of thrombopoietin receptor agonists: New insights for an old treatment. Am J Hematol 2022;97:10-7.
33. Chen F, Todd S, Miah H, Allsup D, Cooper N, Bagot C, *et al.* The outcome of splenectomy in refractory ITP is poor: An analysis of real world UKITP registry data. In: Hemasphere, editor. Madrid Spain: European Hematology Association; 2024.
34. Alvarez Román MT, Fernández Bello I, Arias-Salgado EG, Rivas Pollmar MI, Jiménez Yuste V, Martín Salces M, *et al.* Effects of thrombopoietin receptor agonists on procoagulant state in patients with immune thrombocytopenia. Thromb Haemost 2014;112:65-72.
35. Garabet L, Henriksson CE, Lozano ML, Ghanima W, Bussel J, Brodin E, *et al.* Markers of endothelial cell activation and neutrophil extracellular traps are elevated in immune thrombocytopenia but are not enhanced by thrombopoietin receptor agonists. Thromb Res 2020;185:119-24.
36. Garabet L, Ghanima W, Monceyron Jonassen C, Skov V, Holst R, Mowinckel MC, *et al.* Effect of thrombopoietin receptor agonists on markers of coagulation and P-selectin in patients with immune thrombocytopenia. Platelets 2019;30:206-12.
37. Garabet L, Ghanima W, Hellum M, Sandset PM, Bussel JB, Tran H, *et al.* Increased microvesicle-associated thrombin generation in patients with immune thrombocytopenia after initiation of thrombopoietin receptor agonists. Platelets 2020;31:322-8.
38. Justo Sanz R, Monzón Manzano E, Fernández Bello I, Teresa Álvarez Román M, Martín Salces M, Rivas Pollmar MI, *et al.* Platelet apoptosis and PAI-1 are involved in the pro-coagulant state of immune thrombocytopaenia patients treated with thrombopoietin receptor agonists. Thromb Haemost 2019;119:645-59.
39. Lambert C, Maitland H, Ghanima W. Risk-based and individualised management of bleeding and thrombotic events in adults with primary immune thrombocytopenia (ITP). Eur J Haematol 2024;112:504-15.
40. Broome CM, McDonald V, Miyakawa Y, Carpenedo M, Kuter DJ, Al-Samkari H, *et al.* Efficacy and safety of the neonatal Fc receptor inhibitor efgartigimod in adults with primary immune thrombocytopenia (ADVANCE IV): A multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2023;402:1648-59.
41. Al-Samkari H. 2025 update on clinical trials in immune thrombocytopenia. Am J Hematol 2024;99:2178-90.
42. Xu M, Liu J, Huang L, Shu J, Wei Q, Hu Y, *et al.* A novel scoring model for predicting efficacy and guiding individualised treatment in immune thrombocytopaenia. Br J Haematol 2024;205:1108-20.