



Refractory primary immune thrombocytopenia (ITP): current clinical challenges and therapeutic perspectives

Nicola Vianelli¹ · Giuseppe Auteri^{1,2} · Francesco Buccisano³ · Valentina Carrai⁴ · Erminia Baldacci⁵ · Cristina Clissa⁶ · Daniela Bartoletti^{1,2} · Gaetano Giuffrida⁷ · Domenico Magro⁸ · Elena Rivolti⁹ · Daniela Esposito¹⁰ · Gian Marco Podda¹¹ · Francesca Palandri¹

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Abstract

Chronic primary immune thrombocytopenia (ITP) can today benefit from multiple therapeutic approaches with proven clinical efficacy, including rituximab, thrombopoietin receptor agonists (TPO-RA), and splenectomy. However, some ITP patients are unresponsive to multiple lines of therapy with prolonged and severe thrombocytopenia. The diagnosis of refractory ITP is mainly performed by exclusion of other disorders and is based on the clinician's expertise. However, it significantly increases the risk of drug-related toxicity and of bleedings, including life-threatening events. The management of refractory ITP remains a major clinical challenge. Here, we provide an overview of the currently available treatment options, and we discuss the emerging rationale of new therapeutic approaches and their strategic combination. Particularly, combination strategies may target multiple pathogenetic mechanisms and trigger additive or synergistic effects. A series of best practices arising both from published studies and from real-life clinical experience is also included, aiming to optimize the management of refractory ITP.

Keywords Immune thrombocytopenia (ITP) · Refractory ITP · Rituximab · Thrombopoietin receptor agonists (TPO-RA) · Combination therapy · Real-life clinical practice

✉ Francesca Palandri
francesca.palandri@unibo.it

- ¹ IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Istituto Di Ematologia “Seràgnoli, Bologna, Italy
- ² Dipartimento Di Medicina Specialistica, Diagnostica E Sperimentale, Università Di Bologna, Bologna, Italy
- ³ Dipartimento Di Biomedicina E Prevenzione, Università Tor Vergata, Rome, Italy
- ⁴ AOU Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy
- ⁵ AOU Policlinico Umberto I, Rome, Italy
- ⁶ A.O. Ospedali Riuniti Marche Nord, Pesaro, Italy
- ⁷ AOU Policlinico - Vittorio Emanuele, Catania, Italy
- ⁸ AO Pugliese Ciaccio, Catanzaro, Italy
- ⁹ Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Reggio Emilia, Italy
- ¹⁰ Presidio Ospedaliero San G. Moscati Di Aversa - ASL Caserta, Caserta, Italy
- ¹¹ Medicina III, Ospedale San Paolo, ASST Santi Paolo E Carlo, Dipartimento Di Scienze Della Salute, Università Degli Studi Di Milano, Milano, Italy

Introduction

Immune thrombocytopenia (ITP) is a hematological disorder that comprises immune-mediated platelet destruction associated with a variable extent of bleeding [1]. Considering adult patients, ITP is generally an acquired condition with chronic features and has an incidence of 3.3 per 10,000 individuals in Europe [2]. Remarkable progresses have been achieved with regard to the characterization of immune-mediated phenomena and the role of endogenous thrombopoietin (TPO) underlying ITP pathogenesis, highlighting novel mechanisms which have been translated into new treatment opportunities [3, 4]. Thanks to the advent of novel therapeutic approaches over the past decades, ITP patients can now often benefit from an overall reduced risk of major bleeding, with a satisfactory quality of life (QoL) [5, 6].

Notwithstanding such progresses, a small portion of ITP patients still does not respond to conventional treatments, even after multiple lines of single-agent therapies. Refractory ITP is associated with a significant worsening of QoL and with a very difficult clinical management. To further

complicate matters, the diagnosis of refractory ITP is still driven by exclusion, and clinicians' experience plays a major role in correctly addressing it [3]. Thus, efforts focused on refractory disease elucidation are strongly needed, as well as a harmonization of current guidelines. Over the past decades, evidence gathered from clinical practice has been indicating a promising role of combination therapies, particularly if simultaneously targeting multiple biological mechanisms.

Information on definition and therapy of refractory ITP is scarce. To provide an overview of current knowledge on this important clinical issue, a thorough search of the literature was conducted using PubMed (US National Library of Medicine and the National Institutes of Health) and Web of Science (Thomas Reuters Online Academic Citation Index), with publication dates ranging from 1956 to March 2020. To ensure that an extensive range of publications were identified, broad search terms for primary immune thrombocytopenia, ITP, refractory ITP, rituximab, splenectomy, thrombopoietin receptor agonists (TPO-RA), and clinical/epidemiological variables (e.g., incidence, prevalence, frequency, diagnosis, bleedings, thrombosis, complications, survival, outcome) were utilized with the addition of alternative spellings and umbrella terms, e.g., immune thrombocytopenia and hemorrhages. Furthermore, we reviewed the literature cited in the identified papers.

Based on this research, we summarize the available data on refractory ITP, including diagnosis, epidemiology, clinical presentation, symptom burden, thrombotic/hemorrhagic risk, prognosis, and treatment strategies.

The challenges for a correct diagnosis of refractory ITP

According to current guidelines, ITP can be diagnosed in the presence of isolated thrombocytopenia (platelet count $< 100 \times 10^9/l$) without anemia or leukopenia and without alternative causes of thrombocytopenia [1]. In clinical practice, a response to ITP-specific treatments represents the best confirmation of the diagnosis of ITP.

According to Psaila et al., about 10% of ITP patients become refractory to treatment within 1 year [7]. In these cases, the absence of clinical response dramatically questions ITP diagnosis [3] and should trigger a thorough clinical and laboratory work-up [6, 8] to exclude other underlying diseases, particularly myelodysplastic syndromes (MDS), drug-induced thrombocytopenia, inherited thrombocytopenia, and bone marrow failure syndromes. Also, pseudothrombocytopenia and the presence of type IIB von Willebrand's disease should be excluded.

These conditions present signs and symptoms that may overlap ITP clinical manifestation and mislead towards an

incorrect diagnosis [9–11]. When an underlying condition is diagnosed, patients might indeed benefit from the treatment of the associated disease.

In case of refractory ITP, a cytogenetic study and bone marrow histology is recommended by the International Working Group (IWG) and ASH guidelines, especially if not previously performed [6, 8, 12]. Peripheral blood smear analysis should always be evaluated to exclude other acquired or congenital hematological disorders, which can initially occur with isolated thrombocytopenia (e.g., thrombotic microangiopathies, congenital thrombocytopenia, and acute leukemia). In selected cases, platelet survival study may be performed as it can provide further valuable information [13]; moreover, in selected cases, genomic assays such as whole-genome sequencing and whole-exome sequencing may be performed as well to exclude the presence of MDS, inherited thrombocytopenia, or bone marrow failure syndromes, although further validation of these assays is needed [14].

Despite this plethora of laboratory tests, there is still a high chance of misdiagnosis. The absence of ITP-specific diagnostic tests and the presence of a multitude of disorders potentially sharing ITP features represent two major difficulties for a correct diagnosis of refractory ITP. Therefore, clinicians' experience is, in practice, the most crucial factor to determine a correct diagnosis of refractory ITP, and a certain level of uncertainty should always be acknowledged [3].

The evolving task of defining refractory ITP

Over the years, several definitions of refractory ITP have been proposed. Before the advent of medical alternatives, refractory ITP was generally based on the absence of response or relapse after splenectomy [12]. More specifically, response was defined according to Rodeghiero et al., as failure to achieve a platelet count of $30000/\mu L$ and doubling of baseline platelet counts [12]. In 2010, such definition of refractory ITP has been confirmed and endorsed by ASH guidelines [8]. However, splenectomy is not feasible in a not negligible portion of ITP patients, particularly in the elderly and/or in those with multiple/significant comorbidities. Also, patients may have a certain reluctance to undergo splenectomy, thus refusing the procedure. Furthermore, its indication in children is weak [15].

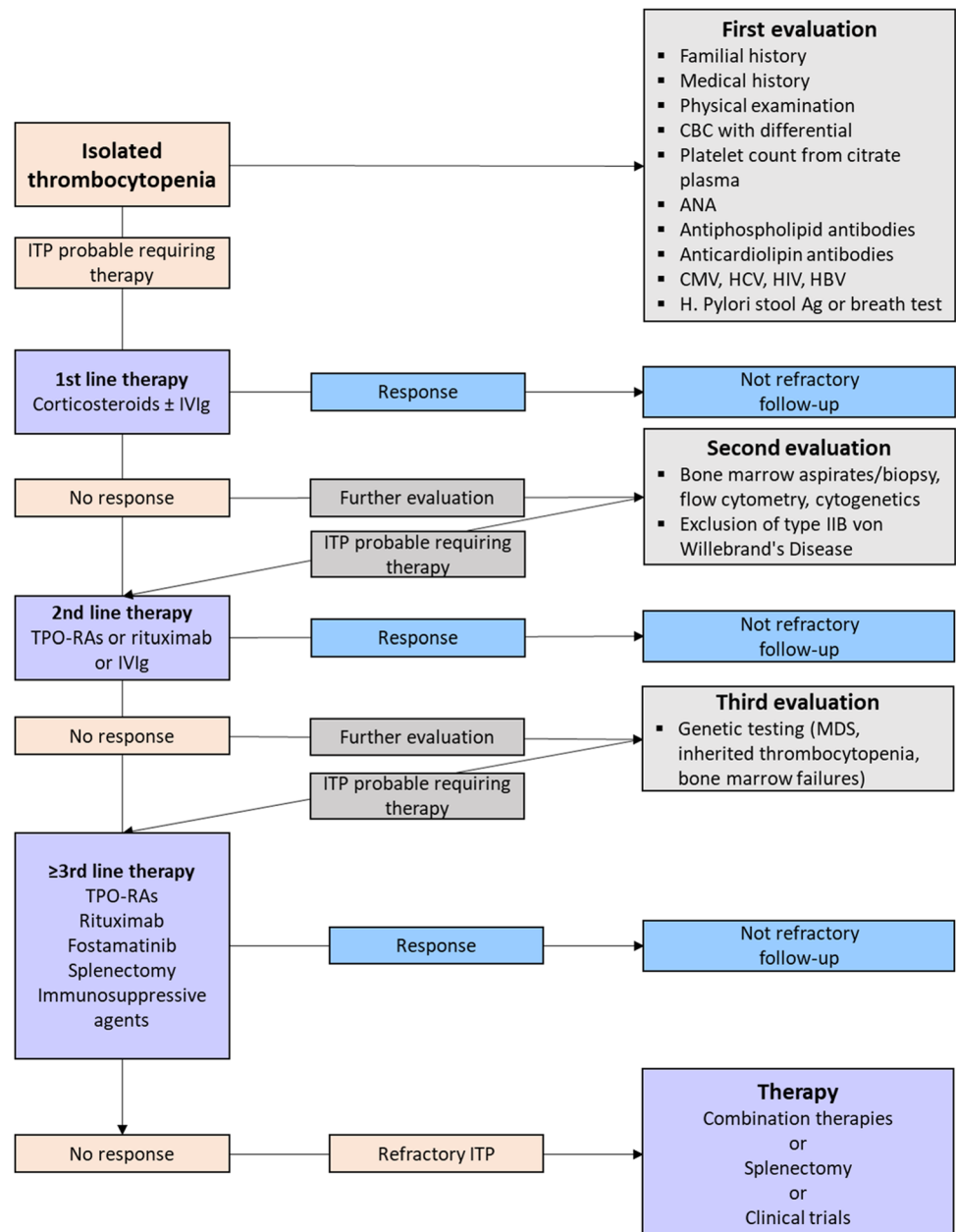
As a result, in 2016, Cuker et al. extended the definition of refractory ITP to patients who require treatment but are unable or unwilling to undergo splenectomy [16]. The exclusion of splenectomy from the definition of refractory ITP has opened a debate about which and how many lines of medical therapy must fail before refractory disease is declared and whether or not an active bleeding syndrome should be present. In 2020, refractory ITP was defined as a total lack

of response to one or more single-agent therapies (including rituximab and TPO-RA) [16]. Shortly thereafter, Miltiados et al. reserved the description of “refractory” for patients whose platelet counts do not respond to ≥ 2 treatments, there is no single medication to which they respond, and their platelet counts are very low and accompanied by bleeding. These refractory patients have not necessarily undergone splenectomy [3]. This definition refers to the failure of single lines of therapy, excluding drug combinations, and requires the presence of active bleeding. However, it does not indicate which therapies should be attempted before declaring refractory ITP nor includes patients with prolonged low platelet count in the absence of bleedings.

In real-life, refractory ITP is often defined as the persistence of low platelet counts despite appropriate use of all conventional therapies deemed safe for the specific patient, regardless of hemorrhagic manifestations. The threshold value to identify “low” platelet count is variable depending on the patient’s age, comorbidities, and concomitant therapies (e.g., antiplatelet or anticoagulant agents).

Figure 1 presents a diagnostic flowchart for refractory ITP.

Fig. 1 Flowchart for the identification and treatment of patients with refractory ITP Ag, antigen. ANA, anti-nuclear antibodies. CBC, complete blood count. CMV, cytomegalovirus. HCV, hepatitis C virus. HBV, hepatitis b virus. *H. pylori*, *Helicobacter pylori*. HIV, human immunodeficiency virus



Single-agent treatments in ITP

First-line therapeutic options include corticosteroids (prednisone or high-dose dexamethasone), clinically used to rapidly increase platelets counts and to reduce or resolve bleedings [16, 17]. Intravenous high-dose immunoglobulins (IVIg) can be also employed up-front, especially to treat patients at high hemorrhagic risk. In certain cases, corticosteroids and immunoglobulins can be administered together to accelerate the increase in platelet count. Although initially effective to control life-threatening bleedings and to ameliorate thrombocytopenia in most cases, corticosteroids and IVIg frequently induce only transitory beneficial effects and are characterized by important side effects [1, 6, 18, 19].

Second-line treatment options comprise splenectomy, rituximab, and thrombopoietin receptor agonists (TPO-RA; eltrombopag, romiplostim) [6, 8]. Other pharmacological approaches include immunosuppressants such as ciclosporin A, mycophenolate mofetil, cyclophosphamide, and other agents [20]. There are currently no indications about which specific order or schedules of administration should be followed [6, 8].

Splenectomy may be considered during the chronic phase of ITP, because it provides a good chance of maintaining a medium- to long-term response and has an acceptable risk/benefit ratio [21]. In a monocenter study, Palandri et al. documented a progressive delay in splenectomy use over time after the failure of several treatments. Despite splenectomy was performed after failure of multiple lines of medical treatments, it maintained sustained efficacy in this truly refractory population [22]. Likewise, Tastaldi et al. have shown that splenectomy has a high efficacy rate and a progressively lower morbidity over time [23]. However, surgical procedure may not be advisable in some cases; moreover, a growing number of patients refuse to undergo splenectomy due to personal reasons, mainly to maintain an active lifestyle [24]. Therefore, different therapeutic options might be more adequate in selected cases.

Rituximab, an anti-CD20 monoclonal antibody, triggers an initial response in 50–60% of cases, which lasts for more than 5 years in 30–40% of patients [25]. Recent studies have shown that rituximab can achieve responses lasting at least 1 year in 40–60% of ITP patients [26, 27]; other authors report a response rate of 21%, maintained for at least 5 years in adult patients, without observing novel long-term toxicities [28]. Additional data underlined that young women should be considered as ideal candidates to obtain the best benefits from this type of treatments [29]. Ultimately, rituximab can achieve long-lasting responses in about only 20–30% of treated patients, with

no significant impact of different dosages and schedules of administration [27]. Notably, non-response to rituximab appears to be associated with an aberrant oligo-/monoclonal expansion of T cell-mediated immune response, whereas the same therapeutic approach can be more effective in case of B cell-mediated responses [30]. Also, a sustained presence of immortalized plasma cells in the spleen with uncontrolled antibodies secretion has been observed in patients failing rituximab [31, 32].

More recently, TPO-RA were shown to be effective in 70–80% of cases, with responses maintained over time in 50–60% of patients [33, 34]. There are also published reports indicating their possible use in a reciprocally sequential schedule of administration to partially overcome resistance/intolerance phenomena [35–42]. Moreover, numerous studies evaluated the long-term efficacy of TPO-RA both as continuous treatment and after discontinuation following complete response, with positive results [33, 36–49]. Notably, TPO-RA have been shown as effective in treating chronic ITP with positive long-term results, especially due to their acceptable safety profile [33, 39, 50, 51]. Platelet response rates are typically between 50 and 90% (depending on the definition of response), and the use of TPO-RA has been shown to significantly increase platelet count and reduce bleeding and the need for rescue therapies, in comparison with control [33, 52–54]. Recently, the long-term efficacies of rituximab and TPO-RA have been deemed as equivalent; however, a slightly improved safety profile has been observed with romiplostim and eltrombopag [8]. Similarly, TPO-RA have been proposed as a safer alternative to splenectomy, due to the possibility of achieving long-term stable responses [8]. While TPO-RA and rituximab have also been used in patients with acute/persistent ITP, the above studies are focused on patients with chronic/refractory ITP. However, given the variability with which a refractory patient is defined, these studies may not all be fully referable to the refractory patient. Further studies, with standardized definition of refractory ITP, are needed to provide solid data on efficacy and safety of these therapies in this setting.

In 2016, an algorithm based on a tiered approach indicating a series of sequential therapeutic options for the treatment of refractory ITP has been published. As indicated by the algorithm, patients not responding to tier 1 approach may benefit from switching towards a combination of multiple agents from the same tier or from another one. In case of refractoriness to the first two tiers, a third line of treatment is advised, although rarely used in the clinical practice [16].

In 2019, the ASH guidelines acknowledged that there was no evidence to support strong recommendations for various management approaches beyond second-line therapy. Therefore, immunosuppressive agents were listed in alphabetical order [8]. Another international expert consensus included eltrombopag, avatrombopag, romiplostim, fostamatinib, and

rituximab among therapies with robust evidence of efficacy for patients at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy. The choice among these treatment strategies should be based on available resources, since not all therapies are available in all countries, toxicity profile, and patient preference [8, 55].

Can combination strategies and recently approved drugs improve results in refractory ITP?

When refractory ITP has been diagnosed, different treatment combinations may be considered, especially if they are active against different targets at the same time [3]. Indeed, additive or synergistic drug activities have been observed during the effective translation of preclinical findings into the clinical setting.

In 2007, before the advent of RTX and TPO-RA, a study explored a combination strategy based on multiagent induction (IVIg, intravenous methylprednisolone, vinca alkaloids, and/or anti-D) possibly followed by maintenance therapy (oral danazol and azathioprine) to treat refractory ITP patients, defined as those who could not achieve response to high-dose oral prednisone (> 1 mg/kg per day) and/or IVIg (1 g/kg). The study showed promising results, with 71% of patients achieving clinical responses with induction combination therapy ($\approx 20\text{--}30 \times 10^9/L$) and 66% of patients who received maintenance therapy with stable responses (platelets counts $\geq 50 \times 10^9/L$) [56]. However, latest evidence suggests that the same strategy may not be effective for treating refractory patients, including those who failed to respond to rituximab and/or TPO-RA [3].

Also, the well-known “CHOP” scheme, based on cyclophosphamide, vincristine, doxorubicin, and prednisone, was used to treat refractory ITP patients, defined as individuals who have failed to respond to an average of 6.8 previous therapies, including corticosteroids and splenectomy. As a result, one half of the treated patients (4/8) achieved complete response (CR) which was maintained over the years [57, 58]. The modification of CHOP scheme with the addition of rituximab, which meanwhile became available, and removal of doxorubicin (R-CVP) did not lead to much different results, with clinical responses observed only in one half of treated patients. Moreover, R-CVP was not generally well-tolerated, and responses were observed only in those patients who previously responded to rituximab monotherapy. As a result, no advantages were highlighted by the addition of rituximab to CVP scheme [59].

A cohort study published in 2018 by Deprè et al. reported a 20-year experience on a total of 400 ITP patients (100 not treated, 300 treated) who were exposed to various

combination therapies following splenectomy (azathioprine + prednisone, mycophenolate mofetil + prednisone, cyclophosphamide + prednisone). This report mainly included patients that did not receive TPO-RA because still unavailable. The results showed a response rate of 50%, without however identifying the best combination, probably due to retrospective nature of the study and the variability of treatments. In the absence of clear findings, the authors argued that optimal treatment decision for refractory ITP should be based on patient-specific considerations [60].

In 2016, a multicenter retrospective study included 37 patients with refractory ITP who received combination therapies with or without TPO-RA. The patients had failed a median of 10.5 previous treatment lines and were followed for a relatively extended period (median observation, 84 months). Patients received either immunosuppressant agents or a combination of these last with TPO-RA. The results showed that only 1/14 patients treated with combined immunosuppressive agents achieved responses, whereas the addition of TPO-RA was able to induce responses in 7/10 patients. These responses were maintained over time (median 15 months). In addition, the study highlighted a general improvement of survival rates, with only 3 ITP-related deaths (two from hemorrhage and one from infection). Overall, the results of this study emphasize the possible clinical benefit which can be obtained by combining conventional treatments with TPO-RA, in terms of increased response rates and reduced mortality [61].

The most encouraging results regarding combination therapy for refractory ITP have been achieved by combining TPO-RA with immunosuppressant agents (mycophenolate mofetil or cyclosporine) and IVIg. In a very recent study, 18 refractory patients received such combination after failure of a mean of 6.5 previous treatment lines, including TPO-RA alone and splenectomy. As a result, 13/18 patients (72.2%) achieved clinical responses, by exhibiting satisfactory platelet counts at the end of treatment (meaning an augmentation of platelet counts $> 30 \times 10^9/l$ and double the baseline after week 1 or sporadic but frequent platelet counts $> 30 \times 10^9/l$ during the observation period). Of the total responding patients, 11/18 reported mild toxicities (headaches, abdominal discomfort). Despite the limited number of patients included in this study, the positive results may nonetheless offer a good alternative treatment of refractory disease [20]. Of note, the combination therapy based on TPO-RA, immunosuppressants, and intravenous immunoglobulins was rationally designed to specifically target three different mechanisms involved in the ITP pathogenesis. Platelet production was actively stimulated by TPO-RA, exploiting the agonistic activity of eltrombopag/romiplostim on the thrombopoietin receptor (cMPL), which in turn boosts megakaryopoiesis and platelet production [62, 63]. Then, intravenous immunoglobulins were employed to inhibit

platelet elimination by blocking Fc receptors and hence autoantibody-mediated platelet phagocytosis [64]. Lastly, immunosuppressant agents such as mycophenolate mofetil or cyclosporine were selected to specifically inhibit T cell activation, due to evidence of an increased relevance of this lymphocyte subpopulation in the etiopathogenesis of ITP [65].

Very recently, two additional drugs (avatrombopag and fostamatinib) have received approval for the treatment of chronic ITP who have demonstrated an insufficient response to previous therapy and are becoming available for real-life use.

Avatrombopag (Doptelet, AkaRx Inc.) is the latest oral TPO-RA to be evaluated as an option for patients with ITP. Like eltrombopag, avatrombopag is a small molecule that binds the transmembrane domain. Its absorption is not reduced by dietary fat or divalent cations (such as calcium); therefore, and unlike eltrombopag that must be taken on an empty stomach or at least 2 h after a meal, avatrombopag can be given with any food [66].

In a phase 2 clinical trial, avatrombopag was compared with placebo in ITP patients (NCT00441090 and NCT00625443). Sixty-four patients were randomized into groups receiving different doses from 2.5 to 20 mg. The ORR (defined as platelet level $\geq 50 \times 10^9/L$) in the groups was as follows: 13% for the 2.5 mg dose, 53% for 5 mg, 50% 10 mg, 80% for 20 mg, and 0% for the placebo group. Durable response was observed in 76% of patients. All patients reported side effects, but most were mild (most common fatigue, headache, and epistaxis) [67]. The subsequent phase 3 study compared avatrombopag (dose, 20 mg daily) to placebo [68]. Forty-nine patients were enrolled in this study: 32 to the avatrombopag arm and 17 to placebo. The median cumulative number of weeks of platelet response was 12.4 vs. 0.0 weeks, respectively ($P < 0.0001$). The patients treated with avatrombopag displayed a greater platelet response rate on day 8 compared with placebo ($P < 0.0001$), as well as reduced use of concomitant ITP medications. The therapy was safe, with the most common AE being headache. Overall, avatrombopag appears to be effective and generally well-tolerated in ITP patients and may be an important therapeutic option, alone or in combination, in patients with refractory ITP, although data from larger cohorts of patients are needed.

Fostamatinib (Tavalisse, Rigel Pharmaceuticals) is an orally bioavailable small-molecule spleen tyrosine kinase (SYK) inhibitor approved for the treatment of adults with chronic ITP refractory to previous therapy [69]. Its unique mechanism of action is based on the potent inhibition of the signal transduction of Fc-activating receptors and B cell receptors (BCR), leading to reduced antibody-mediated platelet destruction [70]. In two identical phase 3 studies, FIT1 (NCT02076399) and FIT2 (NCT02076412), patients

with refractory ITP were randomized into a fostamatinib ($n = 101$) or a placebo ($n = 49$) group [71]. Stable responses were observed in 18% of patients in the fostamatinib arm vs 2% in the placebo arm ($P = 0.0003$). Overall responses were 43% vs 14%, respectively ($P = 0.0006$). The most common side effects were diarrhea, hypertension, nausea, and aminotransferase elevation, and these were mild or easily manageable. The long-term safety and efficacy of fostamatinib were evaluated in a follow-up, open-label extension study including responding patients. Twenty-seven patients (18%) demonstrated a stable response with a median duration of > 2 years; 64 (44%) achieved a response with a median response duration of more than 2 years. Of 71 patients who had failed TPO-RA, 24 (34%) had overall responses to fostamatinib. The most common side effects were similar to the previous study [72].

Notably, fostamatinib has also shown responses in heavily pretreated ITP patients, including those who failed treatment with splenectomy, TPO-RA, and rituximab; therefore, its use in refractory ITP should be recommended.

Several other molecules are currently under clinical investigation.

Rilzabrutinib is an oral, reversible, covalent inhibitor of Bruton tyrosine kinase (BTK) that targets underlying disease mechanisms of platelet destruction without inhibiting platelet aggregation (common with ibrutinib)[73]. The open-label phase I/II study evaluated rilzabrutinib in adults who had inadequate response to prior corticosteroids/TPO-RA but were allowed to continue receiving stable doses of these medications. Preliminary results showed that oral rilzabrutinib achieved clinically significant platelet responses ($\geq 50 \times 10^9/L$) in patients with heavily pretreated ITP irrespective of splenectomy or lack of response to prior ITP therapy and maintained responses for the majority of time. Rilzabrutinib was well-tolerated with only grade 1/2 treatment-related overall adverse events. A Phase 3 study is now underway to further demonstrate the magnitude and durability of rilzabrutinib's clinical benefit.

Mezagitamab (TAK-079) (Takeda, Millennium Pharmaceuticals, Inc.) is a fully human IgG1 λ monoclonal antibody that binds to CD38, allosterically inhibits enzymatic activity, induces apoptosis, and cytolyses cells by antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, reducing NK cells and sub-populations of B and T lymphocytes [74]. A multicenter phase 2 trial is now ongoing to test the efficacy and safety of this compound in patients with persistent ITP, whose diagnosis is supported by a prior response to an ITP therapy (other than a TPO-RA) and severe thrombocytopenia (NCT04278924) [75].

Efgartigimod is a human IgG1 antibody Fc-fragment. This natural ligand of the neonatal Fc receptor (FcRn) has been engineered for increased affinity to FcRn [76]. It blocks FcRn preventing IgG recycling and causing targeted IgG

degradation [77]. The efficacy and safety of this novel therapeutic approach have been recently described by Newland et al. in a phase 2 study [78]. Thirty-eight patients, refractory to previous lines of therapy, were randomized 1:1:1 to receive four weekly intravenous infusions of either placebo ($N = 12$) or efgartigimod at a dose of 5 mg/kg ($N = 13$) or 10 mg/kg ($N = 13$). This short treatment cycle of efgartigimod was shown to be well-tolerated and demonstrated a favorable safety profile as observed in healthy volunteers and myasthenia gravis patients [79]. Efgartigimod induced a rapid reduction of total IgG levels (up to 63.7% mean change from baseline), which was associated with clinically relevant increases in platelet counts (46% patients on efgartigimod vs 25% on placebo achieved a platelet count of $\geq 50 \times 10^9/L$ on at least two occasions, and 38% vs 0% achieved $\geq 50 \times 10^9/L$ for at least 10 cumulative days) and a reduced proportion of patients with bleeding.

Table 1 summarized the main clinical studies on combination strategies and new/investigational drugs in refractory ITP [20, 56, 59, 61, 73, 78, 80–93].

The impact of the SAR-CoV-2 pandemic on refractory ITP

The current COVID-19 pandemic requires revisiting our current approach to major blood disorders, including ITP. In patients with suspected, ongoing, or relapsed ITP — that is not severe enough to cause significant risk of major bleeding — the main risk is to be infected in healthcare settings. This risk must be carefully considered when adapting the diagnostic and therapeutic approach of ITP [94]. The following recommendations are expert suggestions of the authors.

In patients with refractory disease, drugs that can induce profound and prolonged immunosuppression (e.g., rituximab) should be avoided as much as possible, preferring the use of TPO-RA that stimulate megakaryocytopoiesis and with milder and more rapidly reversible immunosuppressive activity [94–96]. A remote monitoring of blood count is recommended during TPO-RA, and self-treatment is suggested for patients treated with romiplostim. In case of inefficacy or intolerance to TPO-RA (around 70%), treatment with low doses of corticosteroids or immunosuppressants may be feasible worldwide. There is no evidence that corticosteroid use increases the risk of developing COVID-19 infection or of worsening its course [97]. However, the use of lower doses of corticosteroids and the administration of intravenous immunoglobulins (IVIg), 400 mg/day for 5 days or 1 g/kg/day for 1–2 days, may be considered. Fostamatinib may also represent a valuable option in this setting. Inclusion in clinical trials remains of utmost importance in refractory ITP but may be limited due to the pandemic. Patients with refractory ITP require frequent clinical and laboratory

evaluations. The use of telemedicine and homecare implementation may reduce the risk of contagium and increase safety during treatment [98].

In ITP refractory patients who acquire a mild COVID-19 syndrome and require treatment for ITP, the dosage and duration of corticosteroids therapy should be cautiously reduced (e.g., initial prednisone dose 20–25 mg/day regardless of body weight, with dose increase if necessary after 3–5 days, up to a maximum of 80 mg/day). Short-term use of steroids (e.g., prednisone 1 mg/kg/day for 5 days) or possibly a cycle of dexamethasone (40 mg/day for 4 days) could also be considered. In any case, prolonged administrations should be avoided, and tapering should be initiated within 2 weeks after the start of therapy. The use of IVIg is generally encouraged and could positively affect the evolution of the infection [99]. There is no contraindication to infusion of plasma obtained from patients recovering from COVID-19. The benefit of starting a TPO-Ras in ITP patients with SARS-CoV-2 infection should be balanced against the risk of thromboembolic events [100]. If the patient were already on TPO-RAs, the dose could be increased to the maximum allowed. For patients hospitalized in the intensive care unit, each therapeutic intervention should be discussed case by case.

Vaccination against SARS-CoV-2 is strongly suggested for all ITP patients. However there are still no clear indications concerning optimal strategy to adopt in refractory patients with platelet count $< 30,000/mm^3$. In these cases, the decision must be made on a case-by-case basis with patients. Particularly, patients in whom treatment with rituximab or immunosuppressive agents is expected to be needed soon should receive the vaccine, if possible, at least one month before the start of these therapies.

The controversial role of treatment on survival of refractory ITP

Patients with refractory ITP have low platelet counts even after being exposed to multiple treatments, including several single agents and/or splenectomy. Bleeding represents the most fatal event, requiring further pharmacological intervention. Refractory ITP patients therefore exhibit a four times higher mortality risk as compared with general population, with 50% of deaths being due to disease-related bleeding and 50% due to infections, likely as a result of heavy and prolonged treatments [101]. A review published in 2000 by Cohen et al. reported a mortality rate of 2.7% due to fatal bleeding among a total ITP population of 1817 individuals. Mortality was assessed as 2% for patients aged < 40 years, while it increased to 48% for patients aged > 60 years. Advanced age, longer disease history, and exposure to multiple treatment lines were identified as important risk factors

Table 1 Main clinical studies on combination strategies and new/investigational drugs in refractory ITP RTX, rituximab, TPO-RA, thrombopoietin receptor agonists. CR, complete response, PR, partial response. IVIg, intravenous immunoglobulin. Definition of response is variable among different studies

Reference	Eligible patients	Medication	Mechanisms of action	No. of patients	Best Response	Last reported response	Toxicity	Major bleedings
Combination strategies								
Choudhry VP et al. Int J Hematol. 1995[80]	Primary ITP, no prior RTX/TPO-RAs	Vinblastine, danazol	Increased lymphodepletion & thrombocytopenosis	16	CR 38%, PR 25%	CR/PR 25% @6 mos	1 intra-cranial hemorrhage	1 intra-cranial hemorrhage
McMillan R, et al., N Engl J Med. 2001[81]	Primary ITP, no prior RTX/TPO-RAs	Cyclophosphamide, prednisone, vincristine, procarbazine/etoposide	Immunosuppression & marrow toxicity	12	CR 58%, PR 17%	CR 50%, PR 0 @ 2yrs	Nausea, alopecia, malaise	3 intra-cranial hemorrhages
Kappers-Klunne MC et al., Br J Haematol. 2001[82]	Primary ITP, no prior RTX/TPO-RAs	Cyclosporine, prednisone (2 schedules)	Increased immunosuppression	20	CR 30%, PR 20%	CR 20%, PR 0 @ 2yrs	Hypertension, headache, muscle pain	None
Williams JA et al., J Pediatr Hematol Oncol. 2003[83]	40% Evans syndrome, no prior RTX/TPO-RAs	Vincristine, methylprednisone, cyclosporine	Increased immunosuppression & marrow toxicity	10	CR/PR 80%	CR 20%, PR 0 @ 2yrs	Peripheral neuropathy, constipation, jaw pain, alopecia, nausea	None
Boruchov DM et al., Blood 2007[56]	Primary ITP, no prior RTX/TPO-RAs	IVIg, anti-D, vincristine, vinblastine (induction) danazol, & azathioprine (maintenance)	Accelerated clearance of auto-antibodies, inhibition of components of the complement cascade, reduced activity of the monocyte-macrophage system, lymphodepletion, & increased androgen-induced thrombocytopenosis	17	CR/PR 65%	CR/PR 65% @4 mos	ileus	None (6 thromboses)
Hasan A et al., American journal of hematology 2009[59]	Primary ITP, prior RTX, non-prior TPO-RAs	Second-dose RTX vs RTX, cyclophosphamide, vincristine, prednisone vs double-dose RTX	Increased lymphodepletion ± marrow toxicity	20 vs 8 vs 8	CR 50%, PR 20% vs CR 38%, PR 0 vs CR 50%, PR 13%	CR 5%, PR 0 @ 2 yrs vs CR 0, PR 0 @ 2 yrs vs CR 0, PR 0 @ 2yrs	Allergy	None

Table 1 (continued)

Reference	Eligible patients	Medication	Mechanisms of action	No. of patients	Best Response	Last reported response	Toxicity	Major bleedings
Arnold DM et al., Blood. 2010[84]	Primary ITP, no prior RTX/TPO-RAs	Azathioprine, cyclosporine, mycophenolate mofetil	Immunosuppression	19	CR 11%, PR 63%	57% relapse @2 yrs	Infections, tremors, gum hypertrophy	None
Gomez-Almaguer D et al., Blood. 2010[93]	Evans syndrome	RTX & alemtuzumab	Increased lymphodepletion	11	CR 45%, PR 55%	CR/PR 0 @ 2 yrs	Severe infections	9% died (unreported cause)
Wang S, Int J Hematol. 2012[85]	Primary ITP, no prior RTX/TPO-RAs	rhTPO & danazol vs danazol alone	Increased thrombocytopenia	73 vs 19	CR/PR: 60% vs CR/PR:37%	Not reported	Visual field defect	1 intra-cranial hemorrhage
Cui ZG, et al., Chin Med J (Engl). 2013[86]	Primary ITP, no prior TPO-RAs	rhTPO & cyclosporine vs rhTPO alone	Increased thrombocytopenia and immunosuppression	19 vs 17	CR/PR: 82% vs CR/PR: 50%	Not reported	None	None
Li J, et al. Clin Dev Immunol. 2013[87]	Primary ITP, no prior RTX	Prednisone & cyclosporine vs prednisone & rapamycin	Increased immunosuppression	45 vs 43	Not reported	Sustained response: 39%		
Sustained response: 68%	None	11% and 7% bleedings						
Zhou H, et al. Blood. 2015[88]	Primary ITP, no prior RTX	RTX & rhTPO vs RTX	Increased immunosuppression ± thrombocytopenia	77 vs 38	CR: 45% vs CR:23%	CR: 25% vs CR:19% @ 2 yrs	Infections, one myocardial infarction	1 intra-cranial hemorrhage
Choi PY, et al., Blood. 2015[89]	Primary and secondary ITP, unclear if prior RTX/TPO-RAs	Dexamethasone, cyclosporine and RTX	Increased immunosuppression	20	CR/PR: 60%	CR/PR: 55% @1 yr	Hypertension	None
Li Y, et al., Eur Rev Med Pharmacol Sci. 2015[90]	Primary ITP, no prior RTX/TPO-RAs	RTX & TPO-RAs	Increased thrombocytopenia and immunosuppression	14	CR 50%, PR 43%	CR 36%, PR 43% @2 yrs	Infections	1 intra-cranial hemorrhage
Mahevas M, Blood. 2016[61]	Primary ITP, prior RTX, non-prior TPO-RAs	Supportive therapy vs immunosuppressant vs TPO-Ras & immunosuppressant vs TPO-RAs & IVIg/cyclosporine	Increased thrombocytopenia and immunosuppression	12 vs 14 vs 10 vs 5	NR vs CR/PR 7% vs CR/PR 70% vs NR	CR/PR 0 @ 2 yrs (all arms)	Infections, thrombosis	None

Table 1 (continued)

Reference	Eligible patients	Medication	Mechanisms of action	No. of patients	Best Response	Last reported response	Toxicity	Major bleedings
Feng FE, Lan-cet Haematol. 2017[91]	Primary ITP, prior RTX and TPO-RAs allowed	Danazol & ATRA vs danazol alone	Increased thrombopoiesis and immunosuppression	45 vs 48	CR/PR: 82% vs CR/PR: 44%	CR/PR: 62% @ 1 yr vs CR/PR: 25% @ 1 yr	Hypertension, gastrointestinal disorders, headache	2% serious bleedings
Wang J, Exp Ther Med. 2019[92]	Primary ITP	RTX vs cyclosporine vs RTX & cyclosporine	Increased immunosuppression	79 vs 86 vs 84	CR: 33%, PR: 25% vs CR: 13%, PR: 36% vs CR: 58%, PR: 17%	Not reported	Hypertension, gastrointestinal disorders, dizziness, infections	None
Gudbrandsdottir S et al. British journal of haematology 2020[20]	Primary ITP, prior TPO-RAs allowed. Children included	TPO-RAs, cyclosporine, and mycophenolate ± IVIg	Accelerated clearance of auto-antibodies, inhibition of components of the complement cascade, reduced activity of the monocyte-macrophage system, immunosuppression & increased thrombocytopoiesis	18	CR/PR: 72%	Not reported	Headaches, hypertension, abdominal discomfort	None
Recently approved drugs								
Bussel JB et al., Blood 2014, 123 (25):3887–3894[67]	Primary ITP, prior RTX and TPO-RAs allowed	Avatrombopag	Increased thrombopoiesis	32	CR/PR: 65.6%	Durable CR/PR: 34.4%	Vomiting and headache	None
Markham A, Drugs 2018, 78 (9):959–963[69]	Primary ITP, prior RTX and TPO-RAs allowed	Fostamatinib	Spleen tyrosine kinase (SYK) inhibitor. Inhibition of the signal transduction of Fc-activating receptors and B cell receptors (BCR), leading to reduced antibody-mediated platelet destruction	146	CR/PR: 44%	CR/PR: 18% @ 28 mos	Diarrhea, hypertension, nausea, epistaxis, and abnormal liver function tests	None
Drugs under clinical investigation								
Kuter DJ et al., Blood 2020, 136, 13–14[73]	Primary ITP, prior RTX and TPO-RAs allowed	Rilzabrutinib	Inhibition of Bruton tyrosine kinase (BTK)	32	CR/PR: 44%	Not reported	None	None

Table 1 (continued)

Reference	Eligible patients	Medication	Mechanisms of action	No. of patients	Best Response	Last reported response	Toxicity	Major bleedings
Newland et al., Am J Hematol. 2020;95:178–187[78]	Primary ITP, prior RTX and TPO-RAs allowed	Efgartigimod vs placebo	Block of neonatal Fc receptor preventing IgG recycling, and causing targeted IgG degradation	26 vs 12	CR/PR: 46% vs CR/PR: 25%	Not reported	None	None

for hemorrhage and infections [102]. In 2006, George et al. reviewed published evidence from the early 2000s, documenting an average hemorrhage-related mortality of 1% over 1079 ITP patients [103]. In 2004, McMillan et al. reported a higher mortality rate (15%) in 105 splenectomy-refractory patients; in particular, deaths were due to hemorrhage and infections in 10% and 5% of cases, respectively [57].

Although the above mortality data have been obtained from studies performed in the pre-rituximab and TPO-RAs, the mortality rate observed in the past can be compared with those obtained from the studies conducted with newer drugs. In these latter studies, mortality was not included among endpoints that focused on the achievement of a safe platelet count, the reduction of incidence of bleeding events, and the reduction in the proportion of patients needing rescue or concomitant medications. Nevertheless, systematic reviews and meta-analysis have shown that these drugs are superior to the use of placebo or standard of care (SOC) in the achievement of these therapeutic results [52–54].

Overall, the combination of these latest therapeutic options with conventional treatments is showing promising results and seems to significantly reduce the severe and fatal bleeding occurrence in refractory ITP patients [61].

Conclusion

The increased knowledge on ITP pathogenesis and the availability of new drugs, particularly rituximab, TPO-RAs, and fostamatinib, offer today novel therapeutic chances that may significantly ameliorate clinical outcome.

Nevertheless, refractory disease is still extremely challenging, concerning both diagnosis and treatment. In these cases, combination strategies and investigational agents might be of particular benefit. Novel and future single or combinatory treatments can exploit possible additive or synergistic effects arising from the simultaneous or sequential association of different drugs; from a biological perspective, multiple target abrogation could induce a good response and thus extend treatment options for patients who once would have been considered as untreatable.

The improvement of a diagnostic and therapeutic algorithm requires extreme cooperation among hematologists, considering the rarity of this clinical condition and its severity. Additionally, the COVID-19 pandemic has led to a re-evaluation of the therapeutic algorithm, favoring drugs with less immunosuppressive activity.

Overall, real-life experiences, expert consensus papers, and international guidelines can optimize the clinical management of refractory ITP, offering improved survival chances, a better control of bleeding risk and better quality of life to patients and to their families.

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