

Adult Chronic Primary Immune Thrombocytopenia: Safety and Efficacy of Thrombopoietin Receptor Agonists and Rituximab

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Introduction & Background

Primary immune thrombocytopenia (ITP), one of the most common acquired autoimmune bleeding disorders characterized by immune-mediated destruction and defective platelet production, which increases the risk of bleeding [1]. The pathophysiology of ITP was considered to be due only to accelerated autoantibody-mediated platelet destruction in the reticuloendothelial system (RES), particularly in the spleen [2-3]. However, some evidence shows that ITP also results from defective platelet production [4-5]. Persistence of ITP beyond 12 months is the definition of chronic ITP [6]. Patients affected with ITP have increased risk of bleeding that may range from minor presentations such as petechiae and bruising to the most life-threatening and dangerous events such as intracranial hemorrhage, and diminished health-related quality of life (HRQoL) [7-8]. The primary goal of the management of chronic ITP is to increase and maintain platelet count in a safe range to avoid life-threatening complications, as well as improving HRQoL. The first-line of therapies included glucocorticoids, intravenous immunoglobulins (IVIG), or intravenous anti-D [6,9-10]. However, relapse or failure to respond to these may urge to the use of other pharmacological agents and modalities, which can include a wide variety of therapies, such as splenectomy, azathioprine, rituximab, vincristine, danazol, vinca alkaloids, and cyclophosphamide [11-12].

The second-line therapies are associated with high costs, severe adverse effects, and toxicities [11-12]. Splenectomy is the treatment that has the highest rates of response in patients with chronic ITP (65%) [13-14]. However, the inability to reliably predict whether an individual patient will respond, as well as the risk associated with a surgical procedure like splenectomy in both the short and long term including bleeding and infection, lead many patients and physicians to defer surgery in favor of medical therapy. The overall prognosis of ITP is good, with less than two percent mortality, but the latter can rise to 10% for a subgroup of patients with chronic severe ITP refractory to splenectomy. Recent consensus statements and guidelines recommend thrombopoietin receptor (TPO-R) agonists as second- and third-line agents for ITP treatment [6-10]. There are two TPO-R agonists, the non-peptide Eltrombopag and the peptide Romiplostim. Both are effective in increasing platelet counts with relatively low toxicity.

Both TPO-R agonists stimulate megakaryocytes, induce their maturation and proliferation, and thereby increase platelet counts in approximately 80% of ITP patients in randomized controlled trials [15-16] and 74% of the patients treated in real-life practice [17]. On the other hand, rituximab is a treatment of choice for many patients with chronic ITP. Various autoimmune diseases, including ITP, are treated with Rituximab, which is a chimeric anti-CD20 monoclonal autoantibody [18-19]. Binding to CD20 induces profound albeit transient B-cell depletion by producing antibody-dependent cytotoxicity, complement activation, and/or induction of apoptosis [20]. Rituximab reduces platelet antibodies level by depleting B cells, resulting in a 60% improvement in platelet count of patients with immune thrombocytopenia (ITP). Despite the proved effectiveness of both TPO-R agonists and rituximab in the treatment of chronic ITP that is refractory to first-line therapy with corticosteroids, IVIG, or anti-D, there is no evidence to guide the second-line treatment for those patients.

The choice of second-line agent for ITP that is refractory to first-line regimens has been a subject of debate. Since there are no evident guidelines that sequence the second-line treatments of ITP, deciding which drug would provide optimal results is challenging. TPO-R agonists and Rituximab are essential components of second-line therapies. Although both drugs have proven relatively similar efficacy, the decisions should be based on multiple additional factors, including the safety of the drug, unfavorable effects, and costs. However, comparative evidence of TPO-R agonists and Rituximab is narrowed, which highlights a gap in the literature regarding efficacy, safety, and side effects. Given the importance of this topic, and the life-threatening risks imposed on patients suffering from chronic ITP, literature review will illustrate a comparison between TPO-R agonists and Rituximab in terms of efficacy, safety, and side effects.

Methods

The focus of this literature review is to compare the second-line ITP treatments, TPO-R agonists, and Rituximab, in terms of efficacy, safety, and side effects. English language papers published within the last ten years were identified through searches of the PubMed database using the MeSH keywords idiopathic thrombocytopenic purpura, therapy, drug therapy. Studies were limited to human

studies. Included articles are compatible if they had primary data retrieved from clinical trials on adults aged above 19. Excluded studies were those addressing thrombocytopenic purpura due to any underlying disease such as infections, medications, autoimmune diseases, non-English paper, animal studies, age less than 19 years old, pregnant women.

Results

We searched the PubMed database using the keyword idiopathic thrombocytopenia purpura that gave 3409 total articles. Studies published within ten years were 1393 papers, of them 1360 were conducted on humans only. After applying English language inclusion criteria, 1183 papers were provided, and clinical trial inclusion came out with 142 papers. A final result of 111 papers was given after applying the adults (19 plus) age group, four of them were duplicates (Table 1).

After screening through articles, this review included 40 relevant studies (N= 6540 total patients), 14 of them were randomized control trials, one study collected data from five randomized control trials, two case reports, three cohorts, 20 non-randomized clinical trials. Twenty-one papers were full articles, and twenty were only abstracts. Three studies elicited the TPO-R agonist mode of action (N= 126 patients). Four studies discussed the efficacy and safety of Eltrombopag (N= 981 patients) one of those studies was evaluating Eltrombopag in Chinese patients at a starting dose of 25 mg instead of the standard dose of 50 mg that is usually used, and another one studied the efficacy and safety of Eltrombopag in Japanese patients starting with an initial dose of 12.5 mg. One study talked about the pharmacokinetics of Eltrombopag (N= 199 patients); one paper showed Eltrombopag's effect on platelet function (N= 22 patients). Eight papers evoked the safety and efficacy of Romiplostim (N= 2398 patients); one of them was specific for long term use of Romiplostim in Japanese patients with chronic ITP (N= 44 patients), and one article talked about remission after treatment with Romiplostim (N= 949 patients). Eleven papers described Rituximab's efficacy and safety (N= 1113 patients), one paper studied its efficacy and safety in Japanese patients, and rituximab's mode of action and effect on platelets was explained in one paper (N= 55 patients). Concerning the cross-resistance between Eltrombopag and rituximab, two studies confirmed its absence (N= 217 patients). Four papers raised the treatment effect on bone marrow, one of them talked about the effect of TPO-R agonists in general (N= 32 patients), two discussed the Eltrombopag's effect (N= 279 patients) and one focused on Romiplostim's effect (N= 169 patients). The following figure (Figure 1) summarizes the flow chart of the current literature review.

Discussion

In this literature review, we evoked a challenging topic, second-line treatment of chronic primary immune thrombocytopenia purpura. The importance of this topic is based mainly on the life-threatening bleeding complications that might occur in ITP patients, which are related to low platelets count, especially in patients that failed to respond to first-line treatments. On the other hand, deciding the most appropriate second-line drug requires careful considerations, decreasing the bleeding risks while bearing in mind its safety and the possible side effects that may occur. In this review, based on the currently available data, we compared the safety and efficacy of thrombopoietin receptor agonists (Eltrombopag and Romiplostim) and Rituximab in 6540 ITP patients. Our study suggests safer and more significant benefits with thrombopoietin receptor agonists as a second-line drug for chronic immune thrombocytopenia purpura than Rituximab.

Immunomodulatory effect of thrombopoietin receptor agonists Macrophages and monocytes mediate autoimmune platelet destruction in ITP [21,22,23-24]. Macrophages carrying Fcγ receptors are involved in the phagocytosis of platelets coated with antibodies [25], which induces antigen presentation and production of proinflammatory cytokine [26-27]. The prospective study conducted by Xin-Guang Liu et al. aimed to prove the immunomodulating effect of TPO-R agonists used for the management of ITP, investigated the monocyte's Fcγ receptor (I, II and III) phenotype and phagocytic ability after Eltrombopag treatment for six weeks [28]. This study showed that the activating FcγR I and FcγR II levels decreased after the six weeks of treatment, whereas the inhibitory FcγR III mRNA and protein level increased, and the FcγR IIa/IIb ratio significantly decreased in responding patients. Besides, this study proved that the Transforming Growth Factor-1 (TGF-1 is an anti-inflammatory cytokine) level increased markedly in patients responding to Eltrombopag therapy.

Moreover, two other articles showed that TGF- β levels increased markedly after treatment with TPO-R agonists compared with healthy controls [29-30]. Furthermore, the study conducted by Gudbrandsdottir et al. showed that the levels of TGF- β 1 and sCD40L increased after six months of TPO-R agonists treatment, which reflects increased platelets turnover [31]. Eltrombopag-induced platelet function was studied by Haselboeck et al., which showed that platelet function parameters change significantly after Eltrombopag use in both ITP patients and controls, and venous thromboembolism risk increased in ITP patients despite low platelet counts [31].

Efficacy and platelet response

The current literature results showed that thrombopoietin receptor agonists are superior to Rituximab as second-line therapy for patients with chronic ITP. Thrombopoietin receptor agonists were associated with a better response compared to rituximab. Of patients treated with Eltrombopag, 50-75% achieved a platelet count of 50×10^9 , 80%-90% in patients treated with Romiplostim, compared to 54% in those treated with Rituximab and relapsing may occur in 30% of them. Bleeding risk decreased from 57% to 15% after treatment with Eltrombopag; the bleeding rate in patients receiving Romiplostim was 33% versus 38% in patients treated with Rituximab.

Eltrombopag is a non-peptide, thrombopoietin agonist that induces proliferation and differentiation of bone marrow megakaryocytes by interacting with their thrombopoietin transmembrane receptor [32]. Thus Eltrombopag played a significant role in increasing platelets count and reducing bleeding events in ITP patients. Tarantino et al. reviewed prospective data from five clinical trials that aimed to evaluate the efficacy and safety of Eltrombopag, all of them showed a marked decrease in bleeding events and clinically significant bleeding, accompanied by an increase in platelet counts [33]. Two other studies discussed the interethnic pharmacokinetics of Eltrombopag and the possibility of initiating therapy with lower starting doses in East-Asian patients while having the same efficacy and safety. The table below shows all the characteristics of these studies (Table 2).

Romiplostim, a thrombopoietin-mimetic, was evaluated in several clinical trials as a second-line regimen for chronic ITP. The reviewed studies showed a marked increase in platelet response after treatment with Romiplostim versus placebo, as well as a decreased risk of bleeding with a notable decrease in the use of concomitant drugs. Two studies showed that the platelet response was higher in nonsplenectomized patients. However, the second

study conducted by Khellaf et al. showed that long-term response for more than two years was 65%, which was comparable between splenectomized and nonsplenectomized patients [34]. The table below (Table 2) presents the characteristics of the full articles collected that discuss the efficacy of Romiplostim. Michel et al. study described the efficacy and safety of Romiplostim in patients > 65 years old versus < 65 years old, slightly higher platelet response was reported in patients older than 65 years, the risk of bleeding (> grade 3) and thromboembolic events was slightly higher, but it was not statistically significant [35]. Thus this study proves that patients > 65 years tolerated well the treatment with Romiplostim. Kuter et al. evaluated long-term treatment with Romiplostim; in this article, a stable dose of 5-8 µg/kg maintained a long-term response for five years with a platelet count ranging from 50 - 200 × 10⁹/l with a lower rate of bleeding and rescue treatments [36]. In the same perspective a study conducted by Shirasugi et al. evaluated the efficacy and safety of Romiplostim for three years and a half in Japanese patients with ITP, 96% of patients achieved a platelet response > 50 × 10⁹/l, and only 18% of them needed a rescue treatment [37]. Bussel et al. study evaluated remission after Romiplostim defined as platelet count for > 50 × 10⁹/l for ≥ 26 consecutive weeks after Romiplostim withdrawal and without any other medication [38]. Mechanism of remission may be due to the activity of regulatory T-cell, B-cell, the inhibitory FcR, and induction of fragment crystallizable receptor IIB (FcRIIb) [39-40]. Remission was evident, especially in patients with ITP of less than one-year duration, the mean dose before remission was 4.6 µg/kg, and the median time of remission was 42 weeks. 77.5% of patients achieved remission after nine weeks and lasted for 43 weeks, 15% started remission after four to six weeks of treatment, 7.5% restarted therapy with Romiplostim after remission due to relapse.

Rituximab, a CD20 targeting chimeric monoclonal antibody, is a second-line off-label pharmaceutical agent used for ITP in several countries either before or after splenectomy [41] that induce depletion of B-cells through apoptosis, complement activation and cytotoxicity [20]. B-cell lymphocytes, except plasma cells, express CD20 on their surface [42]. The collected publications studied several regimens; most commonly used (in six trials) was 375mg/m² weekly for four weeks. The overall response to treatment ranged from 72% at six months, 69% at 12 months, and 60-80% at 18 months. The complete response CR, which was defined as platelets count ≥ 100 × 10⁹/L, reached 48% at six months, 45% at 12 months, and 40-58% at 18 months. The partial response PR, defined as platelets count ≥ 50 × 10⁹/L, was 24% at six months, 24% at 12 months. The relapse rate was estimated to be 55-68% in one year. Several publications proved that relapse rate increases with the increase in patient's age and weight, and the interval time between diagnosis and the beginning of therapy. Zaja et al. investigated the efficacy of a regimen consisting of 2 doses of 1000 mg at day one and 15 for 52 weeks [43], the overall response was 44% at week 8 and the sustained response with at least minor response (> 30 × 10⁹) of 35% at week 52, the study proved that this regimen has similar efficacy as the standard regimen of 375mg/m². The table below presents the characteristics of three other significant clinical trials (Table 2).

Safety of second-line agents

Eltrombopag is proved to be safe for ITP management. Across all collected articles, no noted treatment-related significant adverse events. Tarantino et al. evaluated the safety of Eltrombopag in five clinical trials and proved it to be safely used, side effects were minimal and reversible, and no reported treatment-related

deaths [33]. The most common undesirable effects were low-grade diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, and fatigue [15]. Transient elevation in liver enzymes that are not associated with hepatic dysfunction is also observed. The safety was also studied by Tomiyama et al., which showed the undesired effects in six weeks phase and after that in six months [44]. The table below presented the characteristics of these studies (Table 3).

Romiplostim's most common side effects were nasopharyngitis and headache; 20% of patients had a total of 14 serious unwanted effects. Oral hemorrhage was the only adverse reaction associated with the drug [45]. Kuter et al. studied the safety and efficacy of Romiplostim over five years, and according to their study, the rate of harmful effects did not increase with time over the five years, and they did not report any new side effects [36]. Besides, thromboembolic events occurred in 6.5% of patients, and they were not related to the platelets count. The rate of the adverse events was similar between Romiplostim and placebo groups (91% vs. 92% respectively) in the study done by Shirasugi Y et al., and the most common of them was headache, nasopharyngitis, peripheral edema, back, and extremities edema [37].

Safety of Rituximab is an object of real solicitude, and its use was associated with severe and even fatal infections that should be taken into consideration, such as Cytomegalovirus, Pneumocystis Jiroveci Pneumonia, Parvovirus B19, Progressive Multifocal Leukoencephalopathy (PML) resulting from reactivation of John-Cunningham Polyomavirus [46,47-48]. The searched articles studied the safety of Rituximab, showing that even though the percentage of the side effects of this drug was relatively low, however, the side effects are serious and could be fatal (Table 3). Death is reported in 5% of patients taking Rituximab; the primary causes were bleeding and severe infections. The most commonly reported adverse event was intolerance to Rituximab, which can also be severe, causing hypotension, dyspnea, and reversible serum sickness.

Thrombopoietin receptor agonists and bone marrow changes
Bone marrow changes and cytopenia were a concerning side effect for TPO-R agonists treatment since they increase the reticulin deposition in the bone marrow; they were a probable cause of the bone marrow fibrosis seen in patients with ITP [49-50]. Several published clinical trials studied the bone marrow of patients treated with TPO-R agonists in order to evaluate changes before and after therapy, all of them concurred that the treatment is not associated with any clinically significant increase in bone marrow reticulin or collagen. Even though some biopsies showed a mild increase in reticulin, however, these changes were completely reversible after stopping the drug. The characteristics and main points of these clinical trials are mentioned in detail in the below table (Table 4).

The table below (Table 5) summarizes the characteristics of the second-line treatments of ITP, showing the percentage of platelet response, bleeding rate, adverse events, and deaths related to the treatment.

The current study provides a comprehensive overview of the literature available to date, involving all of the original studies that were relevant to our research question. However, some limitations should be taken into consideration while interpreting the conclusion of this article. This study reviewed clinical trials about second-line ITP treatments; however, our study has not included any case controls, review articles, or cohort studies. Other limitations are that this article included clinical trials in

the last ten years done on humans (no animal trials included). It is worth mentioning that the reviewed articles were written in the English language only.

In conclusion, our study focused on the second-line treatment of primary ITP refractory to first-line regimens. The choice of second-line regimen is of significant importance to prevent the fatal consequences of bleeding that could occur while considering drug safety. Our review proved that Eltrombopag and Romiplostim are better than Rituximab for the treatment of refractory ITP in terms of safety and efficacy. Moreover, the relapse rate in patients treated with TPO-R agonists was lower than in those treated with Rituximab. On the other hand, both Eltrombopag and Romiplostim were safe and efficacious. Although patients treated with Rituximab had a better platelet response than patients treated with Eltrombopag. However, the bleeding risk was lower in patients treated with Eltrombopag. We suggest that more comparative clinical trials should be done to determine the best TPO-R agonist for each group of patients according to age, time from diagnosis to treatment, weight, sex, and time between diagnosis and treatment in both splenectomized and nonsplenectomized patients, to get a better prediction of the response and decrease the odds of treatment failure.

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