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RESEARCH ARTICLE

ADULT CHRONIC PRIMARY IMMUNE THROMBOCYTOPENIA: SAFETY AND EFFICACY OF THROMBOPOIETIN RECEPTOR AGONISTS AND RITUXIMAB.

***Zeina Al Achkar, Nusrat Jahan, Cesar Peralta, Humera Batool and Jamila Begum Jabar Ali**

Internal Medicine, California Institute of Behavioral Neuroscience and Psychology, Fairfield, USA

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ABSTRACT

Primary immune thrombocytopenia is an autoimmune bleeding disorder characterized by destruction and impaired production of platelets. The affected patients have an increased risk of bleeding, which could be lethal. Multiple drugs are available; the most commonly used as second-line are Thrombopoietin receptor (TPO-R) agonists and Rituximab. However, choosing the best drug is still under consideration, particularly for all the adverse reactions. We conducted a review of the literature search on PubMed to compare the safety and efficacy of TPO-R agonists and Rituximab. Based on our search, TPO-R agonists are associated with a better platelet response, fewer side effects, and less complications. Further studies are needed to determine possible clinical and therapeutic implications of TPO-R agonists.

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INTRODUCTION

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).

Corresponding author: *Zeina Al Achkar,
Internal Medicine, California Institute of Behavioral Neuroscience and Psychology, Fairfield, USA.

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 regiments 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.

Table 1. Keywords search after applying inclusion criteria in PubMed

Keyword	PubMed	Number of hits
Idiopathic thrombocytopenia purpura/ Drug therapy/ Therapy	MeSH	3409
Inclusion/Exclusion criteria	Number of hits	
Ten years		1393
Humans		1360
English language		1183
Clinical trials		142
Age: 19 and above		111

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.

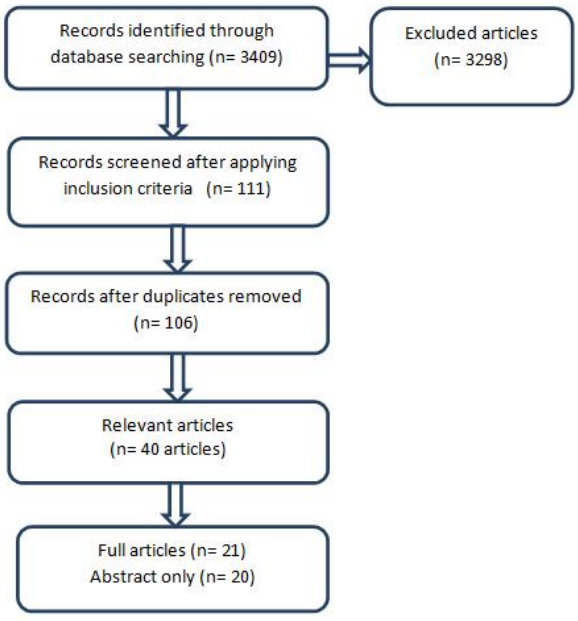

Figure 1. Flow chart showing the process of current literature review

Table 2: The list and the characteristics of the reviews about efficacy

Author/publication year	Title	Study design	Sample size	Main points
Cines et al. 2017 August.	Safety and efficacy of Romiplostim in splenectomized and nonsplenectomized patients with primary immune thrombocytopenia.	Data pooled from 13 studies: five controlled studies, six single-arm studies, two open-label extension studies.	111 patients: 395 splenectomiz-ed, 716 nonsplenecto-mized.	Platelet response rates (>50 × 109): 82% splenectomized (used more rescue treatments), 91% nonsplenectomized. Sustained response (> 50× 109 for 9 out of 12 weeks): 68% splenectomized 80% nonsplenectomized. Rescue medication use decreased 70% in Romiplostim group vs. placebo.
Yang R1 et al. 2017 January.	Multicenter, randomized phase III study of the efficacy and safety of Eltrombopag in Chinese patients with chronic immune thrombocytopenia.	Randomized control trial.	115	Platelet count > 50 × 109 was achieved in 57.7% of patients treated with Eltrombopag vs. six % in placebo-treated patients. Time to response and duration of response were better in Eltrombopag, with a 72% reduction in the odds of bleeding. In Chinese patients, a starting dose of 25 mg could elevate platelets count vs. 50 mg for non-Asian patients, attributed to higher plasma exposure of Eltrombopag in East-Asian patients.
Zwaginga et al. 2015 March.	Multi-center randomized open label phase II trial on three Rituximab dosing schemes in immune thrombocytopenia patients.	Randomized control trial.	150	Three arms are included: Arm A: 375 mg/m^2 once weekly, Arm B: 375 mg/^{2} twice weekly in early responders (if no response another two once-weekly, Arm C: twice weekly 750 mg/m2. CR: > 150 × 109/L, PR: > 50 × 109/L, MR: > 30 × 109/L. Response: Arm A: 52% (CR 22%, PR 20%, MR 11%), Arm B 47% (CR 16%, PR 19%, MR 12%), Arm C 49% (CR 18%, PR 20%, MR 10%). DFS from CR at 2 years: Arm A 89%, Arm B 43%, Arm C 76%. Response delays other treatments. Early responding patients, female sex, and younger patients had a better response.
Khellaf et al. 2014 November 20.	Safety and efficacy of Rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients.	Prospective cohort observational study.	248	Two regimens were used: 4 infusions of 375 mg/m^2 for 173 patients, two fixed infusions of one gram, two weeks apart for 72 patients. Overall initial response was observed in 61% (> 30 × 10^9 &> 2 times baseline).39% of patients achieved a lasting response for two years. The response pattern was similar between the two regimens. The median time to relapse: 25 months.
Tarantino et al. 2013 Apr.	Efficacy of Eltrombopag in management of bleeding symptoms associated with chronic immune thrombocytopenia.	Randomized control Trial.	794	This publication reviewed five studies. Bleeding: decreased from 50- 73% to 26- 39% by week 2. Odds of clinically significant bleeding were 65% lower than the placebo in RAISE study. Bleeding adverse events: markedly reduced, and the majority were Grade 1-2. Most common side effects: diarrhea (low grade), nasopharyngitis, nausea, upper airway infection, fatigue, mild and transient elevation in liver enzymes. No evidence of bone marrow fibrosis, cataract, hematologic malignancies.
Mahévas et al. 2013 October.	Efficacy and safety of Rituximab given at 1,000 mg on days 1 and 15 compared to the standard regimen to treat adult immune thrombocytopenia.	Retrospective multicenter observational study.	107	Two regimens were used: Standard regimen SR 375 mg/m^2weekly for four weeks, and Rheumatoid arthritis regimen one gram on day one & 15. At three months: The overall response OR in SR was 54% and 60% in RA regimen. At 12 months: OR in SR was 36% and 50% in the RA regimen. Long term response: 36 months for SR the OR was 31%, and 20.5 months for the RA regimen, the OR was 48%. Late relapse after 12 months occurred in two cases of SR and one case of RA regimen. Young patients and those with a lower number of previous therapies had higher rates of complete response & overall response at 12 months.

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Kuter et al. 2012 May.	Health-related quality of life in nonsplenectomized immune thrombocytopenia patients receiving Romiplostim or medical standard of care.	Randomized control trial.	234	After 52 weeks of treatment: the Romiplostim group showed better improvement in all scales of the ITP-PAQ scale than the SOC group except fatigue. In the Romiplostim group, 61-70% of patients exceeded MID value on ITP-PAQ vs. 40-49% in SOC-treated patients. The activity score exceeded the MID only in the Romiplostim group. 61-70% of patients in the Romiplostim group exceeded MID value on ITP- patient assessment questionnaire vs. 40-49% in the SOC- treated patients. In responders: both Romiplostim and SOC groups exceeded the MID in all scales; however, the increase in HRQoL benefit was higher in the Romiplostim group.
Tomiyama Y1 et al. 2012 May.	A lower starting dose of Eltrombopag is efficacious in Japanese patients with previously treated chronic immune thrombocytopenia.	Randomized control trial.	23	The area under the curve exposure to Eltrombopag was 87% greater in East-Asian patients than non-East-Asians. The starting dose in Japanese patients was 12.5 mg (50 mg standard dose); the maximum dose was 50 mg (75 mg standard dose). Six weeks (double-blinded): Platelet count > 50×10^9 in 60% of Eltrombopag group vs 0% in placebo group. At week 3, 33% of patients taking 12.5 mg responded to treatment. Bleeding risk decreased. The dose of 12.5 mg to 50 mg was effective for Japanese patients. After dose adjustment, the response increased to 60% at week four and 67% at week five. Six months open-label phase: average dose 33.7 mg, 44% responded. During the first three weeks, 22% responded to a dose of 12.5 mg. Moreover, the response ranged from 47.8- 69.6% between week four and week 26. Bleeding risk at baseline was 40%, decreased to 27% at week 2, and returned above baseline after four weeks of stopping treatment. In patients with high bleeding risk, a starting dose of 25 mg is safer than 12.5 mg.
Khellaf et al. 2011 Octobre 20.	Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a Romiplostim compassionate-use program	Retrospective observational cohort study.	80	Platelet response: > 50×10^9/l was 74% (54% nonsplenectomized vs 45% splenectomized). Long term response > 2 years was 65% (comparable between splenectomized and nonsplenectomized). 79% of the patients has a sustained response (platelets > 106×10^9). 21% of patients are still taking Romiplostim despite a platelet count of 38×10^9/l, but with benefit (fewer or lower dose of concomitant treatment, less bleeding signs). Factors predicting response: - Lower bleeding scores are associated with a better response. - Women had less response than men (nonresponders: 33% of women vs. 14% men). Rescue therapy was used in19% of patients, and the majority of them were nonresponders.

RA: Rheumatoid arthritis, CR: complete response, PR: partial response, MR: moderate response, RFS: relapse-free survival, DFS: disease-free survival, ITP-PAQ: ITP-patient assessment questionnaire, SOC: standard of care, HRQoL: Health-related quality of life.

Table 3: Safety of second-line treatments of ITP

Author/publication year	Title	Study design	Sample size	Main points
Cines et al. 2017 August.	Safety and efficacy of Romiplostim in splenectomized and nonsplenectomized patients with primary immune thrombocytopenia.	Data pooled from 13 studies: five controlled studies, six single-arm studies, two open-label extension studies.	111 patients: 395 splenectomiz-ed, 716 nonsplenecto-mized.	Exposure-adjusted rates of serious side effects in nonsplenectomized patients were 53% lower in the Rompilostim group vs. placebo and 49% lower in splenectomized patients. Risk of bleeding decrease in the Romiplostim vs. placebo (higher in splenectomized patients). Splenectomized patients in both groups had a slightly higher risk of infection Thromboembolic adverse events rate was similar between groups.
Zwaginga et al. 2015 March.	Multi-center randomized open label phase II trial on three Rituximab dosing schemes in immune thrombocytopenia patients.	Randomized control trial.	150	Side effects were similar between all arms, 5.7% of them were evidentlyrelated to rituximab and were completely reversible. Probably related to treatment side effects were six out of 11 events.
Khellaf et al. 2014 November 20.	Safety and efficacy of Rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients.	Retrospective observational cohort study.	248	Adverse events: 19%. The most common was intolerance to the infusion (15%), which was severe in three of them (hypotension, dyspnea, discomfort, reversible serum sickness). The infection rate is 3%. One case of hypogammaglobulinemia without infection at 24 months. Other side effects: skin rash (11), intestinal discomfort (9), transient chills & fever (8), minor laryngeal discomfort (6), paresthesia (4), headache (3), hypertension and tachycardia (3). One case of transient neutropenia after seven months of treatment. One patient had heart failure after 18 months, and one inflammatory polyneuropathy after four months. 5% (13) of patients died, two of them from massive bleeding due to refractory ITP, three from a severe infection, two of unknown cause, the rest was not attributed to Rituximab

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Tarantino et al. 2013 Apr.	Efficacy of Eltrombopag in management of bleeding symptoms associated with chronic immune thrombocytopenia.	Randomized control Trial.	794	In the five studies reviewed, there is a marked reduction in clinically significant bleeding, and the majority was Grade 1-2. These results appeared within two weeks of treatment and lasted across the treatment period. Most common undesired effects: diarrhea (low grade), nasopharyngitis, nausea, upper airway infection, fatigue, mild and transient elevation in liver enzymes. No evidence of bone marrow fibrosis, cataract, hematologic malignancies.
Mahévas et al. 2013 October.	Efficacy and safety of Rituximab given at 1,000 mg on days 1 and 15 compared to the standard regimen to treat adult immune thrombocytopenia.	Retrospective multicenter observational study.	107	Safety: Two patients developed hypogammaglobulinemia at eight months. No severe adverse events were related to Rituximab infusion. One patient in each group developed community acquired pneumonia, and one patient in the standard regimen group had bullous pemphigoid.
Tomiyama et al. 2012 May.	A lower starting dose of Eltrombopag is efficacious in Japanese patients with previously treated chronic immune thrombocytopenia.	Randomized control trial.	23	⁾six weeks (double-blinded): Incidence of adverse events was73% in Eltrombopag vs 25% in the placebo group. The most common are nasopharyngitis and increased ALT. The reported drug-related adverse effect was 40% in the Eltombopag group vs. 13% in the placebo group.One patient withdrew from the study after having a transient ischemic attack. ⁾six months open-label phase: Similar mild to moderate adverse effect as the six weeks. Drug-related adverse events: 48% in Eltrombopag. No deaths related to the treatment. Minimal changes in peripheral blood smear in nine patients. Thrombocytopenia occurred in three patients; only one of them experienced clinical side effects.
Khellaf et al. 2011 Octobre 20.	Romiplostim safety and efficacy for immune thrombocytopenia in clinical practice: 2-year results of 72 adults in a Romiplostim compassionate-use program	Retrospective observational cohort study.	80	Side effects: arthralgia 26%, fatigue 13%, nausea 7%. Thrombocytosis: > 400 × 109/l in 19%, >1000 × 109/l in 4%. Two elderly patients > 70 years old had transient ischemic events despite a low platelet count (100 × 10^9).

Table 4. Bone marrow changes in ITP patients treated with Eltrombopag and Romiplostim.

Author/ publication year	Title	Study Design	Sample size	Main points
Brynes et al. 2017.	A 2-Year, Longitudinal, Prospective Study of the Effects of Eltrombopag on Bone Marrow in Patients with Chronic Immune Thrombocytopenia.	Phase 4 open-label clinical trial.	162	Baseline BM biopsies are negative for collagen, 94% normal reticulin (MF=0), 6% Mf=1 with slight increase in reticulin. After one year: 4% positive for collagen, 69% MF=0, 28% MF=1, 2% MF=2, 2% MF=3. After 2 years: 89% MF=0, 11% MF=1, none MF=2 & 3. No BM-fibrosis related side effects, no symptoms based on cell count or peripheral smear. Noted megakaryocyte hyperplasia in the majority of patients (baseline 9% >> 98% at one year & two years). Erythrocytes hyperplasia in 10-12% of patients. Myeloid hyperplasia in 10-21% of patients. Trabecular bone thinning 50% at baseline, 50% at one year, 38% at two years.
Janssens A1 et al. 2016 June.	Changes in bone marrow morphology in adults receiving Romiplostim for the treatment of thrombocytopenia associated with primary immune thrombocytopenia.	Prospective Phase IV Open-Label Multi-Center Study	169	BM biopsies taken after one, two, and three years of treatment with Romiplostim. Bauermeister scale (0–4) is used to evaluate reticulin and collagen in specimens. Of the evaluated 131 biopsies, 6.9% (9 patients) had an increase of ≥ 2 grades on the scale with two including collagen. Follow up biopsies showed reversible changes after stopping treatment in three of the nine patients, one of them including collagen. One patient had neutropenia, two had anemia, which is not related to therapy. Cytopeniaoccurred in 33% of patients with BM changes and 14% without changes in BM; none of them were clinically significant. Cytopenia and BM changes in three patients, two patients had anemia, one had neutropenia, and one had both. Undesirable events did not change between patients with and without BM changes.
Rizvi H1 et al. 2015 May.	United Kingdom immune thrombocytopenia registry: retrospective evaluation of bone marrow fibrosis in adult patients with primary immune thrombocytopenia and correlation with clinical findings.	Retrospective multi-center clinical trial.	32	Reticulin increased in 31.25% of patients treated for ITP (Bauermeister scale: grade1-2, European Consensus scale grade 0-1), which was positively related to ethnicity 0.3%, but not related to disease severity, co-morbidities or symptoms.
Brynes RK1 et al. 2015 July.	Evaluation of bone marrow reticulin in patients with chronic immune thrombocytopenia treated with Eltrombopag: Data from the EXTEND study.	Randomized control trial	117	233 biopsies taken from 117 patients treated for 5.5 years. 97% MF-0 & MF-1 in any year. 2% MF-2 - and 1% MF-3 at 25 months. 18 patients with ≥ 3 times evaluated biopsies remained at MF-0 over five years, five had one grade increase, and five had one grade decrease. Biopsies post-treatment in five patients (two of them with BM findings): one had MF-1 after six months, four had MF-0 after 0.4 to eight months. Reticulin grade changed in 2 & MF-0 in one specimen and MF-1 in another, & the reticulin grade decreased in both. Megakaryocytes hyperplasia 82-100%, erythrocytes hyperplasia 13-27%, myeloid hyperplasia 6-13%, trabecular thinning 39- 70%. No clinically relevant changes or symptoms.

BM: bone marrow, MF: marrow fibrosis.

Table 5. Summary of efficacy and safety of second-line treatments of ITP

	Eltrombopag	Romiplostim	Rituximab
Platelet count > 50×10^9	50-70%	80-90%	50-60% (30% may relapse)
Bleeding rate	15%	33%	38%
Adverse events:	6-34%	20%	40-48%
⎫ Headache	28%		1.5%
⎫ Nasopharyngitis	25%		
⎫ Upper respiratory tract infection	23%		
⎫ Fatigue	17%	13%	
⎫ Thromboembolic events	6%		
⎫ Increased ALT	2%		
⎫ Increased AST	2%		
⎫ Malignancy	3%		
⎫ Cataract	5%		
⎫ Pneumonia	2%		1.5%
⎫ Arthralgia		26%	
Death related to treatment	None	None	5%

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 Fcy 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 immune-modulating effect of TPO-R agonists used for the management of ITP, investigated the monocyte's Fcy receptor (I, II and III) phenotype and phagocytic ability after Eltrombopag treatment for six weeks (28). This study showed that the activating FcyR I and FcyR II levels decreased after the six weeks of treatment, whereas the inhibitory FcyR III mRNA and protein level increased, and the FcyR IIa/IIb ratio significantly decreased in responding patients. Besides, this study proved that the Transforming Growth Factor-β1 (TGF-β1 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-β1 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/m^2 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 × 10^9/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 × 10^9/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 × 10^9) of 35% at week 52, the study proved that this regimen has similar efficacy as the standard regimen of 375mg/m^2.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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