Scholars LITERATURE

La Prensa Medica Argentina

Review Article

DOI: https://doi.org/10.47275/0032-745X-376
Volume 108 Issue 5

Efficacy of Thrombopoietin Receptor Agonists and Rituximab in Treating Immune Thrombocytopenic Purpura: Systematic Review

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Citation: Nitish N, Sagar D, Sri Aryavalli A (2022) Efficacy of Thrombopoietin Receptor Agonists and Rituximab in Treating Immune Thrombocytopenic Purpura: Systematic Review. Prensa Med Argent, Volume 108:5. 376. DOI: https://doi.org/10.47275/0032-745X-376

Received: September 15, 2022; **Accepted:** October 01, 2022; **Published:** October 06, 2022

Introduction

Idiopathic thrombocytopenia purpura (ITP), previously referred to as immunological thrombocytopenic purpura, is an autoimmune condition that can affect adults and kids. Primary immune thrombocytopenic purpura (ITP), also known as immune thrombocytopenia, is characterized as independent thrombocytopenia without alterations to the bone marrow and in the lack of other thrombocytopenia-causing conditions [1]. Increased peripheral platelet destruction is the primary feature of this disorder, and the majority of patients exhibit anti-platelet membrane glycoproteins antibodies. Hemorrhage is by far the most serious consequence and the one with the highest risk is intracranial. In children, bleeding morbidity is 1 out of 100, and in grownups, it is 5 out of 100. Adults with ITP run a significant risk of suffering a serious hemorrhage, especially if they are elderly or have a history of bleeding [2]. Compared to ITP that is due to other conditions, such as autoimmune disease (like systemic lupus erythematosus), viral infections (like chronic hepatitis C virus), lymphoproliferative neoplasms, etc., primary ITP is distinguished by isolated thrombocytopenia.

ITP is categorized as acute (3 months), recurrent (3-12 months), or chronic (more than 12 months) and can be either primary or due to other underlying illnesses. ITP in children frequently develops suddenly after acute viral disease and is normally brief, with prompt remission occurring in at least 70% of afflicted children, as opposed to ITP in adults, which usually has a gradual onset and continues a chronic course. People with ITP generally do not need healthcare unless their platelet count drops to 30 to $50x10^9$ /L or their risk of blood loss increases due to surgery or childbirth, despite the fact that a peripheral platelet count of 100,109 /L without any obvious actual reason tends to make for an arbitrary diagnosis [3].

The main cytokine promoting thrombopoiesis is thrombopoietin. The lack of a significant proportionate rise in thrombopoietin levels due to extreme thrombocytopenia is a crucial factor in the pathogenesis of ITP. For patients who suffer from chronic ITP, the main objective of treatment is to reduce the probability of hemorrhage by raising platelets to an acceptable level of a minimum of 30,000-50,000 per L with minimal adverse effects. The main aim of the current therapeutic approaches have been to reduce platelet deterioration (like immunosuppressive drugs, glucocorticosteroids, splenectomy, intravenous immunoglobulins, intravenous anti-D, and monoclonal antibodies directed at B cells). Even though these therapies are frequently helpful, not everyone responds to them, and they may also have unfavorable side effects [4-6].

There are a few secondary treatment options for ITP that is immune to corticotherapy, IVIg, or anti-D Ig. Rituximab and the thrombopoietin receptor agonists are more effective than the earlier drugs [7,8]. Chimeric antiCD20 antibody rituximab is widely used as two lines of therapy. About 21% of people experience a lengthy response to rituximab [9]. Although a dose of $100mg/m^2$ has similar effectiveness, the suggested dose is $375mg/m^2$ once a week for 4 weeks [10]. An intricate manipulation of the immune system is part of the mechanism of action. In one investigation, the stabilization of T-lymphocyte dispersion [11], and the regular value and functioning of the regulatory T-lymphocytes [12], were linked to the efficacy of the treatment.

The TPO mimetic thrombopoietin receptor agonists (TPO-RAs) can connect to and engage TPO receptors, which promotes the development, multiplication, and division of megakaryocytic cells, which in turn increases platelet formation. Numerous randomized controlled studies (RCTs) including adult and pediatric ITP have examined the clinical effectiveness and toxicity of two main TPO-RAs, Romiplostim and Eltrombopag [13]. Romiplostim and Eltrombopag are presently suggested as second-line treatment alternatives for adults with adult ITP. In nations such as Australia, Japan, and others, eltrombopag has been given the all-clear to be used in children older than one year [14,15]. Thrombopoietin receptor agonists are suggested for adults with a hazard for hemorrhage who relapse after splenectomy, who have potential complications to splenectomy, or who struggled with one therapy, as per the American Society of Hematology's 2011 proof-based practice recommendation for immune thrombocytopenia. People in danger of blood loss who have tried corticosteroids or IVIg but failed may also be evaluated for such medications if they have not had a splenectomy.

The present study aims to assess the efficacy of thrombopoietin receptor agonists and rituximab in treating immune thrombocytopenic purpura.

Methodology

The present review followed the guidelines according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [PRISMA].

The Source of Data Collection

A literature search was conducted using an electronic database including PubMed, and Google Scholar from January 1st, 2000 to September 1st, 2022. References for textbooks and selected articles were screened to identify any relevant studies. The author extracted the necessary information. All available titles and abstracts were identified and scanned to determine the studies that seemed to be appropriate. When information from the title and abstract was unclear in determining the paper's relevance, full-text articles were thoroughly investigated by both reviewers. Also, papers that had cited these articles were identified through Science Citation Index (http://www.isinet.com), to identify potentially relevant subsequent primary research.

Search Content

The keywords that were used to identify the relevant studies on PubMed and Google Scholar included the following keywords.

Keywords: ((Thrombopoietin Receptor Agonists) AND Rituximab) AND Immune Thrombocytopenic Purpura AND ("2000/01/01"[PDat]: "2022/9/31"[PDat]).

The medical subject headings (MeSH) used on PubMed included the following keywords:

((("receptors, thrombopoietin" [MeSH Terms] OR ("receptors"[All Fields] AND "thrombopoietin"[All Fields]) OR "thrombopoietin receptors" [All Fields] OR ("thrombopoietin" [All Fields] AND "receptor" [All Fields]) OR "thrombopoietin receptor"[All Fields]) AND ("agonists"[Subheading] OR "agonists" [All Fields])) AND ("rituximab"[MeSH Terms] OR "rituximab" [All Fields])) AND ("purpura, thrombocytopenic, idiopathic" [MeSH Terms] OR ("purpura" [All Fields] AND "thrombocytopenic"[All Fields] AND "idiopathic"[All Fields]) OR "idiopathic thrombocytopenic purpura" [All Fields] OR ("immune"[All Fields] AND "thrombocytopenic" [All Fields] AND "purpura"[All Fields]) OR "immune thrombocytopenic purpura" [All Fields]) AND ("2000/01/01"[PubDate]: "2022/9/31" [PubDate])

Eligibility criteria: The full-text studies were assessed and selected based on the following inclusion and exclusion criteria.

Inclusion criteria:

- Studies published from the year 2000-2022.
- Studies published in English language only.
- Studies including participants with Immune Thrombocytopenic Purpura.
- Studies conducted on humans only.
- Studies demonstrating efficacy of thrombopoietin receptor agonists and rituximab in management of ITP.

The exclusion criteria was as follows:

- Review articles, case reports, abstracts and editorials.
- Systematic reviews.

Quality assessment

Critical appraisal of the studies was conducted by the CASP checklist to assess the quality of the studies. This tool is used for critically evaluating the included studies based on 10 specific questions. The 10 items include: Item 1 = Clear identification of objectives; Item 2 = Appropriate methodology; Item 3 = Adequate research design; Item 4 = Appropriate recruitment approach; Item 5 = Effective process for data collection; Item 6= Clear specification of study outcomes; Item 7 = Ethical considerations; Item 8 = Appropriate method of data analysis; Item 9 = Clear statement of results and Item 10 = Applicability of study and provides new insights.

Based on these criteria each study was assessed. The 10 questions were categorized as yes, no or unclear. The quality of the study was categorized as high (7-10), moderate (4-6) and low (1-3) depending on the final scores.

Results

Search and selection or articles

Figure 1 demonstrates the process of retrieving and screening the studies for inclusion in this systematic review and meta-analysis. The search strategy yielded a total of 501 articles. After excluding the duplicate records, title and abstract screening of 131 articles were conducted. 19 full text articles were assessed for eligibility and finally, 7 studies met the inclusion criteria and were processed for qualitative analysis.

Characteristics of studies included in the review

The main characteristics of the studies included are shown in Table 1. These included: author, year, study design, methodology, treatment and conclusion.

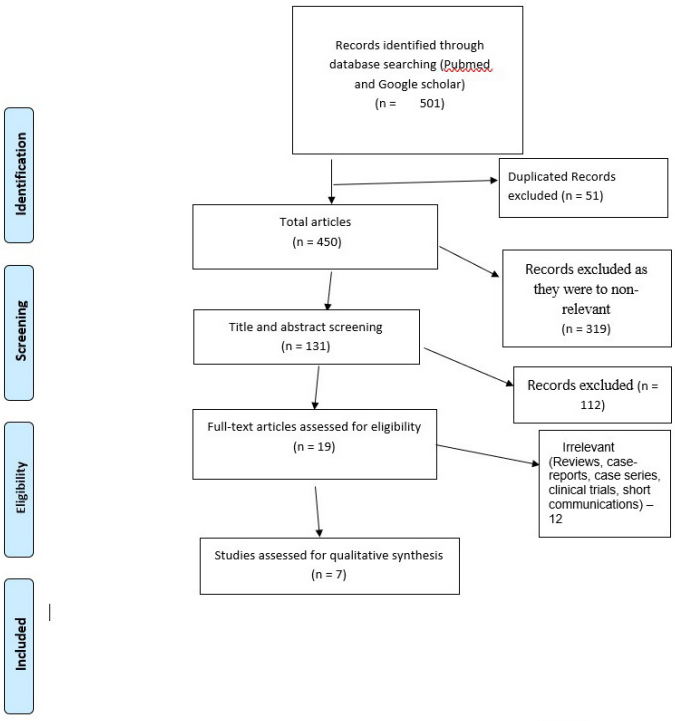

Figure 1: Flow diagram illustrating the literature search and selection criteria (according to PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

Table 1:

Author, year	Study design	Methodology	Treatment	Conclusion
Veneri D, et al. (2015) [16]	Case report	31-year-old	Romiplostim 1 mg/kg once every seven days for six weeks and rituximab 375 mg/m^2 once weekly for four weeks	The platelet count increased from the haemogram's severe thrombocytopenia, i.e., (2×109/L0) to 252×109/L.
Mei H, et al. (2021) [17]	Randomized phase III trial		an early dose of 2.5 or 5 mg of hetrombopag (referred to as the HETROM-2.5 group or HETROM-5 group, respectively), once a day, or to corresponding placebo groups in a ratio of 4:4:1:1 for 10 weeks.	Throughout the course of the 2-month treatment period, hetrombopag outperformed the placebo in terms of inducing a platelet response, lowering the risk of bleeding, and requiring less rescue therapy. Over the course of 24 weeks, hetrombopag continued to elicit a lasting platelet response.
Michel M, et al. (2020) [18]	observational multicenter international study	Pregnant population	Eltrombopag (n = 8) or romiplostim (n = 7) were used to treat 15 pregnant women with ITP (pregnancies, n = 17, and neonates, n = 18) during pregnancy.	It appears safe for both the mother and the fetus to temporarily use eltrombopag or romiplostim in pregnant women with ITP who are at least resistant to corticosteroids and IV immunoglobulin and receive medication due to blood loss symptoms, deep thrombocytopenia, and/or in anticipation of delivery.
González-Porras JR, et al. (2019) [19]	Review	Retrospective studies (retrospective findings in 401 patients with ITP)	Eltrombopag and romiplostim are two TPO-RAs.	According to reported retrospective research, more than 3/4th of patients who moved to the alternative TPO-RA did so and kept their response to the new medication or got one. Significantly, the majority of patients who changed because the first TPO-RA was ineffective reacted to the alternative TPO-RA, showing that there is no cross-resistance between the two medications.
Zhang Y, et al. (2011) [20]	Scoping review	Eltrombopag 50 mg or placebo was administered to 114 patients with ITP 2:1 in a Phase III trial	By day 43, a considerably higher percentage of patients in the eltrombopag group were responding than in the placebo group (59% vs 16%; odds ratio [OR] 9.61; 95% CI, 3.31- 27.86; P 0.0001)	When taken orally every day for up to six months, eltrombopag showed clinically significant advantages by raising platelet counts, reducing blood loss incidents, and enhancing life quality while posing manageable adverse effects.
Bussel JB, et al. (2007) [21]	Phase II, randomized, double-blind, placebo-controlled;	117 ITP patients	Eltrombopag 30 mg (30) 50 mg (30) 75 mg (28); placebo (29); concurrent maintenance; immunosuppressive treatments permitted 6 week PC	Eltrombopag reduced blood loss hazard and raised platelet counts in individuals with refractory or recurrent ITP, according to the report's results.
Cheng G, et al. (2011) [22]	Phase III, international, randomized, double-blind, placebo-controlled (RAISE);	197 ITP patients	Eltrombopag dose was varied between 25 and 75 mg based on response, placebo (62) vs. eltrombopag 50 mg (135), concurrent maintenance, and immunosuppressive medications were permitted.	increased by eight times the probability of answering

The present systematic review shows that Eltrombopag and RTX showed clinically significant advantages by raising platelet counts, reducing blood loss incidents, and enhancing life quality while posing manageable adverse effects**.**

Mechanism of action of Rituximiab

According to Neunert C, et al. (2016) [23], RTX successfully treats SLE-ITP. The monoclonal antibody RTX, which targets human CD20, depletes B cells and is utilized as a biological therapy for several autoimmune diseases. Immunoglobulin synthesis to activate T cells and boost cytokine production is the function of B cells in inflammatory autoimmune disorders. Because it decreases the memory of B cells and then restores the B-cell lineage, RTX is clinically effective in treating inflammatory autoimmune diseases [24]. Pathogenic autoantibodies are produced by activated B cells during SLE, and immune complexes are deposited in multiple organs. RTX is therefore believed to be beneficial in treating SLE-ITP as well as other SLE organ abnormalities. Laboratory analysis in the instance at hand revealed B-cell activation (elevated ANA and PA-IgG titers). A study postulated that RTX works in this case because it targets B cells. From the time of start, the RTX response takes around 20 days [25]. Considering this reasonably quick response, RTX may be a good alternative for active individuals SLE-ITP puts them at a high risk of bleeding. Additionally, RTX may be able to maintain remission in patients with refractory SLE-ITP without splenectomy; nevertheless, earlier research has indicated that stopping RTX during the maintenance phase may result in an SLE-ITP flare [26,27].

For adults as well as children with ITP, the very first long-term follow-up research reported an immediate reaction rate of about 60% [9]. Children who initially responded had a higher than 60% likelihood of sustaining platelet counts of 50 109/L and a higher than 80% probability of doing so at two years. The continued presence of autoreactive B cells in the BM and germinal centers is one explanation for the lack of a prolonged response to rituximab [9]. Patients undergoing anti-CD20 Ab treatment also retains the majority of their plasma cells [9,28]. Liang Y, et al. (2012) [29], verified the positive initial reaction frequency of 68% (33%-100%) in a systematic evaluation of children with primary ITP. A better response was seen in 23 patients with secondary ITP, ranging from 64% to 100%. The average system response was three weeks, and the average response time was 12.8 months. There is no “standard” dose for rituximab in children, according to Liang Y, et al. (2012) [29], Although the most common dose is still 375 mg/m2 given over 4 weeks, there are a few small groups of kids who responded just as well to a single dose of 375 mg/m2 or to lower dose regimens of 100 mg/dose [28,29]. Continuous follow-up is required because late relapses following rituximab remission are likely. For patients who have relapsed, additional doses of rituximab may be recommended.

Rituximab side effects are most frequent after the first infusion, when fever, illness of serum, and hypotension have all been noted.

Children are more likely than adults to experience serum sickness, thus delaying the infusion and pre-medicating with antihistamines or corticosteroids might lessen these side effects [30]. With additional doses, reactions become less severe [31]. Any immunosuppressive drug administration raises the possibility of infection. There have been cases of varicella, meningoencephalitis, pneumonia, and recurrence of hepatitis C in children during the three to six months prior to the reconstitution of B cells [29]. The synthesis of Igs should continue following rituximab administration because the majority of plasma cells do not contain CD20 on their surface. Humoral immunity should also be preserved. Rituximab use has also been linked to progressive multifocal leukoencephalopathy, neutropenia, hematologic malignancies, and acute breathing difficulties [30]. The majority of toxicity reports include elderly individuals and kids with autoimmune hemolytic anemia, mixed fluctuating immunodeficiency, and other conditions that call for extra immunosuppressive medications rather than ITP patients [30].

Mechanism of action of TPO-A

Thrombopoietin controls the physiological processes that lead to the formation and maturation of platelets (TPO). TPO, which is produced in the liver, encourages the survival and development of megakaryocyte-derived hematopoietic cells, which then raise platelet numbers and function. The creation of medications that mirror the effects of TPO appears to be a logical course of action because of the autoantibodies that induce ITP to inhibit the proliferation of megakaryocyte precursors and result in megakaryocyte death [31,32]. Early in the 1990s, recombinant proteins that were either glycosylated (rhTPO) or pegylated (PEG-rHuMGDF) to extend plasma t1/2 were produced as the first-generation thrombopoietic growth factors.

The hunt for nonimmunogenic thrombopoietic development elements was sparked by hopeful results from prior effectiveness trials amidst the rejection of the first-generation recombinant TPOs. The TPO peptide mimetics, TPO nonpeptide mimetics, and TPO antibody mimetics are the three broad categories into which all second-generation TPO mimetics fall [33]. Only two of these medications, romiplostim, and eltrombopag, have received FDA approval to date. They were available for sale in August and November of 2008, respectively [34]. Patients who suffer from long-term ITP and who have not responded to corticosteroid or IVIG first therapy are eligible for both medications. The FDA-restricted Risk Evaluation and Mitigation Strategy (REMS) distribution system now governs the prescription of these medications in order to monitor their long-term safety profile [35]. Romiplostim and eltrombopag, also known as TPO mimetics or TPO receptor agonists, connect to and stimulate the TPO receptor through the JAK-STAT signal transduction pathway.

Agonists of the thrombopoietin receptor (TRA) are indicated in newly diagnosed cases in order to support the platelet count during the first year after diagnosis in the hopes of achieving spontaneous hematological remission, in contrast to some clinicians who reserve this type of treatment is exclusively for ITP patients who are refractory to it [36]. There is no homology between the two approved TRAs (Romiplostin and Eltrombopag) and the thrombopoietin structure. Both medications promote the development and proliferation of the megakaryocytes by attaching to the thrombopoietin receptor c-Mpl on the megakaryocytes, increasing platelet production [37].

In a recent phase III trial 100% of Chinese ITP patients who had not recovered or had relapsed after prior treatment, hetrombopag's effectiveness and safety were assessed. Throughout the double-blind treatment course, significant improvements were seen with hetrombopag therapy at an initial dose of either 2.5 or 5 mg every day compared to placebo for both primary and secondary efficacy objectives. In this phase III investigation, it was discovered that hemothrombopag was well tolerated and had a safety profile similar to that of a placebo in ITP adults. In general, hetrombopag treatment at a starting dose of 2.5 or 5 mg was well received. Upper respiratory tract infections, urinary tract infections, immune thrombocytopenic purpura, and blood in the urine were the most common adverse events (AEs) in patients receiving heparin within 24 weeks of treatment. In addition, a prior trial showed that patients who could not tolerate romiplostim may successfully move to eltrombopag [32], and the lack of overlapping adverse events (AEs) promoted switching when TPO-RA was stopped because the AE was not caused by a class effect [37].

According to a new comprehensive study, even after slight variations that could be explained by possible error, varying time frames, therapies, and subject varieties in these studies, the whole efficacy of Romiplostim and Eltrombopag appear to be comparable. However, there is no evidence to support superiority or a safety advantage for one TPO over the other. Headaches, epistaxis, upper respiratory infections, liver enzyme function abnormalities, particularly with the Eltrombopag regimen, thrombosis, enhanced bone marrow reticulin, thrombocytopenia following the cessation of therapy, and myelodysplastic syndromes are among the frequently reported adverse events linked to TPO-RAs [38,39]. Compared to patients in the control group, people in the TPO-RA groups required fewer rescue drugs. In the research, the frequency of bleeding episodes was considerably less in patients receiving Romiplostim compared to placebo, whereas in the Bussel et al. study, the frequency of hemorrhage events was greater in the Romiplostim group [26].

Eltrombopag's effectiveness and safety were assessed over a 6-month period in a recent Phase III multinational, randomized, double-blind, placebo-controlled trial (RAISE) [22]. In patients receiving eltrombopag during the course of the 6-month course of therapy, the chances of reacting (characterized as a platelet count of 50-400 109/L) were 8 times higher than in the placebo group (95% CI, 3.59 -18.73; P 0.0001). Compared to the placebo group, a considerably larger proportion of patients who received eltrombopag reacted at 75% or above of assessments [26].

Tpo-RAs are not advised during pregnancy and there is very little experience, despite encouraging published studies on the use of romiplostim or eltrombopag for ITP during pregnancy having been published [40,41]. It is comforting that no serious adverse effects and no thrombosis occurred based on the 15 individuals reported in a recent study. Tpo-RAs during pregnancy should be administered with special caution in individuals with lupus and/or antiphospholipid antibody syndrome-associated ITP, albeit placental infarction has been previously reported [42,43]. Tpo-RA exposure near the end of pregnancy appears to have little effect on fetal thrombopoiesis, as evidenced by the fact that just 1 neonate had thrombocytosis, which is consistent with recombinant Tpo [44]. On the other hand, 3 of the 6 newborns who experienced severe neonatal thrombocytopenia came from the same mother who had formerly undergone a splenectomy [45,46]. There was no connection between the mother's platelet response or length of treatment and the newborn's platelet level.

In a substantial, multicenter, randomized, placebo-controlled experiment of eltrombopag treatment for chronic ITP, significantly more patients in the eltrombopag group than in the placebo group

attained platelet counts of 50,000 per L or higher. Additionally, over half of the patients who received eltrombopag experienced increases in platelet counts of at least 50,000 per L within two weeks. A prospective assessment revealed a significant decrease in hemorrhage occurrences both during and after the study's conclusion, which coincided with the increase in platelet count. About half of the patients who had eltrombopag had platelet counts that were 50,000 or higher per L 1 week after the conclusion of therapy, and they typically went back to normal within 2 weeks. These findings are consistent with those of an earlier study [21], conducted on patients with chronic ITP, which found that daily administration of eltrombopag 50 mg for up to 6 weeks improved platelet counts to 50,000 per L or more in 70% of patients.

In another study, patients were randomly assigned in a 1:1:1:1 ratio to receive a placebo or eltrombopag 30 mg, 50 mg, or 75 mg daily for up to 6 weeks or until the platelet counts reached 200,109 /L by Bussel JB, et al. (2007) [21]. Throughout the research, the eltrombopag 50-mg (37%) and 75-mg (50%) groups experienced an increase in platelet count to 109/L earlier and more frequently than the placebo (4%) and eltrombopag 30-mg (14%) groups. Regardless of severity, the incidence of bleeding as measured by the World Health Organization bleeding the scale was 14%, 17%, 7%, and 4% in the groups receiving a placebo and the doses of 30, 50, and 75 mg of eltrombopag, respectively (P value not provided). Eltrombopag reduced bleeding risk and raised platelet counts in individuals with relapsed or refractory ITP, according to the study's findings. Eltrombopag and romiplostim bind to separate TPO-R sites on the megakaryocyte membrane, therefore if one of them doesn't work, the selection of another agent might be justified. A few case studies that support the efficacy of this strategy have been published [47,48]. An introspective French pilot study has studied this tactic more thoroughly [49]. 23 individuals out of the 46 instances included in the trial were moved to the second agent if romiplostim or eltrombopag as the first option failed. Based on the IWG response criteria, the response rate to eltrombopag following romiplostim was 46% with one CR and five R after three months of follow-up. After eltrombopag, romiplostim responded at a rate of 80%. Eltrombopag also helped 6/11 (55%) patients whose severe platelet count volatility necessitated halting romiplostim by stabilizing their platelet count. A few times, adverse effects were the driving force behind switching, which was accomplished effectively in both directions. As a result, there is a high chance that the outcome will be successful if the patient is changed to the second TPO-R agonist when one of the two is ineffective or there are other reasons that make it difficult to administer it. A key factor in the decision to transition from romiplostim to eltrombopag was patient desire. People have been found to seek switching to eltrombopag due to their choice of an oral over a topical method of treatment, the difficulty of using romiplostim vials, and the cost-effectiveness of the medication. Moreover, a recent search performed statistical research on the outcomes of 106 patients between 2009 and 2015 who changed TPO-RA medications across 17 cooperating facilities in Italy. They used data from 106 participants who swapped TPO-RA agents [15]. The outcomes agreed with statistics that had already been reported. 67% of participants shifted TPORAs because of the initial TPO-RA ineffectiveness. 65% of patients generally reacted after changing, and both TPO-RA change sequences were excellent. In comparison to people who changed for effectiveness causes, those who changed for other purposes were inclined to keep a treatment (80% versus 57.8%; $p = 0.03$).

Combination of rituximab with a thrombopoietin receptor (TPO-R)

It has been seen that TPO-R agonist and modern therapy with rituximab were considered for a 31-year-old patient who seemed to be at a significant chance of fatal haemorrhage [16]. Rituximab 375 mg/m^2 every week for a month and romiplostim 1 mg/kg every week for 40 days were administered as indicated. As expected, during the course of the following seven days, the platelet count rose to 10^9/L, and the hemorrhagic symptoms gradually subsided. After the TPO-R agonist was stopped, a month later, the platelet count became $252x10^9$ /L, within the average limits ($284x10^9$ /L), and held constant throughout time. This demonstrates that the combination of rituximab with a thrombopoietin receptor (TPO-R) agonist immediately resulted in a long-term rise in platelet count in a young patient with a serious immune thrombocytopenic purpura (ITP) who was refractory to intravenous immunoglobulin (IVIg) and steroids.

Conversely, after brief use of TPO-R agonists alone, a study achieved durable remissions in 8/28 (29%) persons with chronic ITP [11]. The participants were prescribed a TPO-R mimic at least half a year after a splenectomy or rituximab medication, as they were originally non-responsive to steroids. The scientists came to the conclusion that TPO-R mimics have effects other than just promoting megakaryocyte proliferation in ITP. It has been documented that the TPO-R agonists turned positive in the recovery of T CD4+ regulation stability and stimulation of the JAK/STAT signaling pathway in ITP patients as well as a marked decline in the serum titer of antiplatelet antibodies and the rescue of T CD4+ regulatory cells in an ITP animal model. TPO-R might therefore also have immunomodulatory outcomes as a result. Practical research investigating the outcomes of brief TPO-R therapy in combination with standard therapy in individuals who had extreme ITP at diagnosis, in our view, will be quite interesting [50].

It may take longer to thoroughly investigate some TPO-R agonist side effects, such as the formation of bone marrow fibrosis, and the majority of the patients don't seem to want to continue them indefinitely. Sometimes in cases of secondary ITP, such as when combined with indolent lymphoproliferative disorders or even in other conditions that could be worsened by serious thrombocytopenia, such as aplastic anemia or myelodysplastic syndromes, these new medications are being investigated more and more.

Future Perspectives

The choice between splenectomy, rituximab, and TPO-R agonists is the optimum course of action following the failure of the first therapy, which is typically based on corticosteroids. There are currently no evidence-based data to establish a preferred sequential sequence among these treatments. Personal differences including illnesses, age, sex, profession, and lifestyle can in reality become deciding factors in the decision. Future research is urgently required to find clinical and biological prognostic variables of extended response because there are currently no valid patient-specific response markers, whether medical or hereditary, for the various therapy choices. With the use of specially crafted clinical trials, the best course of action for individuals with persistent ITP who are also in danger of hemorrhage should be examined.

Conclusion

In individuals who are unable to take TPO-RAs or who show no discernible increase in platelet counts with either eltrombopag or romiplostim, a non-TPO-RA treatment would be the best alternative. Nevertheless, if TPO-RAs are well absorbed and only partially successful (platelet counts more than twice as high as a baseline, although 75 mg/day may be utilized in some ITP patients who fail to respond to dosages),

the best strategy is to adopt a combination approach including TPO and rituximab. Further large-sample studies are required to determine the long-lasting efficacy of these medications in patients with ITP.

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