American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e933788
DOI: 10.12659/AJCR.933788

Received: 2021.06.29
Accepted: 2021.09.28
Available online: 2021.10.27
Published: 2021.12.04

Avatrombopag Effectively Maintained Platelet Counts in a Patient with Immune Thrombocytopenia Who Was Intolerant to Tyrosine Kinase Inhibitor Therapy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG **Hillary S. Maitland**

Division of Hematology/Oncology, Department of Medicine, Emily Couric Clinical Cancer Center, University of Virginia, Charlottesville, VA, USA

Corresponding Author: Hillary S. Maitland, e-mail: hsm5r@virginia.edu
Financial support: Publication support for this case report was funded by Dova Pharmaceuticals (Durham, NC), a Sobi company, which is the manufacturer of Doptelet (avatrombopag). The funder was involved in the writing and review of this manuscript

Conflict of interest: HM received consultant fees and speaker fees from Sobi, Takeda

Patient: Female, 47-year-old
Final Diagnosis: Idiopathic thrombocytopenia
Symptoms: Bruising • diarhea • thrombocytopenia
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Unusual or unexpected effect of treatment

Background: First-line treatments for patients with immune thrombocytopenia include corticosteroids, intravenous immunoglobulin, and anti-D. These may be followed by second- and third-line options, including thrombopoietin receptor agonists and the tyrosine kinase inhibitor fostamatinib. These treatments have different mechanisms and divergent adverse event profiles. We show that fostamatinib-associated adverse events can be mitigated with fostamatinib dose reduction and the introduction of avatrombopag, and that response can be maintained with avatrombopag monotherapy.

Case Report: A 61-year-old woman with a history of chronic refractory immune thrombocytopenia since 2006 had previously received steroids, rituximab, splenectomy, and eltrombopag without achieving platelet count stability. The patient reported flu-like symptoms in February 2020, with platelet counts ranging from 25×10^9/L to 50×10^9/L and isolated occurrences $<10\times10^9$/L. Platelet counts did not respond to eltrombopag 75 mg/day, 2 courses of rituximab, or multiple courses of prednisone. Within 2 weeks of starting fostamatinib 150 mg twice daily, she reached a platelet count of 523×10^9/L. She experienced new-onset diarrhea associated with fostamatinib, so the dose was reduced to 75 mg twice daily, and avatrombopag 20 mg/day was added to augment platelet recovery. Platelet levels remained in the supratherapeutic range. She was transitioned to avatrombopag 40 mg/day monotherapy and then 20 mg/day owing to continued supratherapeutic platelet counts.

Conclusions: Avatrombopag can be used in combination with fostamatinib to augment platelet response and reduce the severity of adverse events associated with fostamatinib, while maintaining adequate therapeutic response in chronic immune thrombocytopenia. Avatrombopag 40 mg/day monotherapy was quite effective in achieving and maintaining high platelet counts.

Keywords: Fostamatinib • Platelet Count • Purpura, Thrombocytopenic, Idiopathic • Receptors, Thrombopoietin

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933788

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Immune thrombocytopenia (ITP) is an autoimmune disorder in which patients experience thrombocytopenia (platelet count <100×10^9/L) [1]. Treatment is aimed at achieving a safe platelet count (>20-30×10^9/L) to prevent episodes of severe bleeding [2]. Guideline-recommended first-line therapy for ITP is corticosteroids, intravenous immunoglobin, anti-D, or a combination of 2 to 3 of these drugs [2]. Patients who are relapsed or refractory to corticosteroids have several second-line or later treatment options. Those supported by robust clinical evidence include thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, and splenectomy [2,3]. These treatments act via a variety of mechanisms. Generally, TPO-RAs act by stimulating platelet cell production, and rituximab, fostamatinib, and splenectomy act by reducing immune cell destruction of platelet cells. More specifically, TPO-RAs bind to the thrombopoietin (TPO) receptor and stimulate megakaryocyte progenitor proliferation and increased platelet production [4-6]. TPO-RAs that are indicated for use in ITP in the United States and Europe include avatrombopag and eltrombopag, which are orally formulated, and romiplostim, which is injectable [7-12]. Although not approved for the treatment of ITP, rituximab is sometimes used as an off-label treatment in these patients. The anti-CD20 monoclonal antibody, rituximab, depresses B-cell counts and may also modify T-cell activity [13-15]. For rituximab responders, treatment results in a significant rise in platelet counts [13]. However, a randomized, placebo-controlled phase 3 trial demonstrated that overall and complete response rates were similar in adult patients with ITP who were treated with rituximab or placebo [16]. Fostamatinib acts through yet another mechanism by inhibiting spleen tyrosine kinase (Syk) and thus blocking Syk signaling-mediated platelet destruction in patients with ITP, resulting in increased platelet counts in responders [17]. Splenectomy is also an option; because the spleen is the primary site of platelet clearance and autoantibody production, spleen removal results in durable platelet response [18]. However, recent treatment guidelines recommend that splenectomy be reserved for patients who have failed medical therapies [2].

Adverse events play a role in treatment decisions; agents with different mechanisms have different safety profiles. With TPO-RAs, there is a potential for increased risk of thrombosis (approximately 6-7%) [7,9,11,19]. The B-cell-depleting effects of rituximab can result in increased risk of hypogammaglobulinemia and infectious complications [20]. Tyrosine kinase inhibitor-associated adverse events can occur with the Syk inhibitor fostamatinib and include diarrhea and hypertension in about one-third of treated patients [17]. Nausea, dizziness, and liver enzyme increase are also relatively common (> 10% of treated patients) [17].

Combination therapy in patients with ITP provides a potential opportunity to improve efficacy by targeting different mechanisms of disease pathology and to reduce adverse events. For example, some small studies have reported some benefits to TPO-RA combined with steroids as first-line [21] and later-line [22,23] treatment for patients with ITP. Additionally, studies have shown that switching to another TPO-RA if the first TPO-RA fails results in a high number of patients who are able to maintain or achieve response with the new treatment [24]. Fostamatinib and avatrombopag are the 2 most recently approved agents for the treatment of ITP (April 2018 and June 2019, respectively) [25,26].

This case study reviews the treatment of a 61-year-old woman who had a history of chronic refractory ITP and who had previously received steroids, rituximab, splenectomy, and eltrombopag, all of which failed to result in a stable platelet count. Although treatment with fostamatinib resulted in stable platelet counts, a combination of low-dose fostamatinib and avatrombopag was initiated to alleviate treatment-associated diarrhea while maintaining a stable platelet count. The outcome of this combination therapy is described here.

Case Report

This was a 61-year-old woman who was diagnosed with ITP in 2006. Her past medical history included Meniere disease and an undefined connective tissue disorder; past surgeries included tonsillectomy, appendectomy, lysis of adhesions, carpal tunnel release, and splenectomy with subsequent drainage of abscess. The patient did not smoke cigarettes and drank about 1 alcoholic beverage per week.

The patient presented on February 18, 2020, with a platelet count of 18×10^9/L, which was a reduction compared with her previous visit (166×10^9/L, January 14, 2020). She had been receiving tapering doses of oral eltrombopag; at the time of the visit, her dose was 25 mg/day, which was increased to 50 mg/day because of the low platelet count. She responded to treatment with an increased platelet count of 117×10^9/L (March 3, 2020); however, on March 17, 2020, it had decreased to 14×10^9/L despite the higher dose of eltrombopag. She was switched from eltrombopag to oral fostamatinib 100 mg twice daily and had a good initial response, but, after about 2 weeks, her platelet counts dropped significantly (10×10^9/L). The dose of fostamatinib was increased to 150 mg twice daily, but the patient continued to experience bruising and she started herself on prednisone. Her platelet count was 25×10^9/L on April 14, 2020, and she was switched from fostamatinib to eltrombopag (75 mg/day). The patient was seen again on May 4, 2020, reporting she had presented to the Emergency Department over the weekend (May 2, 2020) with a platelet count of 1×10^9/L. The patient was started on intravenous rituximab (375 mg/m^2) the

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

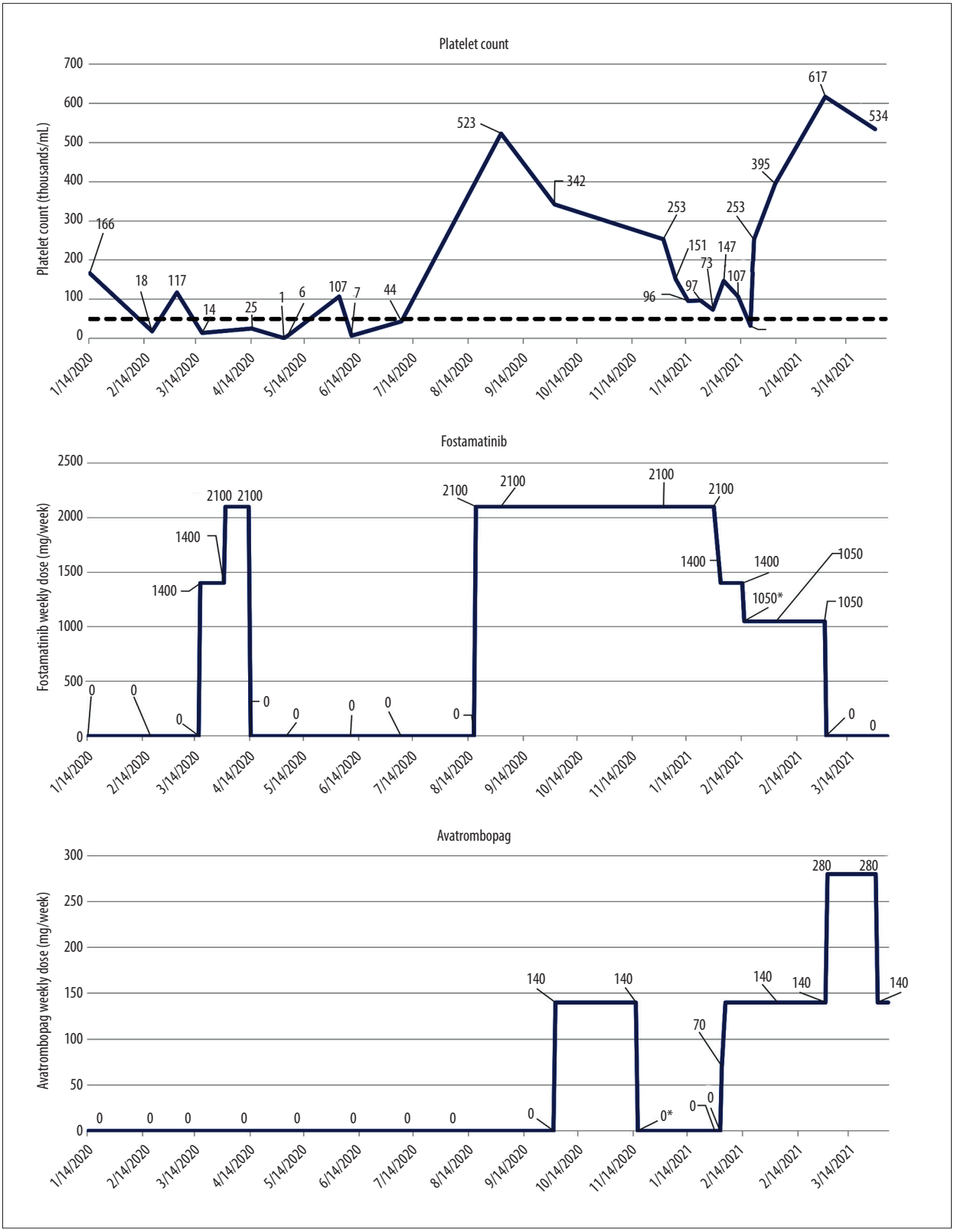

Figure 1. Platelet count, fostamatinib dose, and avatrombopag dose over time. * Indicates that an approximate date was used.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

following day, and on May 8, 2020, a spiral computed tomography scan revealed no accessory or regenerative splenic tissue. Rituximab treatment resulted in improved platelet counts; however, on June 9, 2020, her platelet count dropped to 7×10^9/L after being 107×10^9/L the week prior. At this visit, the patient restarted eltrombopag at 50 mg/day; this was titrated up to 75 mg/day 1 week later owing to an inadequate platelet response. On July 7, 2020, the patient was being treated with eltrombopag at 75 mg/day and her platelet count was stable at 44×10^9/L. The patient was seen at the University of Virginia for a second opinion on September 1, 2020, and reported that she had been having very little response on eltrombopag 75 mg/day and that she had switched to fostamatinib 2 weeks prior (150 mg orally twice daily); her platelet count was 523×10^9/L, and it was recommended that she continue on fostamatinib.

Her platelet count trended down through the end of September 2020, at which point she was started on eltrombopag 75 mg/day in addition to the fostamatinib 150 mg twice daily, and on October 1, 2020, her platelet count had increased to 342×10^9/L. The eltrombopag was then changed to avatrombopag 20 mg/day owing to liver function test abnormalities, and the avatrombopag was subsequently discontinued because of persistently high platelet counts. While on fostamatinib alone (150 mg twice daily), the patient's platelet counts began to slowly drift downward, and her count was 73×10^9/L on December 29, 2020. At this time, the patient reported having some difficulty with diarrhea, a known toxicity of fostamatinib. On January 2, 2021, she restarted avatrombopag 20 mg every other day and decreased fostamatinib to 100 mg twice daily; platelets increased to 147×10^9/L on January 4, 2021. Due to continued difficulty with diarrhea, her dose of fostamatinib was reduced to 75 mg twice daily to help reduce the associated diarrhea, and avatrombopag was increased from 20 mg every other day to 20 mg/day to maintain platelet counts. On February 2, 2021, the patient was doing well with the combination; her diarrhea had improved and her platelet count was 395×10^9/L. The patient was seen again on March 2, 2021, and reported that she was having increasing difficulty with diarrhea related to fostamatinib. Her platelet count was quite high at 617×10^9/L. Given the supratherapeutic platelet count and the difficulty with fostamatinib-associated diarrhea, fostamatinib treatment was discontinued, and the patient was switched to avatrombopag monotherapy with the dose increased to 40 mg/day. The platelet count was 534×10^9/L on March 30, 2021, so the avatrombopag dose was decreased to 20 mg/day. The platelet counts and dosing for fostamatinib and avatrombopag over time are shown in **Figure 1**.

Discussion

This case study demonstrates that TPO-RAs can be used in combination with other classes of drugs to alleviate adverse events by allowing for a dose reduction while still maintaining a safe platelet count. TPO-RAs have a unique mechanism of action relative to other agents used to treat ITP and in theory may provide synergistic effects in combination with other therapies, particularly in patients who are resistant or refractory to treatment. There are few reports of TPO-RA combination therapy for ITP, and these generally report on combinations with steroids. A small study reported that first-line eltrombopag plus high-dose dexamethasone improved response rate in newly diagnosed ITP (vs historical data of dexamethasone monotherapy) [21]. A small study of eltrombopag and high-dose dexamethasone in patients with chronic ITP reported complete response (platelet count $\geq100\times10^9$/L) in 10 of 11 patients [22]. It has also been reported that a TPO-RA combined with a low steroid dose (2.5-5 mg prednisolone) can benefit patients who were not responding to treatment [23]. A small retrospective study of combination therapy with TPO-RA (either eltrombopag or romiplostim), immunosuppressants, and intravenous immunoglobin in pediatric or adult patients with ITP reported that 13 of 18 were considered responders with this combination treatment [27]. The present case study is the first report of combination treatment with fostamatinib and a TPO-RA, as fostamatinib is a relatively new agent [25].

It should be noted that while TPO-RAs are mechanistically similar, they have different pharmacokinetic, safety, and efficacy profiles; therefore, switching between them because of inconvenience, lack of efficacy, or unacceptable adverse events is a reasonable treatment approach [24,28]. For example, eltrombopag chelates polyvalent cations and should be taken either without a meal or at least 2 h before or 4 h after medications or products that contain polyvalent cations (eg, calcium-rich food, antacids, and mineral supplements) [9,29]. This is not the case for avatrombopag, as it does not have the potential to chelate polyvalent cations [7,29]. Another difference is that, in patients who are treated with eltrombopag, there is a need to monitor liver function, and dose adjustments can be necessary in certain populations (eg, Asian patients and patients with liver impairment) [9,30]. In contrast, clinical trials of avatrombopag have reported only a few incidences, most of which were transient, of increased liver function tests with treatment [30,31]. Regarding efficacy, a recent review of retrospective clinical data for patients who had switched from one TPO-RA to another reported that 78% of patients achieved or maintained a response after switching [24]. In patients who switched due to lack of efficacy, 65% had improved platelet counts after switching [24]. Prior to fostamatinib treatment, the patient in the present case study had been treated with eltrombopag on multiple occasions. Although she would initially respond, she developed liver function abnormalities requiring a change of therapy. Despite this, she had an excellent response to a different TPO-RA, avatrombopag.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Although the diarrhea experienced by the patient was assumed to be caused by fostamatinib, as diarrhea is a known toxicity of the drug [32], it was not possible to rule out other potential causes for her diarrhea. We note that the patient had been treated with fostamatinib previously and did not experience diarrhea, and the onset of diarrhea was approximately 4.5 months after the initiation of fostamatinib. However, the diarrhea did improve after fostamatinib dose reduction and was completely resolved after discontinuing fostamatinib.

Conclusions

In this first report of combined fostamatinib and avatrombopag for the treatment of a patient with ITP, it was found that the addition of avatrombopag to fostamatinib could allow for a reduction in fostamatinib dose to mitigate adverse events that the patient was experiencing, while augmenting platelet response. The potential benefits of this combination may be due to the different mechanism of action of each drug. The patient ultimately was taken off fostamatinib and it was demonstrated that avatrombopag 40 mg/day monotherapy was quite effective in achieving and maintaining high platelet values. The evidence presented in this case study provides support for further studies of combined fostamatinib and avatrombopag for the treatment of patients with ITP who experience unacceptable adverse events or inadequate efficacy on fostamatinib alone.

Acknowledgements

Editorial support in the form of manuscript writing and styling was provided by Sarah Bubeck, PhD (drafting of the initial manuscript), and Michael R. Page, PharmD, RPh (content outline development) of BioCentric, Inc. (Collingswood, NJ). This support was funded by Dova Pharmaceuticals (Durham, NC), a Sobi company. Dova and Sobi reviewed and provided feedback on the manuscript.

Department and Institution Where Work Was Performed

Division of Hematology Oncology, Emily Couric Clinical Cancer Center, University of Virginia, Charlottesville, VA, USA.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: Report from an international working group. Blood. 2009;113(11):2386-93
2. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780-817
3. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia [published correction appears in Blood Adv. 2020;4(2):252]. Blood Adv. 2019;3(23):3829-66
4. Broudy VC, Lin NL. AMG531 stimulates megakaryopoiesis in vitro by binding to Mpl. Cytokine. 2004;25(2):52-60
5. Erickson-Miller CL, Delorme E, Tian SS, et al. Preclinical activity of eltrombopag (SB-497115), an oral, nonpeptide thrombopoietin receptor agonist. Stem Cells. 2009;27(2):424-30
6. Shirley M. Avatrombopag: first global approval. Drugs. 2018;78(11):1163-68
7. DOPTELET (avatrombopag) [prescribing information]. Durham, NC: Dova Pharmaceuticals, Inc; 2019. Accessed June 15, 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210238s001lbl.pdf
8. European Medicines Agency. Doptelet, INN (avatrombopag); 2021. Accessed June 15, 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/doptelet-epar-product-information_en.pdf
9. PROMACTA (eltrombopag) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018. Accessed June 15, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022291s021lbl.pdf
10. European Medicines Agency. Revolade, INN (eltrombopag); 2021. Accessed June 15, 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/revolade-epar-product-information_en.pdf
11. NPLATE (romiplostim) [prescribing information]. Thousand Oaks, CA: Amgen Inc.; 2018. Accessed June 15, 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125268s163lbl.pdf
12. European Medicines Agency. Nplate, INN (romiplostim); 2021. Accessed June 15, 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/nplate-epar-product-information_en.pdf
13. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood. 2001;98(4):952-57
14. Stasi R, Cooper N, Del Poeta G, et al. Analysis of regulatory T-cell changes in patients with idiopathic thrombocytopenic purpura receiving B cell-depleting therapy with rituximab. Blood. 2008;112(4):1147-50
15. Audia S, Samson M, Guy J, et al. Immunologic effects of rituximab on the human spleen in immune thrombocytopenia. Blood. 2011;118(16):4394-400
16. Ghanima W, Khelif A, Waage A, et al. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): A multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015;385(9978):1653-61
17. Bussel J, Arnold DM, Grossbard E, et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials. Am J Hematol. 2018;93(7):921-30
18. Chaturvedi S, Arnold DM, McCrae KR. Splenectomy for immune thrombocytopenia: down but not out. Blood. 2018;131(11):1172-82
19. Rodeghiero F, Stasi R, Giagounidis A, et al. Long-term safety and tolerability of romiplostim in patients with primary immune thrombocytopenia: A pooled analysis of 13 clinical trials. Eur J Haematol. 2013;91(5):423-36
20. Lucchini E, Zaja F, Bussel J. Rituximab in the treatment of immune thrombocytopenia: What is the role of this agent in 2019? Haematologica. 2019;104(6):1124-35
21. Gómez-Almaguer D, Herrera-Rojas MA, Jaime-Pérez JC, et al. Eltrombopag and high-dose dexamethasone as frontline treatment of newly diagnosed immune thrombocytopenia in adults. Blood. 2014;123:3906-8
22. Magro D, Levato L, Piro E, et al. High-dose dexamethasone and eltrombopag in chronic immune thrombocytopenia: A single institution experience. Haematologica. 2017;102(s3):63
23. Ghanima W, Cooper N, Rodeghiero F, et al. Thrombopoietin receptor agonists: Ten years later. Haematologica. 2019;104(6):1112-23
24. González-Porras JR, Godeau B, Carpenedo M. Switching thrombopoietin receptor agonist treatments in patients with primary immune thrombocytopenia. Ther Adv Hematol. 2019;10:2040620719837906

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

25. FDA. FDA approves fostamatinib tablets for ITP. Accessed June 15, 2021. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fostamatinib-tablets-itp
26. Dova Pharmaceuticals. Dova Pharmaceuticals announces FDA approval of supplemental New Drug Application for DOPTELET® (avatrombopag) for treatment of chronic immune thrombocytopenia (ITP). Accessed June 15, 2021. Available from: https://dova.com/wp-content/uploads/2019/06/doptelet-itp-approval-press-release-6-26-19.pdf
27. Gudbrandsdottir S, Leven E, Imahiyerobo A, et al. Combination of thrombopoietin receptor agonists, immunosuppressants and intravenous immunoglobulin as treatment of severe refractory immune thrombocytopenia in adults and children. Br J Haematol. 2020;189(2):e37-40
28. Kuter DJ, Macahilig C, Grotzinger KM, et al. Treatment patterns and clinical outcomes in patients with chronic immune thrombocytopenia (ITP) switched to eltrombopag or romiplostim. Int J Hematol. 2015;101:255-63
29. Al-Samkari H, Kuter DJ. Optimal use of thrombopoietin receptor agonists in immune thrombocytopenia. Ther Adv Hematol. 2019;10:2040620719841735
30. Jurczak W, Chojnowski K, Mayer J, et al. Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol. 2018;183(3):479-90
31. Bussel JB, Kuter DJ, Aledort LM, et al. A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia. Blood. 2014;123(25):3887-94
32. TAVALISSE (fostamatinib) [prescribing information]. South San Francisco, CA: Rigel Pharmaceuticals, Inc.; 2020. Accessed September 24, 2021. Available from: https://tavalisse.com/downloads/pdf/Tavalisse-Full-Prescribing-Information.pdf

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]