

Transitioning From Thrombopoietin Agonists to the Novel SYK Inhibitor Fostamatinib: A Multicenter, Real-World Case Series

DAVID M. HUGHES,¹ PharmD, BCOP, CHARINA TOSTE,² DNP, APN, CHRISTOPHER NELSON,³ ACNP-BC, JULIET ESCALON,⁴ ANP, FRANCES BLEVINS,⁵ PA-C, and BHAVESH SHAH,¹ RPH, BCOP

From ¹Department of Pharmacy, Boston Medical Center, Boston, Massachusetts; ²OptumCare Cancer Clinic, Las Vegas, Nevada; ³Avera Medical Group Oncology & Hematology, Aberdeen, South Dakota; ⁴Mount Sinai Health System, New York, New York; ⁵Department of Medicine, Boston University, Boston, Massachusetts

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: David Hughes, PharmD, BCOP, 830 Harrison Avenue, Boston, MA 02118. E-mail: david.hughes@bmc.org

<https://doi.org/10.6004/jadpro.2021.12.5.6>

© 2021 Harborside™

Abstract

Fostamatinib is an oral spleen tyrosine kinase (SYK) inhibitor used for the treatment of adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Clinical and operational barriers may exist that warrant bridging or switching from thrombopoietin receptor agonists (TPO-RAs), such as volatility or unpredictability of platelets, adverse events, and quality of life or patient preference. While fostamatinib demonstrated durable platelet responses, the safety and efficacy in combination, bridging, and/or switching with TPO-RAs is not well documented. The objective of this article is to provide guidance from real-world case studies for a safe and effective strategy for the transitioning of patients from TPO-RAs to fostamatinib, with some degree of overlap between the two agents. Currently, the evidence does not exist to guide the safe and effective use of combination therapy or transition between therapies in ITP. This case series highlights the importance to further understand the complexities of managing this disease, as well as successfully combining, bridging, and/or switching patients over to fostamatinib without the need for rescue therapy or increase in adverse events. The need for real-world evidence that guides providers on the safety and efficacy of short- and long-term combination therapy of fostamatinib and TPO-RAs is crucial. The rationale for combination therapy is to target different pathways, platelet destruction, and production without added toxicities. Additionally, gradual tapering off of TPO-RAs may provide a more favorable clinical outcome when switching to fostamatinib. The need for additional data is necessary to provide clinicians with guidance when managing patients with ITP.

CASE STUDIES

Case Study 1

A 25-year-old Hispanic female was diagnosed with chronic immune thrombocytopenia (ITP) at the age of 16 in Guatemala (2012) presenting with symptoms of gingival bleeding, petechiae, and easy bruising. Her platelet count was 9,000/ μL without causality. She was initiated and maintained on prednisone 20 mg twice daily, and her platelets increased to 87,000/ μL .

In 2/2013 she presented with a platelet count of 23,000/ μL and was continued on prednisone for 2 weeks, followed by a 2-week taper. Her platelet count ranged from 4,000/ μL to 37,000/ μL over the next few months, and she had transient improvements with a course of dexamethasone and was deemed to be steroid refractory. A bone marrow biopsy was performed that was consistent with a diagnosis of ITP. During this time, she was placed on observation and remained asymptomatic without evidence of bleeding.

Shortly after, she consulted with another hematologist for a second opinion and was subsequently started on weekly romiplostim (initial dose 2 $\mu\text{g}/\text{kg}$ and never titrated up) from 1/2014 to 3/2014. Unfortunately, she was unable to continue with her weekly visits to the clinic because of school commitments and transportation issues, so the decision was made to start her on eltrombopag 50 mg daily (3/2014-11/2016). She had a transient response to eltrombopag, so mercaptopurine was added to her treatment regimen in 6/2016. An additional dose of intravenous immunoglobulin (IVIG) was given in 7/2016 prior to her travel back to Guatemala. In 11/2016, she returned from her trip with a platelet count of 9,000/ μL . Eltrombopag and mercaptopurine were discontinued, and romiplostim was restarted. Her platelet counts did not improve with romiplostim despite titrating her up to the maximum dose of 10 $\mu\text{g}/\text{kg}$.

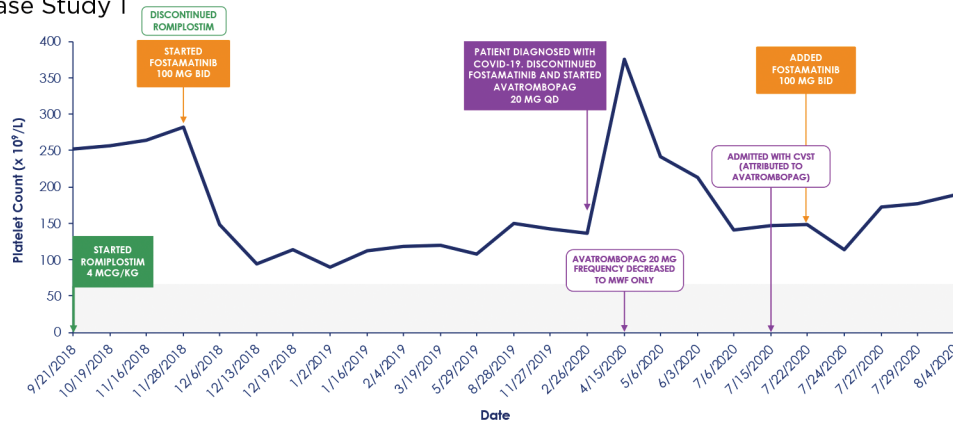
In 1/2017 she was diagnosed with Evans syndrome (Coombs positive), and was retreated with dexamethasone and mycophenolate in 6/2017 and restarted on romiplostim. Three weeks later, she was admitted to the hospital with a platelet count of 1,000/ μL and an intracranial hemorrhage. She responded to the res-

cue regimen consisting of IVIG, steroids, and platelet transfusion, and was discharged on romiplostim. She was given a 4-week course of rituximab (completed in 7/2017) with intermittent IVIG infusions to maintain a platelet count > 20,000/ μL . Her platelets were well controlled (80,000/ μL -459,000/ μL); however, in 12/2017, she presented with recurrent intracranial bleeds and was found to have a positive lupus anticoagulant and von Willebrand disease that was responsive to desmopressin.

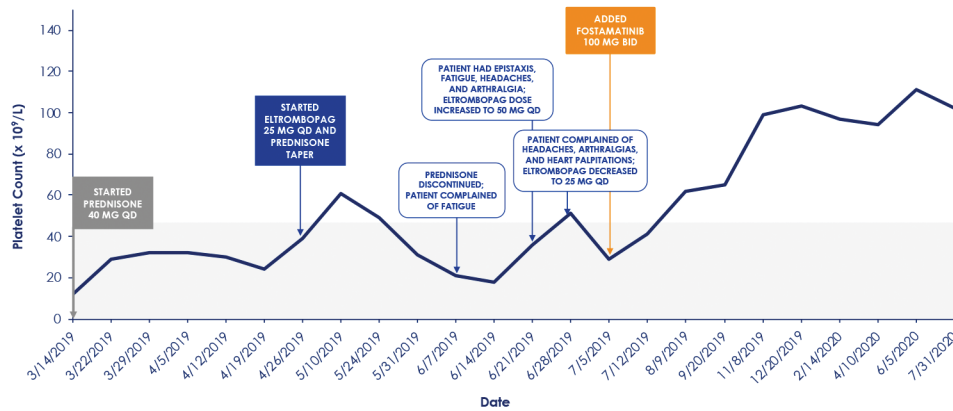
She was maintained on romiplostim 4 $\mu\text{g}/\text{kg}$ until 11/2018, at which time weekly visits were becoming increasingly unmanageable. Taking this into consideration, her options for oral therapy were discussed; however, due to her lack of response to eltrombopag, she was offered a trial of fostamatinib 100 mg twice daily. Her last dose of romiplostim was given in 11/2018 with a platelet count of 264,000/ μL (Figure 1). She was started on fostamatinib 100 mg twice daily 1 week after her last dose of romiplostim. In 12/2018 her platelet counts stabilized, and she remained asymptomatic without the need for rescue medication. In 1/2019 her platelets were 89,000/ μL , and she was diagnosed to have a transient mild neutropenia with an absolute neutrophil count (ANC) of 1,400. There were no reports of infectious complications, hypertension, or other identifiable adverse events during this time. Her platelets ranged from 108,000/ μL to 376,000/ μL through 4/2020, and her visit frequency had been decreased to once every 3 months.

In 4/2020 she reported a mild headache, and an immediate family member tested positive for COVID-19, for which she subsequently tested positive for. At the time of her diagnosis, not much was known regarding the impact of ITP therapies on COVID-19, so the decision was made to stop fostamatinib and start avatrombopag 20 mg daily. However, recent publications suggest that spleen tyrosine kinase (SYK)-dependent mechanisms are involved in the pathogenesis of COVID-19 (Fu et al., 2020), and fostamatinib is currently under investigation at the National Institutes of Health (NIH) for the treatment of hospitalized patients with COVID-19-related acute lung injury (Nadeem et al., 2019).

Case Study 1



Case Study 2



Case Study 3

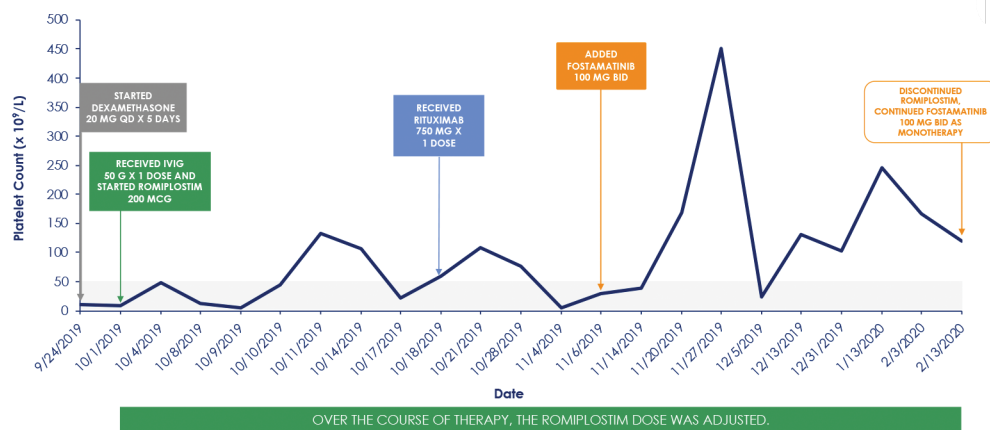
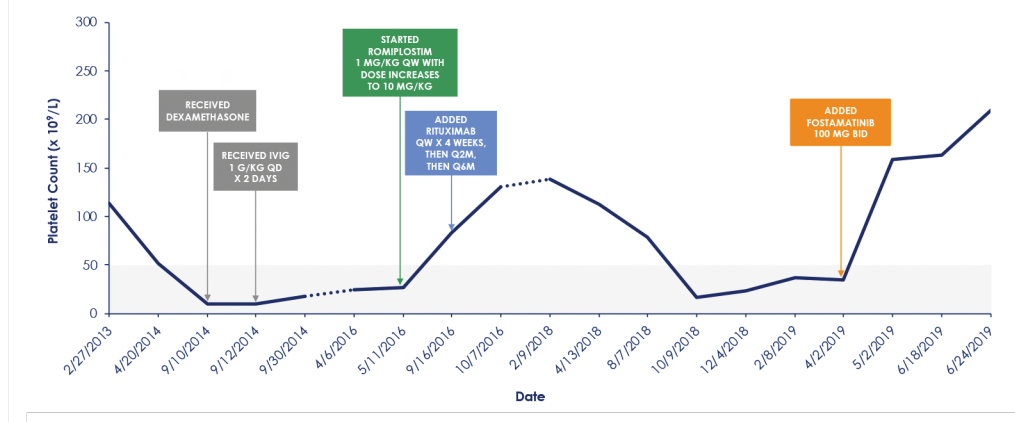


Figure 1. Patient cases.

The patient’s platelet counts abruptly increased to 376,000/ μ L, and the dose of avatrombopag was decreased to 20 mg 3 times weekly. Three months after initiating her on avatrombopag, she presented with complaints

of a moderate headache, nausea, and vomiting, and was admitted with an extensive cerebral venous sinus thrombosis. Therapeutic anticoagulation was initiated, and she was discharged on apixaban 5 mg twice daily. Given the known risk

Case Study 4



Case Study 5

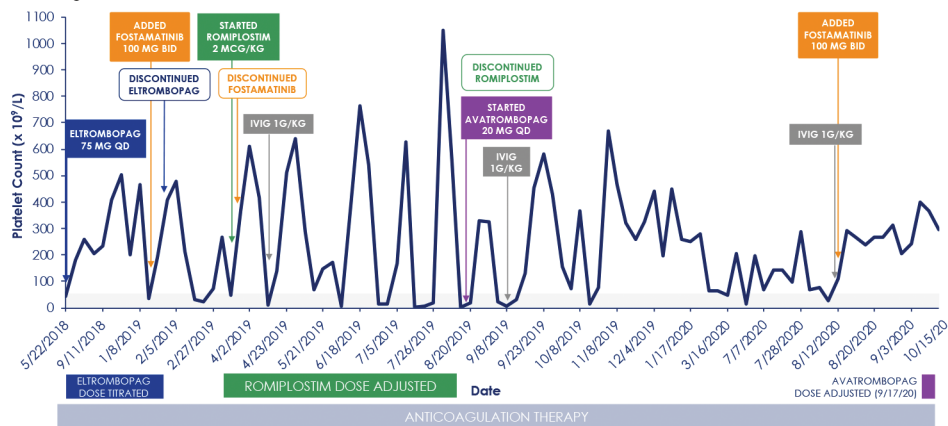


Figure 1. Patient cases (cont.).

of thrombosis with TPO-RAs, the decision was made to transition her back to fostamatinib. Her history of intracranial bleeding made it crucial that her platelets were maintained at a normal level while on concomitant anticoagulation. She was started on fostamatinib 100 mg twice daily in 7/2020 with a platelet count of 148,000/ μL and bridged with avatrombopag 20 mg three times weekly. Her platelet count remained at 150,000/ μL and the decision was made to decrease the dosing interval of avatrombopag to twice weekly. Two weeks later, her platelet count stabilized at 146,000/ μL , and avatrombopag was decreased to once weekly. Her platelet count was 166,000/ μL 2 weeks after cessation of avatrombopag while on fostamatinib 100 mg twice daily without any patient-reported side effects. Her most recent platelet count in 10/2020 was 167,000/ μL . She remains on apixaban 5 mg

twice daily without any bleeding issues, recurrent thromboses, or adverse events.

Case Study 2

A 28-year-old male presented to urgent care with hemorrhaging epistaxis. His past medical history consisted of anxiety (controlled with alprazolam). The complete blood count (CBC) revealed a platelet count of 9,000/ μL . He was immediately transferred to the emergency department and transfused with 2 units of platelets. At discharge, he was referred to hematology and a complete patient workup, including comprehensive metabolic panel (CMP), an anti-nuclear antibody (ANA) test, and bone marrow biopsy, which were consistent with a diagnosis of ITP in 3/2019.

At the initial hematology consult, his platelet count was 12,000/ μL , and he complained of

fatigue. He also reported his anxiety had been slightly exacerbated since his initial overt bleeding episode in the emergency department. He requested oral medications due to his dependency on public transportation and inability to maintain frequent clinic visits. He started treatment with prednisone 40 mg daily with weekly monitoring in 3/2019. While he showed a mild response to prednisone, his platelet count plateaued at 32,000/ μ L in 4/2019. In addition, he started to experience anxiety exacerbations, which he attributed to prednisone, impacting his quality of life (QOL). Alprazolam was increased, and a prednisone taper was initiated since he was no longer willing to continue prednisone. During his taper, his platelet count dropped rapidly to 20,000/ μ L, and eltrombopag 25 mg daily was started in late 4/2019. His platelet count dropped to 18,000/ μ L, and he started to report symptoms of fatigue and recurrent anxiety, in addition to experiencing intermittent epistaxis. Eltrombopag was increased to 50 mg in 6/2019. The following week, his platelet count was 36,000/ μ L, but he reported side effects of headaches and arthralgia, which were classified as grade 2 per the Common Terminology Criteria for Adverse Events (CTCAE).

One week later, he presented with a platelet count of 51,000/ μ L with worsening side effects (grade 3) along with heart palpitations. Eltrombopag dosage was immediately decreased to 25 mg daily in 7/2019. Fostamatinib 100 mg twice daily was added to his treatment regimen 1 week later with the intent to discontinue eltrombopag. His baseline platelet count prior to starting combination regimen of eltrombopag/fostamatinib therapy was 29,000/ μ L. After initiating combination therapy, his platelet count had increased to 41,000/ μ L without reported side effects. His platelet count has been monitored monthly for the past 12 months, with an average platelet count ranging from 90,000/ μ L to 100,000/ μ L. Alprazolam use has decreased back to pre-ITP baseline. He remains asymptomatic with stable platelet counts and does not wish to discontinue the combination therapy at this time.

Case Study 3

A 75-year-old male was referred to hematology for increased bruising and platelets of 14,000/

μ L discovered at his annual physical in 9/2019. His past medical history was consistent for dyslipidemia (controlled on atorvastatin) and hypertension (controlled on lisinopril). A complete workup revealed a normocellular marrow on bone marrow biopsy, peripheral smear negative for blasts or schistocytes, positive antiplatelet antibodies, and a positive ANA. This confirmed a diagnosis of ITP.

His initial platelet count in the hematology office was 11,000/ μ L, and he was treated with dexamethasone 40 mg once daily for 4 days. His platelet count dropped to 8,000/ μ L. In 10/2019, he was given IVIG 400 mg/kg for 3 days along with daily dexamethasone 40 mg with no improvement in platelet count. Romiplostim 2 μ g/kg was initiated at this time, and 2 days later, his platelet counts increased to 34,000/ μ L and then quickly decreased to 4,000/ μ L over the next several days. An additional two doses of IVIG 400 mg/kg were administered, and romiplostim was increased to 3 μ g/kg once weekly. Four days following IVIG administration, platelets increased to 107,000/ μ L but then dropped the following week to 22,000/ μ L. The dose of romiplostim was then increased to 6 μ g/kg along with IVIG; however, his platelet count dropped to 4,000/ μ L.

Fostamatinib 100 mg twice daily was started along with the current dose of romiplostim 6 μ g/kg in 11/2019 (with a plan to taper romiplostim in the future). Blood pressure at time of fostamatinib initiation was 153/80 mm Hg, and antihypertensives were titrated up (prior to fostamatinib). Fostamatinib and romiplostim were continued and weekly platelet counts over the next 3 weeks were 30,000/ μ L, 39,000/ μ L, and 168,000/ μ L, respectively. Two weeks after fostamatinib initiation in 12/2019, platelets rose to 450,000/ μ L, and his romiplostim was held. The next week, his platelet count dropped to 24,000/ μ L without bleeding episodes. Romiplostim 8 μ g/kg was restarted on 12/4/19 and continued to be administered for the next 2 weeks, and platelet count rose to 131,000/ μ L. As opposed to abrupt discontinuation of romiplostim, the dose was decreased gradually to 3 μ g/kg over the next two consecutive weeks. Platelet counts were 246,000/ μ L and 166,000/ μ L in 1/2020. Platelet count in 2/2020 (10 weeks after

fostamatinib was initiated) was 119,000/ μL , and the decision was made to discontinue romiplostim. The following week, his platelet counts were stable at 109,000/ μL . He has since been admitted to an outside facility, and his care was assumed by another hematologist at this facility.

Case Study 4

A 63-year-old Hispanic female was diagnosed with ITP in 2013. Her past medical history included HIV (poorly controlled on antiretroviral therapy), asthma since childhood, reactive airway disease, hepatitis C virus (treated with interferon in 2013), hypertension, attention deficit hyperactivity disorder, osteoarthritis, and anxiety. She also has a documented social history of prior cocaine use. At initial presentation in 2/2013, platelets were 114,000/ μL . In 4/2014, she presented with fatigue, insomnia, hematuria, bruises, and petechiae present in the upper and lower extremities, with a platelet count of 51,000/ μL . Four months later (9/2014), her platelets dropped to 10,000/ μL , and she was started on dexamethasone 40 mg for 4 days. The patient's platelet count remained at 10,000/ μL , and 2 days later, she was given IVIG 1 g/kg for 2 days.

She has a documented history of poor adherence to medications and clinic appointments, and over the next several years, her platelet count stabilized around 20,000/ μL , accompanied by intermittent bruising and epistaxis. In 5/2016, she was initiated on romiplostim 1 $\mu\text{g}/\text{kg}$ weekly. She was gradually titrated up to a dose of 10 $\mu\text{g}/\text{kg}$ once weekly, and the highest platelet level achieved was 83,000/ μL (in 9/2016). She continued to have persistent fatigue, bruising, petechiae, and intermittent epistaxis. She reported these symptoms interfered with her QOL and worsened her anxiety and insomnia. In 9/2016, she was administered rituximab 375 mg/ m^2 IV once weekly for four doses while continuing her weekly dose of romiplostim 10 $\mu\text{g}/\text{kg}$. Following completion of the four doses, she was given rituximab every other month for three doses and then maintained on every-6-month dosing, during which the highest platelet counts achieved were 138,000/ μL (2/2018). In 10/2018, platelet counts dropped to 16,000/ μL with recur-

rent symptoms of epistaxis, diffuse bruising, and petechiae. She did not receive any rescue medication at that time. She continued on the same treatment course of romiplostim 10 $\mu\text{g}/\text{kg}$ and rituximab every 6 months.

In 4/2019, fostamatinib 100 mg twice daily was added to the current combination of rituximab every 6 months and romiplostim 10 $\mu\text{g}/\text{kg}$ once weekly when her platelet count was 35,000/ μL . The next month, her platelet count increased to 159,000/ μL (highest since diagnosis) and continued to increase until a peak was reached in 6/2019 at 210,000/ μL . Since fostamatinib initiation, she has remained asymptomatic with normal platelets (without dose escalation of fostamatinib).

Case Study 5

A 69-year old male with a past medical history of pulmonary marginal zone lymphoma (MZL) presented in 9/2012 for a consultation and workup for severe thrombocytopenia. At the time of evaluation, he had a platelet count of 23,000/ μL . Immune thrombocytopenia was suspected, which was later confirmed with a bone marrow biopsy. He was started on prednisone 60 mg once daily, and his platelet count rose to 62,000/ μL .

Given his MZL, he was initially treated with rituximab 375 mg/ m^2 weekly for 4 weeks. He subsequently underwent a splenectomy and was started on eltrombopag 50 mg once daily (with titration up to 75 mg once daily). Due to his lack of response to eltrombopag, he was transitioned to romiplostim (doses ranging from 3 to 7 $\mu\text{g}/\text{kg}$ once weekly). While on romiplostim, his platelet response was sporadic, and his course was complicated by multiple deep vein thromboses (DVT) and a pulmonary embolism warranting anticoagulation. He was unresponsive to romiplostim and was restarted back on eltrombopag. His platelets responded initially, but fluctuations again required frequent clinic visits and constant dose adjustments. Eltrombopag was discontinued indefinitely in 1/2019 when he had another thrombotic event requiring amputation of his right greater toe.

Fostamatinib 100 mg twice daily was initiated in 1/2019 when his platelet counts were

192,000/ μ L (36,000/ μ L 2 days prior) while continuing eltrombopag 25 mg daily for 4 days of overlap before discontinuation. In 2/2019, his platelet count was 480,000/ μ L; however, 2 weeks later, his platelet count dropped to 31,000/ μ L, and the dose of fostamatinib was increased to 150 mg twice daily in order to avoid bleeding complications while on full-dose anticoagulation. In 3/2019, his platelets were still 47,000/ μ L, and the decision was made to switch back to romiplostim 2 μ g/kg. Fostamatinib was discontinued 1 week later after an abrupt increase in platelets to 365,000/ μ L, and he was maintained on weekly romiplostim.

In 8/2019, he was switched to avatrombopag 20 mg daily due to volatile platelet counts on romiplostim. Eleven days after initiation of avatrombopag, he was readmitted with a pulmonary embolism (platelet count at the time was 376,000/ μ L). Over the next 9 months, he would warrant numerous dose modifications of avatrombopag (increases and decreases), developed recurrent DVTs, a lower extremity hematoma, and intracranial bleeding requiring multiple interruptions in his anticoagulation.

Finally, given his numerous admissions (> 3 in last year) and volatile platelet response, the decision was made to restart fostamatinib with a slow titration off of avatrombopag given his bleeding and thrombotic risk. A combination approach was used in the short term as a means to safely transition him over to fostamatinib.

Fostamatinib 100 mg twice daily was initiated in 8/2020, and he remained on his current dose of avatrombopag (40 mg on Monday, Wednesday, and Friday; 20 mg on all other days). Platelet count at initiation was 110,000/ μ L, and platelet counts were checked weekly. His platelet counts rose to 249,000/ μ L, 314,000/ μ L, and 207,000/ μ L over the following weeks. The dose of avatrombopag was lowered to 20 mg once daily while continuing on fostamatinib 100 mg twice daily. Platelet counts in 9/2020 were 242,000/ μ L and 398,000/ μ L (2 weeks apart), and as such, his avatrombopag dosing was lowered to 20 mg three times weekly. Most recently in 10/2020, his platelet count was 366,000/ μ L and remains stable on apixaban 5 mg twice daily. He continues to be monitored closely, and the team managed to ensure the best possible outcomes and avoid any future thrombotic events.

Immune thrombocytopenia (ITP) is a heterogeneous disease that includes a complex interplay of abnormalities, including immune dysregulation, antiplatelet autoantibodies, defects in cellular immunity, and altered platelet production, ultimately resulting in variable bleeding symptoms that often necessitate the use of multiple therapies to achieve a target platelet count to stabilize a patient (Cines et al., 2014; Despotovic, 2018). The hallmark of ITP is mediated by platelet autoantibodies that accelerate platelet destruction and inhibit platelet production (Cines et al., 2009). Corticosteroids and/or intravenous immunoglobulin (IVIG) are typically used as front-line therapy in an attempt to rapidly interfere with the process of platelet destruction for the management of acute bleeding; however, many patients will cycle through multiple lines of therapies in order to manage their platelet counts (Neunert et al., 2019).

Although there are a number of approved treatments for ITP that are utilized as second line, there is no clear guidance by clinical guidelines on sequencing therapy. Rather, from the clinician's perspective, therapy should focus on patient characteristics and avoidance of adverse drug effects from therapy (Neunert et al., 2019). In addition, symptoms associated with low platelet counts (e.g., fatigue, bruising, and bleeding) and quality of life (QOL) often have an impact on treatment considerations.

Thrombopoietin receptor agonists (TPO-RAs), eltrombopag (Promacta) and romiplostim (Nplate), have been available for over a decade, and most recently, avatrombopag (Doptelet) was approved for ITP in 2019. These drugs work to stimulate the megakaryocyte production of platelets to overcome the destruction of platelets in an attempt to achieve a favorable platelet count (McMillan, 2000). However, titration of TPO-RAs is often cumbersome and time intensive.

For example, romiplostim requires weekly visits with lab draws, consuming nurse, pharmacy, and provider time (Amgen Inc., 2008). Eltrombopag has dietary restrictions, drug-food interactions, hepatotoxicity, and dosing variation based on race, further complicating treatment and patient lifestyle. In addition, these agents are also associated with an increased risk of thromboembolism (Dova Pharmaceuticals, Inc., 2018; GlaxoSmith-Kline, 2015), which can be additive to the hypercoagulable state seen in patients with ITP. The lack of clear guidance in sequencing therapies oftentimes results in patients cycling back and forth between multiple lines of available therapies, which include TPO-RAs, rituximab, and most recently, fostamatinib (Tavalisse).

Fostamatinib is a first-in-class, oral spleen tyrosine kinase (SYK) inhibitor approved in 2018 for the treatment of adults with chronic ITP with an insufficient response to a previous treatment (Rigel Pharmaceuticals, 2018). SYK inhibition blocks the signal transduction and activation of Fc γ receptors that play a key role in cellular response, and ultimately prevents the degradation of antibody-coated platelets (Liu & Mamorska-Dyga, 2017). Early trials evaluating the use of fostamatinib required patients receiving a TPO-RA at screening with median platelet levels often $\leq 20,000/\mu\text{L}$ to undergo extensive washout periods (Bussel et al., 2018). However, this may not be realistic, clinically appropriate, or feasible in practice or real-world settings.

Some of the barriers that warrant switching from a TPO-RA to fostamatinib may be due to the unpredictability and volatility of platelets, and patient factors (e.g., weekly clinic visits, transportation issues, or compliance) that may ultimately sway the treatment decision to switch to a more favorable and less cumbersome agent. Given the pharmacokinetic profile of these drugs, onset, duration, and clinical variability, therapy alterations should be made cautiously to avoid abrupt drops in platelet levels and/or bleeding events. There is a lack of published data and guidance on how to safely switch and/or bridge a patient from one treatment and/or class to another. Most clinical trials require a washout period prior to initiating another form of treatment, resulting in variable treatment approaches. The five ITP patient cases

presented in this article highlight real-world experience and provide clinical insight on sequencing a novel agent, fostamatinib, into the treatment armamentarium for ITP.

DISCUSSION

Immune thrombocytopenia is a complex and heterogeneous disease that requires individualized treatment and a personalized approach, with the ultimate goal of therapy to increase platelet count, prevent or minimize bleeding, and prevent drug-related toxicity. The highly variable response rates seen with ITP therapies may be attributed to targeting different mechanisms of immune dysregulation, suggesting that the individual patient may have alternate predominating disease biology. Therefore, it is important to understand the mechanism of disease that can play an integral role in selecting the treatment options available for the ITP patient. The autoantibody-mediated phagocytosis of platelets by macrophages via the Fc γ receptor, requiring SYK signaling, is a key process in the pathogenesis of ITP; although, insufficient platelet production and T-cell mediated platelet destruction also play a role (Newland & McDonald, 2020).

Due to the complexity of this disease, there remains an unmet clinical need for the treatment of ITP. Thrombopoietin receptor agonists (romiplostim, eltrombopag, and avatrombopag) have been used routinely in practice as a subsequent line to increase the production of platelets via stimulation of megakaryocytes. However, their clinical benefit may be blunted due to numerous issues, including (1) lack or loss of response, (2) thromboembolic risk, (3) romiplostim's frequent weekly lab and administration burden for both patients and providers, and (4) significant food, fruit, and vitamin restrictions with eltrombopag.

Fostamatinib provides a novel mechanism of action by inhibiting the SYK signaling pathway, thereby interrupting disease progression by blocking phagocytosis of antibody-coated platelets, and thus serving as another option for the management of ITP. This mechanism may help to assess whether macrophages, which activate SYK pathways, are involved in platelet destruction. The 2019 International Consensus Report on the investigation and management of ITP now

includes fostamatinib as an agent with robust evidence for use as a second-line treatment alongside TPO-RAs and rituximab (Provan et al., 2019). Thus, harboring different mechanisms, the use of available second-line agents either in combination or during the bridging/switching period may be an appealing way to manage the complexity of this disease and avoid undesirable platelet responses seen in patients with ITP.

Case Study 1

The first case highlights a young female unable to adhere to weekly clinic visits for injections due to social determinants that are part of daily living (school, transportation, work). She was initially transitioned from a TPO-RA successfully to fostamatinib without the need for rescue therapy. In this case, the dose of romiplostim was held 1 week before the initiation of fostamatinib given the known pharmacokinetic profiles of these agents. As expected, her platelets dropped quickly but then increased and remained above 100,000/ μ L for more than a year. Her case was further complicated by a COVID-19 diagnosis. Subsequently, after switching from fostamatinib to avatrombopag, she developed a life-threatening thrombosis (a reported warning/side effect of the TPO-RAs) and was started on therapeutic anticoagulation. She successfully and slowly transitioned back to fostamatinib after approximately 1 month of overlap.

Case Study 2

In the second case, the patient had poor tolerance and QOL in response to initial treatment with corticosteroids (anxiety) and subsequent therapy with eltrombopag (headache/arthritis). In this case, the patient preferred the combination treatment approach with eltrombopag and fostamatinib in order to manage his platelet counts, reduce his anxiety level, and achieve a better QOL.

Case Study 3

The third case highlights a patient who was highly refractory to typical therapy: IVIG, corticosteroids, and romiplostim. This patient (as in case study 2) was started on a combination approach of a TPO-RA and fostamatinib without adverse events. When the patient's platelet count rose too high, abrupt discontinuation of romiplostim led to

severe thrombocytopenia. On the second attempt, the dose of romiplostim was gradually decreased over several weeks with successful transition to monotherapy with fostamatinib. In the absence of drug toxicity, this approach demonstrates that (1) combination therapy may be safe for short periods of time, and (2) a gradual taper of a TPO-RA is warranted to prevent abrupt fluctuations in platelet count. As shown in case study 1, dangerous thrombocytopenia from abrupt discontinuation of TPO-RAs can be harmful to the patient, especially if on anticoagulation. It is imperative to recognize these transition strategies in practice to minimize harm to patients.

Case Study 4

Cases 4 and 5 illustrate lack of platelet response to available agents; thus, the need for combination therapy is appealing. In case study 4, a combination of maintenance rituximab, weekly romiplostim, and fostamatinib was used for sufficient platelet control. While theoretically controlling platelets using three unique mechanisms sounds plausible, there is a lack of randomized trials and real-world experience highlighting this strategy. However, this report demonstrates a safe transition without side effects or dramatic fluctuations in platelet counts that could potentially lead to more thrombotic and/or bleeding events.

Case Study 5

As seen in case study 5, another common challenge in practice is the unpredictability of platelet counts in response to available treatment options. Here, a combination approach was used in order to overcome the refractory disease and achieve platelet stabilization. Furthermore, a gradual taper of avatrombopag provided adequate platelet response without abrupt fluctuations requiring rescue medication or thrombocytosis.

CONCLUSION

There is a paucity of data available recognizing combination, bridging, and switching approaches for the treatment of chronic ITP. However, combining, bridging, and/or switching agents with differing, novel mechanisms may be warranted to achieve better platelet stabilization and ultimately prevent complications of poorly controlled ITP.

The unpredictability and volatility of platelets, and increased risk of thrombotic events observed with TPO-Ras, along with patient preference, may influence treatment decisions and are some factors that may warrant switching from a TPO-RA to fostamatinib.

While long-term follow-up data showing platelet stability in the combination setting is not available, this case series provides some clinical insights into the initial management of patients on both fostamatinib and a TPO-RA (in combination), and during a transitional period of tapering off and/or switching. Operational barriers, such as insurance coverage, may be obstacles that limit the utility of these combinations in the absence of clinical trials. Further real-world evidence should be published in this setting to provide guidance to providers in managing ITP where combination or bridging may be needed to optimize patient clinical outcomes. ●

Disclosure

Dr. Hughes, Dr. Toste, Mr. Nelson, and Ms. Escalon have participated on an advisory board for Rigel Pharmaceuticals. Mr. Shah has served on the speakers bureau for Rigel Pharmaceuticals.

References

- Amgen Inc. (2008). Nplate (romiplostim) package insert. https://www.pi.amgen.com/united_states/nplate/nplate_pi_hcp_english.pdf
- Bussel, J., Arnold, D. M., Grossbard, E., Mayer, J., Treliński, J., Homenda, W.,...Duliege, A.-M. (2018). Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials. *American Journal of Hematology*, *93*(7), 921–930. <https://doi.org/10.1002/ajh.25125>
- Cines, D. B., Bussel, J. B., Liebman, H. A., & Luning Prak, E. T. (2009). The ITP syndrome: Pathogenic and clinical diversity. *Blood*, *113*(26), 6511–6521. <https://doi.org/10.1182/blood-2009-01-129155>
- Cines, D. B., Cuker, A., & Semple, J. W. (2014). Pathogenesis of immune thrombocytopenia. *La Presse Médicale*, *43*(4), e49–e59. <https://doi.org/10.1016/j.lpm.2014.01.010>
- Despotovic, J. M. (2018). Emerging therapies in immune thrombocytopenia. *Hematologist*, *15*(4). <https://doi.org/10.1182/hem.v15.4.8728>
- Dova Pharmaceuticals, Inc. (2018). Doptelet (avatrombopag) package insert. https://dova.com/pdf/prescribing-information_patient-labeling.pdf
- Fu, Y., Cheng, Y., & Wu, Y. (2020). Understanding SARS-CoV-2-mediated inflammatory responses: From mechanisms to potential therapeutic tools. *Virologica Sinica*, *35*(3), 266–271. <https://doi.org/10.1007/s12250-020-00207-4>
- GlaxoSmithKline. (2015). Promacta (eltrombopag) package insert. <https://www.novartis.us/sites/www.novartis.us/files/promacta.pdf>
- Liu, D., & Mamorska-Dyga, A. (2017). Syk inhibitors in clinical development for hematological malignancies. *Journal of Hematology & Oncology*, *10*(1). <https://doi.org/10.1186/s13045-017-0512-1>
- McMillan, R. (2000). The pathogenesis of chronic immune (idiopathic) thrombocytopenic purpura. *Seminars in Hematology*, *37*, 5–9. [https://doi.org/10.1016/s0037-1963\(00\)90111-2](https://doi.org/10.1016/s0037-1963(00)90111-2)
- Nadeem, A., Ahmad, S. F., Al-Harbi, N. O., Al-Harbi, M. M., Ibrahim, K. E., Kundu, S.,...AlSharari, S. D. (2019). Inhibition of spleen tyrosine kinase signaling protects against acute lung injury through blockade of NADPH oxidase and IL-17A in neutrophils and $\gamma\delta$ T cells respectively in mice. *International Immunopharmacology*, *68*, 39–47. <https://doi.org/10.1016/j.intimp.2018.12.062>
- Neunert, C., Terrell, D. R., Arnold, D. M., Buchanan, G., Cines, D. B., Cooper, N.,...Vesely, S. K. (2019). American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Advances*, *3*(23), 3829–3866. <https://doi.org/10.1182/bloodadvances.2019000966>
- Newland, A., & McDonald, V. (2020). Fostamatinib: A review of its clinical efficacy and safety in the management of chronic adult immune thrombocytopenia. *Immunotherapy*, *12*(18), 1325–1340. <https://doi.org/10.2217/imt-2020-0215>
- Provan, D., Arnold, D. M., Bussel, J. B., Chong, B. H., Cooper, N., Gernsheimer, T.,...Wong, R. S. (2019). Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Advances*, *3*(22), 3780–3817. <https://doi.org/10.1182/bloodadvances.2019000812>
- Rigel Pharmaceuticals. (2018). Tavalisse (fostamatinib) package insert. <https://tavalisse.com/downloads/pdf/Tavalisse-Full-Prescribing-Information.pdf>