Successful Use of Eltrombopag in a Pediatric Patient With Human Immunodeficiency Virus (HIV)–Associated Thrombocytopenia

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Thrombocytopenia and other hematologic manifestations related to HIV are not uncommon. Treatment of HIV-related thrombocytopenia is challenging: treatment options are not effective in all patients, or less well studied, particularly in the pediatric population. We aim to present and discuss the case of a 13-year-old with HIV and persistent thrombocytopenia who, after failing monthly IVIG infusions, showed normalization of platelet count on the novel thrombopoietin receptor agonist, eltrombopag. A retrospective chart review of the case patient's medical record was conducted. Additionally, a thorough literature review was performed on this topic, including the pathophysiology of underlying HIV-related thrombocytopenia and its treatment modalities. The patient was treated initially with monthly IVIG infusions for about 1 year but did not show a sustained response, particularly in between infusions. After initiation with eltrombopag 50 mg daily, the patient showed a sustained increase in his platelet count. During a brief lapse in eltrombopag treatment, his platelet count dropped, which then increased upon his reinitiation of therapy. He has continued to show a sustained platelet response and has not been symptomatic or required IVIG for more than 1 year. To our knowledge, this is the first report of a pediatric patient with HIV-related thrombocytopenia who has benefited from the use of eltrombopag.

ABBREVIATIONS ARV, antiretroviral; HIV, human immunodeficiency virus; ITP, idiopathic thrombocytopenic purpura; IVIG, intravenous immunoglobulin

KEYWORDS eltrombopag; HIV; pediatric; refractory thrombocytopenia; thrombocytopenia; thrombopoietic growth factors

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Introduction

Hematologic manifestations related to human immunodeficiency virus (HIV) infection are not uncommon, with thrombocytopenia having an estimated prevalence ranging from 5% to 15%.¹ The pathophysiology is likely multifactorial. Recent studies have suggested that the primary mechanism may be immunologic, resulting in accelerated platelet destruction. Additional theories have suggested that infection of megakaryocytes themselves may also play a role causing inadequate platelet production.¹ Treatment of HIV-related thrombocytopenia is challenging. First-line treatment modalities include initiation and optimization of antiretroviral (ARV) therapies, intravenous immunoglobulin (IVIG), and glucocorticoids.

We report the case of a 13-year-old with HIV and persistent thrombocytopenia who, after failing first-line therapies, showed normalization of platelet count on the novel thrombopoietin receptor agonist eltrombopag. To our knowledge, this is the first report of a pediatric patient with HIV-related thrombocytopenia who has benefited from the use of eltrombopag.

Patient Summary

Our patient is a 13-year-old male with perinatally acquired HIV infection, which was diagnosed after having several episodes of thrush. His initial labs on presentation included a white blood cell count of $1.5 \times 10^3/\text{mCL}$ with CD4 T cells less than 1% and a viral load of 50,000 copies/mL. At the time of diagnosis his platelet count was found to be $18 \times 10^3/\text{mCL}$, but he was asymptomatic, without clinical evidence of bruising or bleeding. He was started on an ARV regimen of lamivudine/zidovudine (150 mg/300 mg tablet, 1 tablet twice daily; Combivir, GlaxoSmithKline, Research Triangle Park, NC) and lopinavir/ritonavir (200 mg/50 mg tablet, 2 tablets twice daily; Kaletra, AbbVie, North Chicago, IL). He initially required several platelet transfusions and underwent a bone marrow biopsy, which was normal. His ARV regimen was changed to abacavir (300-mg tablet, 1 tablet twice daily; Ziagen, GlaxoSmithKline), lamivudine (150-mg tablet, 1 tablet twice daily; Epivir, GlaxoSmithKline), and raltegravir (400-mg tablet, 1 tablet twice daily; Isentress, Merck, Whitehouse Station, NJ), to avoid drug interactions with other medications.

and to change to a ritonavir-sparing regimen. On the new regimen, the patient continued to show improvement in CD4 count and by about 3 months after initiation of treatment his viral load was undetectable. However, despite showing response to ARV therapy he continued to show persistent thrombocytopenia.

In order to maintain a platelet count greater than $10 \times 10^3/\text{mCL}$ he was initiated on a monthly infusion of IVIG (Privigen, CSL Behring, Bern, Switzerland). He showed good response to infusions, but this response was not sustained. His platelet count would drop between infusions, often less than $10 \times 10^3/\text{mCL}$, and he would present with epistaxis. In an effort to further improve platelet counts, his ARV regimen was modified to dolutegravir (50-mg tablet, 1 tablet daily; Tivicay, GlaxoSmithKline), abacavir (300-mg tablet, 2 tablets daily), and emtricitabine (200-mg tablet, 1 tablet daily; Emtriva, Gilead Sciences Inc, Foster City, CA), because these agents have a reportedly lower incidence of contributing to thrombocytopenia. With this change he showed a modest increase in platelet count, but it was short-lived. Anti-D immunoglobulin was not used in this patient because the platelet response would have been expected to be similar to IVIG. Steroids were avoided in this patient because of a fear of immunosuppression with chronic steroid use, exacerbating his acquired immunodeficiency.

After almost 2 years of suboptimal response to first-line therapies he was trialed on eltrombopag (Promacta, Novartis, East Hanover NJ), a novel thrombopoietin receptor agonist, at 50 mg orally per day, resulting in a sustained response with platelet count above $30 \times 10^3/\text{mCL}$ (range, $32 \times 10^3/\text{mCL}$ to $88 \times 10^3/\text{mCL}$). The patient had an initial alanine transaminase level of 78 U/L and aspartate transaminase level of 39 U/L which was thought to be due to his antiviral medications. Upon starting eltrombopag his liver function tests remained stable and subsequently decreased to normal. Because of issues with his insurance, he was unable to take eltrombopag for 2 weeks and his platelet count dropped to $17 \times 10^3/\text{mCL}$; however, upon reinitiation of therapy it rose to $84 \times 10^3/\text{mCL}$. He has continued to show a sustained response, without need for additional IVIG infusions, for more than 1 year. In addition, the ability to take a once-daily medication at home significantly enhanced the patient's overall well-being because he no longer required monthly IVIG infusions, and with the improvement in his platelet count he was no longer symptomatic.

Discussion

Thrombocytopenia in HIV. A study by Sullivan et al² has shown the prevalence of patients with HIV and unexplained thrombocytopenia lasting greater than 4 weeks reached upwards of 3.2%. The incidence and causes of thrombocytopenia in HIV are multifactorial and may include primary or acquired etiologies, or may

be associated with coinfection with hepatitis B or hepatitis C virus, or persistent HIV viremia.³ The incidence of platelet abnormalities seems to correlate with increased immunosuppression as a result of disease progression. Cytopenias may also result from underlying opportunistic infections. Medication use may also have a causal relationship with thrombocytopenia; however, ARV therapy may reverse the thrombocytopenia frequently seen in patients with HIV. Although the rate of adverse events, specifically cytopenias and thrombocytopenias, has decreased with the advent of newer ARV therapies, the rate of patients with platelet counts less than $150 \times 10^3/\text{mCL}$ remains at 10% to 15%.⁴ There are several ARV therapies that may contribute to thrombocytopenia, which are shown in the Table.

Immune dysregulation may be the primary reason for thrombocytopenia in HIV patients, owing to reduced platelet survival and ineffective platelet production. HIV infection has been shown to destroy platelets because of the presence of platelet antibodies on the glycoprotein IIb/IIIa complex, leading to apoptosis. Additionally, antibodies found on platelets encourage destruction: macrophages bind to the Fc regions on antibody- or immune complex-bound platelets and are then eliminated via phagocytosis.^{5,6} HIV infection has been shown to impair the clearance of Fc regions, which may also explain thrombocytopenia in this patient population. Additionally, HIV can be directly linked to impaired platelet production through the infecting of platelet progenitor cells, leading to structural abnormalities and impairment of platelet development and maturity, leading to reduced platelet production.⁷⁻⁹

Patients who have HIV-associated thrombocytopenia should initially be optimized on ARV therapy, if not done already. The ARV regimen should include medications in which the incidence of thrombocytopenia is low. There are some reports that zidovudine may increase platelet count in HIV patients.¹⁰⁻¹²

Medications Used in Patients With HIV-Related Thrombocytopenia. In patients who have HIV with thrombocytopenia, the management begins with initiation of ARV therapies.¹²⁻¹⁶ Antiretrovirals, specifically zidovudine, can typically increase the platelet counts of these patients (Table). If the ARV regimen or the addition of zidovudine is not successful in increasing platelet count, additional modalities may be considered.

Intravenous immunoglobulin produces a rapid increase in most of the patients in whom it is used; however, the response is not sustained and may need to be repeated in several doses. Intravenous immunoglobulin has a risk of infusion-related reactions and is infused during the course of several hours, typically in a monitored setting. Intravenous immunoglobulin is thought to prevent platelet destruction by saturating Fc receptor sites on the platelets that are coated with antibodies, thereby decreasing phagocytosis of the platelets.¹⁷

Table. Reported Incidence of Thrombocytopenia With Antiretroviral Agents^{33–46}

Therapeutic Class	Agent*	Reported Incidence of Thrombocytopenia
Nucleoside reverse transcriptase inhibitors	Abacavir	1%
	Didanosine	Not defined
	Lamivudine	1%–4%
	Stavudine	Not defined
	Zidovudine	1%
Nonnucleoside reverse transcriptase inhibitors	Delavirdine	Not defined
Protease inhibitors	Lopinavir/ritonavir	4%
	Atazanavir	Not defined
	Indinavir	<1%
	Nelfinavir	Not defined
	Ritonavir	5%
	Saquinavir	Not defined
	Tipranavir	Not defined
Integrase inhibitors	Raltegravir	≤3%
CCR5 antagonist	Maraviroc	Frequency not defined (bone marrow suppression)
Fusion inhibitor	Enfuvirtide	Frequency not defined

ARV, antiretroviral; CCR5, C-C chemokine receptor type 5

* Thrombocytopenia has not been reported with the following ARV agents: tenofovir alafenamide, tenofovir disoproxil fumarate, etravirine, efavirenz, rilpivirine, darunavir, fosamprenavir, dolutegravir, elvitegravir, cobicistat (pharmacokinetic booster).

Glucocorticoids, including dexamethasone and prednisone, may also be considered to increase platelet count. The duration of therapy should be limited because of side effects, including hyperglycemia, cushingoid response, osteopenia, and weight gain. The use of steroids in pediatric patients should be limited in part because of their effects on growth and bone development.

The off-label use of anti-D immunoglobulin is another novel option. It works by binding to the erythrocyte Rh(D) antigen, allowing the anti-D–bound erythrocytes to competitively bind to the Fc receptors in the spleen, which reduces the destruction of antibody-coated platelets and increases the platelet count.¹⁸ Anti-D immunoglobulin may be loaded as an IV dose and given as repeated maintenance doses every 3 to 4 weeks either intramuscularly or IV. The frequency is determined by clinical response. The IV infusion is typically less than 5 minutes. Significant adverse effects may include anemia from drops in hemoglobin, which should be monitored regularly. The platelet count response is more effective and more sustained compared with IVIG.¹⁹

Other options that may be considered for off-label use include dapsone,²⁰ danazol,²¹ interferon alfa,^{22,23} vincristine,²⁴ thrombopoietic growth factors, including romiplostim and eltrombopag, or splenectomy. We discuss eltrombopag in the next section.

Eltrombopag. Recent consensus guidelines created by the American Society of Hematology and a recent

International Consensus Report for the management and treatment of idiopathic thrombocytopenic purpura (ITP) suggest that first-line treatment options for ITP include IVIG, anti-D, and corticosteroids.^{25,26} Second-line therapies for adults and children who do not respond to first-line treatment include splenectomy, rituximab, thrombopoietin receptor agonists, larger-dose dexamethasone, and immunosuppression. Thrombopoietin receptor agonists stimulate the c-mpl (TpoR) receptor on the megakaryocyte, thereby increasing platelet production. The 2 thrombopoietin receptor agonists now approved for adults with chronic ITP refractory to first-line therapies are eltrombopag and romiplostim, based on data from phase 3 randomized trials.^{27–29} Eltrombopag is given daily by mouth, whereas romiplostim is generally given weekly as a subcutaneous injection. In addition, other uses for these agents are for treatment of thrombocytopenia secondary to hepatitis C–induced cirrhosis and severe aplastic anemia.

The efficacy and safety of eltrombopag for the treatment of children with chronic ITP and platelet counts less than $30 \times 10^3/\text{mCL}$ were established in the petit and petit2 studies, which demonstrated a 40% sustained response to the medication, as defined as a platelet count of $50 \times 10^3/\text{mCL}$ for 6 of 8 weeks in the study.^{30,31} Based on this study, eltrombopag is now approved for children ages 1 to 18 years with chronic ITP refractory to first-line treatment or splenectomy. Recently a phase 3 study for romiplostim was released demonstrating efficacy with no new safety concerns.³² Generally, the

goal of these medications is to achieve a “safe” platelet level of roughly $50 \times 10^3/\text{mL}$ and not to achieve a normal platelet count, and therefore their use is limited to those patients with very low platelet counts. Other side effects include increased transaminases. Because of this, monitoring of bilirubin, aspartate transaminase, and alanine transaminase is suggested. To date, there are few reports of thrombopoietin receptor agonist use in ITP secondary to HIV, and to date none that we are aware of in children. Regarding cost, eltrombopag use for 1 month is roughly equivalent to 1 IVIG infusion.

Conclusion

HIV-related thrombocytopenia can be a challenge to treat. First-line therapies, including IVIG and glucocorticoids, are not effective in all patients. Several other treatment modalities have been tried, including anti-D immunoglobulin, dapsone, danazol, interferon alfa, vincristine, thrombopoietic growth factors, including romiplostin and eltrombopag, or splenectomy, but these are less well studied. To our knowledge this is the first reported case of a pediatric patient who showed a positive response to eltrombopag with a sustained improvement in platelet count and no adverse effects from treatment. Eltrombopag may be a safe alternative to first-line therapies in those patients with HIV and refractory thrombocytopenia; however, additional studies are needed.

ARTICLE INFORMATION

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