Successful Treatment of Amegakaryocytic Thrombocytopenia With Eltrombopag in a Patient With Systemic Lupus Erythematosus (SLE)

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Introduction

Systemic lupus erythematosus (SLE) is an inflammatory connective tissue disease mediated by a deregulated immune system and aberrant production of proinflammatory cytokines leading to multiorgan and tissue damage. Thrombocytopenia is a common complication in patients with SLE, with a prevalence that ranges from 7–30%.1–3 The 2 main mechanisms of thrombocytopenia in SLE are increased platelet destruction mediated by antiplatelet autoantibodies, similar to the mechanism seen in immune thrombocytopenic purpura (ITP), and impaired thrombopoiesis, due to the absence of or a decreased number of megakaryocytes in the bone marrow. The latter disorder is also known as amegakaryocytic thrombocytopenia (AMT). T-cell–mediated and antibody-mediated suppression of megakaryocyte colony formation have both been reported as possible mechanisms of AMT.1 Similar to ITP, treatment modalities include immunosuppressive agents such as prednisone, immunomodulators such as intravenous immunoglobulin (IVIG), and splenectomy. We report a case of SLE-associated AMT successfully treated with eltrombopag (Promacta, GlaxoSmithKline), a thrombopoietin (TPO) nonpeptide mimetic that binds to and activates the TPO receptor leading to increased production of megakaryocytes and platelets. To our knowledge, this is the first reported case of eltrombopag use in SLE-associated AMT.

Case Report

The patient is a 55-year-old African American woman with a medical history of SLE first diagnosed in 1995, fibromyalgia, and Raynaud’s phenomenon. She presented in March 2009 to the emergency room complaining of chest pain and was noted to have a platelet count of 28,000/mm3. The hematology consult service was called for evaluation of thrombocytopenia. The patient’s medications included prednisone 10 mg daily, alendronate, aspirin, and a 5-year history of mycophenolate use that was discontinued several weeks prior to the emergency room visit due to thrombocytopenia (platelet count at that time was 50,000/mm3). Her physical exam was unremarkable; there was no bruising, no active bleeding, and no evidence of hepatosplenomegaly or lymphadenopathy. Laboratory data were as follows: platelets 28,000/mm3, white blood cell count 5.16 × 109/L, hemoglobin 12.7 g/L, normal hepatic and renal function, and normal coagulation studies. The peripheral smear confirmed a reduced platelet estimate with no platelet clumps, normal platelet morphology, and no other cell abnormalities. A bone marrow biopsy and aspiration were performed, showing a normocellular marrow with trilineage maturation but with markedly decreased megakaryocytes (Figure 1). There was no increase in blast cells or dysplasia, and cytogenetic analysis revealed a normal female karyotype.

Based on the bone marrow biopsy findings, review of laboratory values, and lack of response to mycophenolate withdrawal, the diagnosis of amegakaryocytic thrombocytopenia was rendered. Prednisone was increased to 70 mg daily, with no improvement in thrombocytopenia over a course of 3 weeks; therefore, rituximab (Rituxan,
Genentech) therapy was initiated. The patient received 8 cycles of weekly rituximab over the following 2 months, with platelet counts remaining low and never exceeding 30,000/mm³. During that time, the patient developed hematuria, necessitating platelet transfusions, which prevented further bleeding but resulted in only a transient and modest increase in platelet count. Considering the lack of response to corticosteroids and rituximab, cyclosporine 150 mg daily was started, but it was discontinued after 1 week of therapy due to intolerability. Given the failure of the above therapies, we hypothesized that if the mechanism of thrombocytopenia in this patient was a result of autoantibodies to the TPO receptor, we might be able to bypass such blockade by using eltrombopag (Promacta, GlaxoSmithKline) to stimulate the TPO receptor. Eltrombopag is a nonpeptide TPO mimetic that binds to and activates the TPO receptor at a different site from endogenous TPO. After 2 weeks of treatment with oral eltrombopag at 50 mg daily, the patient’s platelet count increased from 22,000 to 64,000/mm³—the highest level since the onset of thrombocytopenia several months earlier. Six weeks after initiation of eltrombopag, the patient’s platelet count increased to 179,000/mm³.

Discussion

ITP is an autoimmune condition in which platelets are opsonized by autoantibodies and prematurely taken up by the reticuloendothelial system, leading to thrombocytopenia. Thrombocytopenia is a common complication in patients with SLE. Autoantibodies to 2 platelet-specific antigens, glycoprotein IIb/IIIa (GPIIb/IIIa) and TPO receptor (c-Mpl), are believed to contribute to thrombocytopenia in patients with SLE. The anti-GPIIb/IIIa antibody binds circulating platelets and facilitates Fcγ receptor-mediated clearance of opsonized platelets by reticuloendothelial phagocytes, similar to the mechanism of platelet destruction in ITP, whereas the anti-TPO receptor antibody blocks TPO signaling, resulting in inhibition of megakaryogenesis in the bone marrow. There are several reports of patients with amegakaryocytic thrombocytopenia, which is associated with impaired thrombopoiesis due to selective absence of megakaryocytes in the bone marrow in the presence of otherwise normal hematopoiesis. In one study of SLE patients with thrombocytopenia, anti-TPO receptor–positive patients had significantly higher frequencies of amegakaryocytic thrombocytopenia with megakaryocyte hypoplasia and poorer therapeutic responses to corticosteroids and IVIG than did anti-TPO receptor–negative patients; notably, most patients in the latter group had anti-GPIIb/IIIa antibody alone.

TPO was first characterized as a megakaryocyte-stimulating factor in the early 1990s by several teams of investigators. TPO binds to its receptor (c-Mpl) on the megakaryocyte membrane and stimulates platelet production and megakaryocyte proliferation and differentiation via phosphorylation of JAK2/STAT5 and MAPK pathways. TPO is mainly produced in the liver, and one suggested model of TPO regulation is a simple feedback loop, where a fall in platelet count results in increased TPO and increased megakaryocyte c-Mpl binding. As expected, levels were found to be increased in amegakaryocytic thrombocytopenia, but surprisingly they were minimally if at all elevated in patients with chronic ITP. TPO levels may identify a special group of SLE patients with AMT that are likely to benefit from therapies other than corticosteroids.

ITP therapy targets the immunologically mediated destruction of platelets with the use of immunosuppressive
agents (eg, corticosteroids, azathioprine), immunomodulation (eg, gamma globulin preparations, monoclonal antibodies), and removal of site of destruction (splenectomy, splenic irradiation). Rituximab, an anti-CD20 chimeric antibody, has been used as a second-line therapy in thrombocytopenia, including SLE-associated amegakaryocytic thrombocytopenia. CD20 is expressed on most stages of B cells, such as immature B cells, naïve B cells, memory B cells, and germinal center B cells, but not early pro-B cells or plasma cells. Rituximab may suppress pathogenic B-cell clones that produce anti-TPO receptor antibodies that are resistant to conventional immunosuppressive therapy, including prednisone and cyclosporine. There is, however, a risk of severe infection with rituximab therapy. In 2006, the US Food and Drug Administration (FDA) alerted physicians to the danger of using rituximab in patients with SLE, after 2 patients treated with the drug died due to progressive multifocal encephalopathy caused by reactivated JC virus. Cyclosporine therapy can be effective in amegakaryocytic thrombocytopenia at a starting dose of 5 mg/kg/day orally, with a target level of 150–350 µg/mL. Cyclosporine takes several weeks to exert its effects, and doses can be tapered with 11 months to exert its effects, and doses can be tapered with normalizing of platelet counts.

Findings of impaired megakaryocyte maturation and platelet production suggested the possibility of megakaryocyte stimulation as a treatment strategy. Recombinant human megakaryocyte growth and development factor, coupled with a polyethylene glycol moiety (PEG-rHuMGDF), was effective in increasing platelets in ITP; however, trials with this drug were stopped due to thrombocytopenia caused by antibodies against PEG-rHuMGDF that crossreacted with native TPO. Although sequence homology with TPO limited the clinical usefulness of this molecule, the knowledge that was gained led to the development of TPO peptide and nonpeptide mimetics. These have high affinity for the TPO receptor, they induce phosphorylation of JAK2 and STAT5 in TPO-dependent cell lines, and they increase megakaryocyte differentiation. The TPO nonpeptide mimic eltrombopag is a small (molecular weight=442 Da), orally available, nonpeptide molecule that has been shown to stimulate TPO-dependent cell lines via JAK2 and STAT signaling pathways to proliferation, megakaryocyte differentiation, and platelet production. It interacts with the transmembrane portion of the TPO receptor rather than at the site of native TPO binding. In studies in which eltrombopag was administered to healthy male volunteers daily for 10 days, a dose-dependent increase in platelet count began at 8 days and peaked at 16 days. In a double-blind randomized-controlled study evaluating the efficacy of eltrombopag at 3 different dose levels in patients with ITP, the primary endpoint of platelet count greater than 50,000/mm³ was achieved in 28%, 79%, and 81% of patients receiving 30, 50, and 75 mg, respectively. In the placebo group, the endpoint was achieved in 11% of patients. The median platelet counts on day 43 for the groups receiving 30, 50, and 75 mg of eltrombopag were 26,000/mm³, 128,000/mm³, and 183,000/mm³, respectively. By day 15, more than 80% of patients receiving 50 or 75 mg of eltrombopag daily had an increased platelet count. Bleeding also decreased during treatment in the 2 groups. The incidence and severity of adverse events were similar in the placebo and eltrombopag groups.

Safety data from 4 randomized, double-blind, placebo-controlled phase II or III studies of eltrombopag that included 485 thrombocytopenic patients with ITP, hepatitis C virus, or chemotherapy-induced thrombocytopenia have been reported. Long-term safety of eltrombopag in ITP is being evaluated in an ongoing, open-label extension trial (EXTEND). Most reported adverse events were mild in severity, headache being the most commonly reported adverse event (17%). Eight patients developed an increase in alanine aminotransferase and hyperbilirubinemia and 2 had pulmonary emboli. Patients who had a history of arterial or venous thrombosis and known risk factors for thrombosis and patients with a history of cardiovascular disease were excluded from eltrombopag trials. Of particular importance is the development of reticulin/collagen deposition in 9 of 19 bone marrow biopsies performed on patients on eltrombopag for at least 13 months. Baseline bone marrow evaluation, however, was not available, so no association could be determined. In earlier studies, administration of very high doses of PEG-rHuMGDF to mice for 7–10 days produced reversible bone marrow reticulin. Furthermore, overexpression of thrombopoietin in mice by transplantation of c-Mpl transfected bone marrow cells caused extensive bone marrow fibrosis, osteosclerosis, and extramedullary hematopoiesis similar to the human disease chronic idiopathic myelofibrosis. Whether eltrombopag might also lead to these changes in the bone marrow has not yet been assessed by bone marrow examination studies. Another potential risk of thrombopoietic growth factor therapy is thrombocytosis. Data from studies of first-generation thrombopoietic growth factors, however, showed that thrombocytosis did not increase the rate of thrombosis, even in patients with cancer. These studies excluded patients with active cardiac or cerebrovascular disease or history of thrombosis. Despite the potential risk of cataract development, thrombosis, thrombocytosis, increased bone marrow reticulin or collagen deposition, tumor/leukemia cell growth, and formation of neutralizing antibodies cross-reactive with native thrombopoietin, studies conducted...
thus far have not yet shown a definite association between eltormbopag and these adverse events.

Two additional TPO mimetics are noteworthy. AKR-501 is a TPO nonpeptide agonist that activates the TPO receptor leading to an increase in megakaryocyte production and platelet counts. Single and multiple oral doses have been tested, and it was found that single doses of 20 mg or more produced a rise in platelet counts as high as 1.75 times the baseline platelet count. No significant side effects were reported. Clinical studies of this drug in ITP, liver disease, and chemotherapy are planned.9 Romiplostim (AMG-531; Nplate) is an engineered peptide TPO mimetic that leads to a dose-dependent increase in platelet count at doses above 1 µg/kg. Phase II and phase III clinical trials of romiplostim in ITP had response criteria similar to those of the eltrombopag studies. Reported adverse events were generally mild and were similar to placebo. Based on efficacy and safety data, the FDA approved romiplostim for ITP patients who had failed at least one prior therapy. The approved initial dose is 1 µg/kg subcutaneously once weekly, with escalation up to 10 µg/kg to reach goal platelet response.11

Conclusion

Thrombocytopenia is a common complication of SLE. Two mechanisms have been proposed for SLE-associated thrombocytopenia, the main mode being peripheral destruction due to platelet autoantibodies, similar to what occurs in ITP. In a small subset of SLE patients, thrombocytopenia is a result of ineffective thrombopoiesis caused by autoantibodies to the TPO receptor that ultimately leads to suppressed megakaryocyte production in the bone marrow and amegakaryocytic thrombocytopenia. This latter group tends to be refractory to corticosteroid and IVIG therapy. Rituximab has been used successfully in the setting of amegakaryocytic thrombocytopenia in some SLE patients, with the main limitations being the potential for severe infection and cost. Cyclosporine has also been utilized with some success in amegakaryocytic thrombocytopenia. TPO receptor agonists are a new group of agents that have proven very effective in ITP. Eltormbopag is an oral medication in this class that acts by stimulating the TPO receptor at a site separate from endogenous TPO, leading to effective megakaryocyte production and an increase in platelet counts. In SLE patients with amegakaryocytic thrombocytopenia who are refractory to other treatments, as in the case of our patient, it may be reasonable to attempt a course of eltormbopag until improvement in platelet counts is achieved, typically in approximately 2 weeks. The long-term safety profile and toxicity of eltormbopag remain to be defined.

References


Review

Acquired Amegakaryocytic Thrombocytopenia: Potential Role of Thrombopoietin Receptor Agonists

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Cela and colleagues report the use of eltormbopag in a 55-year-old woman with systemic lupus erythematosus (SLE) who developed acquired amegakaryocytic thrombocytopenia (AMT) approximately 14 years after diagnosis.1 Initially refractory to corticosteroids and rituximab (Rituxan, Genentech), and intolerant of cyclosporine,
she experienced an excellent response to the second-generation thrombopoietin receptor (TPOR) agonist. This interesting case gives us the opportunity to explore current concepts in the pathophysiology and management of AMT.

SLE is a multisystem disorder with wide-ranging clinical and laboratory manifestations. Of these, thrombocytopenia is a more common finding, with platelet counts less than $100 \times 10^9/L$ found in 8–30% of patients. However, less than 3% of patients have counts below $20 \times 10^9/L$, which is associated with a significant risk of bleeding and usually requires treatment. Purported mechanisms leading to thrombocytopenia in SLE include antibody-mediated platelet destruction and inhibition of megakaryopoiesis by antibodies directed against the TPOR (cMpl). Predictably, the antibody present dictates the clinical features: patients with anti-GPIIb/IIIa antibodies have normal or increased bone marrow megakaryocyte density and, similar to patients with immune thrombocytopenic purpura (ITP), show a good response to conventional immunosuppression. Those with anti-TPOR antibodies demonstrate megakaryocytic hypoplasia and have a poor response to steroids and intravenous immunoglobulin.

AMT is a rare disorder characterized by isolated thrombocytopenia that is often severe (platelet count <20–30 $\times 10^9/L$), as a consequence of a marked decrease or total absence of megakaryocytes in an otherwise normal bone marrow. The prevalence of AMT is unknown, and the literature is limited to case reports and other anecdotal evidence. It can occur alone as an idiopathic entity; in association with lymphoproliferative disorders, SLE, and other autoimmune diseases, infections, solid tumors, nutritional vitamin B12 deficiency, and ethanol abuse; or after exposure to drugs. AMT can also be the initial manifestation of bone marrow disorders such as myelodysplastic syndromes or aplastic anemia.

Due in part to its rarity and in part to its heterogeneous nature, the pathogenetic mechanisms of this disorder have not been well defined; in fact, its etiology is likely to be diverse. Chromium-tagged platelet survival studies in patients with AMT show no evidence of premature platelet destruction or sequestration. In keeping with these findings, cell culture studies have identified intrinsic defects in the progenitor cell of the megakaryocytic lineage (CFU-Mk). Subsequent studies have suggested that AMT can develop as a consequence of cell-mediated inhibition or destruction of megakaryocytes, possibly by monocytes or a clonal population of T-lymphocytes. Contrary to this, in vitro inhibition of megakaryocyte precursor colonies by the addition of plasma from patients with AMT supports the involvement of the humoral immune system. Both anti-TPO and anti-cMpl autoantibodies have been described, which may functionally inhibit the hormonal stimulation of megakaryocytic progenitors by thrombopoietin. These findings, in particular, suggest that thrombocytopenia in SLE may overlap with AMT. Alternatively, AMT may simply be an extreme manifestation of immune-mediated thrombocytopenia in SLE.

There is an interesting comparison to be made with ITP. Although the underlying disease mechanism in ITP has traditionally been recognized as accelerated platelet destruction, recent research has suggested that impaired platelet production also contributes to thrombocytopenia. Since the underlying immune dysregulation in both appears to be similar, one might argue that AMT is just an ITP variant with a decreased number of megakaryocytes. As such, the current definition of ITP might incorporate cases of AMT unrelated to conditions such as SLE or lymphoproliferative disorders.

A wide range of therapies have been used in patients with AMT, including conventional immunosuppressive agents, anti-thrombocytopenic purpura (ITP), show a good response to conventional immunosuppression. Those with anti-TPOR antibodies demonstrate megakaryocytic hypoplasia and have a poor response to steroids and intravenous immunoglobulin. The use of TPO analogs in refractory AMT seems to be a logical choice. Two second-generation TPO agonists, romiplostim (Nplate, Amgen) and eltrombopag (Promacta, GlaxoSmithKline), have been recently licensed for use in patients with primary immune thrombocytopenia (ITP). Romiplostim is a peptide that, like endogenous TPO, binds the external cytokine receptor homology (CRH) domain of the TPO. Eltrombopag is a small nonpeptide molecule that interacts with the transmembrane domain of TPO at a site distant from the CRH domain.

In randomized, placebo-controlled, phase III trials, the use of either romiplostim or eltrombopag in patients with chronic ITP unresponsive to conventional ITP therapies or refractory to splenectomy resulted in platelet response rates (platelet count elevation ≥50 $\times 10^9/L$ for at least 6 of the last 8 weeks in the 6-month treatment period) in excess of 70%. These drugs are tolerated well, but the lack of long-term safety data (median 1 year for eltrombopag; 3 years for romiplostim) remains a concern. That said, their use continues to be appealing for a number of reasons: they are not blood products and thus the risk of viral transmission is avoided and, unlike the majority of conventional therapies for immune thrombocytopenia, they are not immunosuppressive.

Returning to the 55-year-old woman described in the case report, the use of eltrombopag is a rational
decision, following failure of a number of conventional immunosuppressive therapies. Both eltrombopag and romiplostim have been shown to be efficacious in similar scenarios in ITP, and because no head-to-head data exist, there is no evidence to guide the clinician in choosing between the two. There is a theoretical possibility that anti-c-Mpl antibodies might compete with romiplostim for the CRH domain, but again no evidence supports this. The availability of eltrombopag as an oral agent might be considered an advantage in long-term therapy.

The question that remains is whether eltrombopag and romiplostim should be moved upfront in the treatment algorithm of AMT. This is difficult to answer, and comparison with ITP may not be so useful in this context. In a recent, multicenter Italian trial, response to high-dose dexamethasone in patients with newly-diagnosed ITP was 86%, with a relapse-free survival at 15 months of 81%,

this supports the use of steroids as first-line therapy in ITP. By contrast, reports of AMT responsive to steroids are rare, although the scanty literature makes this refractoriness much more difficult to prove.

However, by the time most patients are diagnosed with AMT, they have probably already received an ITP-oriented treatment with steroids. In those patients who fail steroids, TPOR agonists are certainly a valuable alternative, and should be strongly considered to replace the immunosuppression strategy because of both their efficacy and their more favorable safety profile.

References


