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Review Article

Eltrombopag: A Review of Its Use in Patients with Systemic Lupus Erythematosus Associated Immune Thrombocytopenia

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that primarily affects young women of childbearing age. Thrombocytopenia is a relatively common hematologic manifestation of SLE, occurring in approximately 20-30% of SLE patients. The etiology of SLE thrombocytopenia is primarily autoimmune mediated and classified as Immune thrombocytopenia (ITP). Studies have shown that mortality is significantly higher in SLE patients with thrombocytopenia than non-thrombocytopenic patients. The mortality rate of patients in complete remission after treatment is significantly lower than that of patients in incomplete remission. Therefore, complete recovery from thrombocytopenia is important for the survival of patients with SLE. Eltrombopag is an oral Thrombopoietin Receptor (TPO-R) agonist that promotes the proliferation and differentiation of multifetal hematopoietic stem cells and megakaryocyte progenitors. It is also involved in megakaryocyte survival and anti-apoptosis, thereby increasing platelet production. Compared to conventional treatment modalities, Eltrombopag often allows patients to achieve complete remission, and the adverse effects are usually mild and reversible, especially in patients with refractory SLE-associated ITP (SLE-ITP). In conclusion, eltrombopag is a promising and safe option for the treatment of SLE-ITP because of its efficacy and ability to help reduce the dose of steroids and immunosuppressants when combined with other drugs.

Keywords: Eltrombopag; Systemic Lupus Erythematosus; Immune Thrombocytopenia; Thrombopoietin Receptor

INTRODUCTION

Eltrombopag is an oral TPO-R agonist that interacts with the transmembrane structural domain of TPO-R (also termed c-MPL) on the surface of cells in the megakaryocyte lineage [1]. It triggers the activation of downstream signaling pathways, such as the Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) and Ras-Mitogen Activated Protein Kinase (MAPK), which promotes the proliferation and differentiation of multifetal hematopoietic stem cells and megakaryocyte progenitors [2] at the same time; it is involved in megakaryocyte survival and anti-apoptosis, thereby increasing platelet production. Eltrombopag does not compete with thrombopoietin for its binding domain on the thrombopoietin receptor, is different and highly selective, and has no sequence homology with TPO, thus reducing the risk of autoantibody formation [3]. In clinical use, eltrombopag often results in complete remission in patients with ITP, with a low relapse rate, and its adverse effects are usually mild and reversible [4, 5]. Eltrombopag is a novel option for patients who have recurred after splenectomy or who have contraindications to splenectomy, who are at increased risk of bleeding, or who have failed treatment with conventional modalities.

Immune Thrombocytopenia (ITP) is defined as platelet count below 100×10^9/L, with an estimated incidence of 2-4/100,000 adults/year [6]. In this disorder, platelets are destroyed by the immune system, primarily by attacking IgG, GP IIb/IIIa, GP Ib/IX, GP Ia/IIa and other proteins expressed on megakaryocytes and platelets [7,8], resulting in premature

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engulfment and destruction of platelets by the reticuloendothelial system, especially the spleen. SLE is an autoimmune disease characterized by B-cell abnormal activation with overproduction of pathogenic autoantibodies and deposition of immune complexes in various organs [9]. ITP is one of relatively common hematologic manifestations of SLE and the major cause of bleeding. Severe ITP always is closely related to other clinical manifestations, including neurological manifestations, kidney disorders and disease activity [10,11]. Additionally, patients with severe thrombocytopenia have a significantly higher mortality 14.9% than those with moderate and mild thrombocytopenia (8.8% and 0.8%, respectively) [10]. In conclusion, the severity of thrombocytopenia and response to treatment in SLE patients had been confirmed as important prognostic factors to predict survival [12]. Thus, successful management of SLE-ITP is an important part of achieving complete remission.

Current clinical treatment of SLE-ITP usually uses glucocorticoids as first-line therapy. For ITP that relapses after glucocorticoid therapy, second-line therapeutic agents, including azathioprine, cyclophosphamide, danazol, and intravenous aprotinin, are also used. For refractory SLE-ITP, platelet transfusion, intravenous immunoglobulin, and splenectomy are often used clinically. However, these modalities are unsatisfactory in terms of economic burden adverse effects (such as infection) and operative trauma. Eltrombopag exhibits unique advantages for its efficacy, safety, convenience and inexpensiveness for treatment of SLE-ITP in many previous studies [13-17]. In this study, we aim to discuss and emphasize the advantages of Eltrombopag in the treatment of SLE-ITP compared with conventional strategies.

LITERATURE REVIEW

Traditional treatment of SLE-associated ITP

Not all thrombocytopenia secondary to SLE requires treatment, and the initiation of therapy is recommended only in patients with severe platelet deficiency ($<30 \times 10^9$/L), bleeding and severe bruising, or in patients with co-existing hemorrhagic disease. Since the pathogenesis of SLE-ITP is immune system mediated, glucocorticoids and Intravenous Immunoglobulin (IVIG) are recommended as first-line therapy. Oral prednisone is usually given at an initial daily dose of 1 mg/kg and is reduced when platelet level reaches $\geq 50 \times 10^9$/L. Higher or pulsed glucocorticoids may also be used in some patients with poor response to routine dose or serious condition. Although most SLE patients with ITP respond initially to this therapy, only 20% of patients sustain a long-term response [18]. Most patients treated with corticosteroids experience side effects such as sleep difficulties, weight gain, osteoporosis, osteonecrosis, cardiovascular disease, infections, and these GC-related damage that can affect patients even years after discontinuation [19]. In a group of ITP patients treated with corticosteroids, 98% reported at least one side effect, and 38% stopped or reduced their dose due to intolerable side effects. In addition, approximately 19% of patients did not respond to corticosteroids, and most (70%-90%) relapsed when corticosteroids were reduced or stopped.

Intravenous immunoglobulin is a safe and effective clinical option to significantly elevate platelet counts [20]. IVIG has many known targets including T cells, cytokines, immune cell transport, B cells, and complement and Fc receptors. IVIG inactivates self-reactive T cells by competing for and interrupting their interaction with antigen presenting cells. Many clinical trials have shown that 1 g/kg of IVIG is effective in 70-80% of patients with ITP, even for those who do not respond to corticosteroids. The majority of Adverse Events (AEs) associated with IVIG administration are mild and transient. Infusion reactions, usually characterized by headache (5%-20%) or fever (19%), have been reported in 20% to 50% of patients receiving IVIG. More serious adverse reactions to IVIG include thrombosis and hemolysis, with an incidence of approximately 1 in 1000 [21]. However, IVIG requires frequent hospital visits and carries a high financial burden, resulting in poor patient satisfaction and compliance [22]. Currently, IVIG is considered more of a resuscitation option in ITP as a preparation before emergency invasive procedures and is not suitable for long-term use.

When patients do not respond to first-line therapy or require continuous treatment, the disease is called refractory ITP and requires second-line therapy. This includes traditional Disease-Modifying Antirheumatic Drugs (DMARDS), platelet transfusion and splenectomy [23]. In addition, there are many case reports showing the positive effect of intravenous anti-CD20 antibodies (rituximab) in the treatment of SLE-ITP [24,25].

Splenectomy has been the first choice for refractory ITP in the past decades. However, splenectomy carries a high risk of increased arterial and venous thrombosis and bacterial infection. Patients without a spleen have a 200-fold higher risk of dying from sepsis compared to patients with normal spleen function [26]. In addition, it has been observed that the spleen may not be the primary site of platelet destruction and that the effectiveness of splenectomy is primarily influenced by decreased production of anti-platelet antibodies and increased platelet counts. Therefore, splenectomy has become unpopular among doctors in recent years [27].

Traditional Disease-Modifying Antirheumatic Drugs (DMARDS) have shown some promise in treatment of SLE-ITP, including Hydroxychloroquine (HCQ), Azathioprine (AZA), Mycophenolate mofetil (MMF), Cyclosporine A (CsA), Tacrolimus (TAC), and Dapsone [23]. These immunosuppressive drugs usually are used as additional steroid-sparing agents and have achieved varying degrees of efficacy [28]. For example, Arnal et al. showed that in combination therapy with prednisone and HCQ, 64% of patients could achieve long-term responses, which could lead to dose reduction or discontinuation of prednisone [18]. However, the unavoidable problem with long-term immunosuppressants is fatal infections, and their cytotoxicity causes patients irreversible side effects, especially in pregnant women.

The anti-CD20 monoclonal antibody rituximab has immunomodulatory effects similar to IVIG. A major advantage of rituximab is the durable response, which can result in a 50% to 60% increase in PLT counts for 18 months or longer [29]. However, there are few studies on the long-term follow-up of rituximab and little is known about its potential drug-related side effects.

For refractory ITP, platelet transfusions are also used clinically to improve symptoms. However, platelet transfusions are not associated with improved mortality outcomes, and frequent platelet transfusions increase the risk and therapeutic costs [30]. Even in patients for whom platelet transfusions are effective, platelet transfusions are difficult to maintain for long periods of time. Therefore, the use of new therapeutic agents that are safe and convenient is imminent.

Eltrombopag

Platelet maturation is regulated by the megakaryocyte-stimulating factor TPO, a 332-amino acid hormone synthesized primarily in the liver that binds to TPO receptors on the surface of megakaryocytes, induces megakaryocyte maturation and differentiation, and produces platelets [31]. Studies have found that some SLE patients produce platelet autoantibodies against glycoproteins GPIIb/IIIa, TPO and TPO-R, which may be an important mechanism of thrombosis [32], and these patients are more likely to develop thrombocytopenia and have a greater chance of not responding to glucocorticoid and immunoglobulin therapy [33]. Thrombopoietin Receptor Agonists (TRAs) have been introduced as a promising therapeutic approach by activating intracellular signaling pathways such as Janus Kinase/Signal Transducer Activator of Transcription (JAK/STAT) and mitogen-activated protein kinase (MAPK) to mimic endogenous TPO and thereby increase platelet counts [3].

Eltrombopag, asan oral TPO-R agonist,was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with recurrence after splenectomy or who have a contraindication to splenectomy, an increased risk of bleeding, or who have failed at least one other therapy, based on the results of a phase 3 trial published in The Lancet [34]. Studies have shown that Eltrombopag is effective in increasing platelet counts and reducing bleeding in most patients with ITP. Importantly, treatment remained safe and effective in the group that received Eltrombopag for up to 8.8 years. Eltrombopag was also effective in patients who had undergone extensive pretreatment, including splenectomy. Eltrombopag was generally well tolerated in clinical trials, with common adverse events including abnormal liver function, dizziness, blood clots, and muscle aches, but its adverse event profile was not significantly different from placebo and was considered mild and reversible [34-37]. Moreover, Eltrombopag appears to be safe and effective in pregnancy with SLE-ITP compared to immunosuppressants [13] (Table 1).

Table 1: Summary of cases about the use of Eltrombopag in SLE-ITP patients

Reference	Age	Sex	Dose	complete response	Side-effect
Magnano L, et al. [17]	69	Female	25 mg	Yes	None
Cela C et al. [38]	55	Female	50 mg	Yes	None
Maroun MC, et al. [15]	44	Female	50 mg	Yes	None
Cheng G, et al. [34]	46	Female	50 mg	Yes	Urticaria
Bussel JB, et al. [36]	51	Female	50 mg	Yes	None
Scheinberg P, et al. [39]	30	Female	50 mg	Yes	None
Boulon C, et al. [40]	61	Female	50 mg	Yes	Pulmonary embolism
Leng Q, et al. [13]	33	Female	25~50 mg	Yes	None
Natsuki S, et al. [41]	42	Female	50 mg	Yes	None

CONCLUSION

Eltrombopag appears to be an effective and well-tolerated agent for the treatment of SLE-associated ITP. They are able to increase and maintain platelet levels even in refractory and pretreated patients. Many patients can reduce or discontinue other ITP medications while on Eltrombopag. When used in combination with other drugs, it helps to reduce the dose of steroids and immunosuppressants, thus minimizing their cumulative adverse effects and is a promising and safe option for the treatment of SLE-ITP.

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CONFLICT OF INTEREST

The authors have no competing interests to declare

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