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Thrombopoietin Receptor Agonists in Primary ITP

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Abstract

Thrombopoietin (TPO) regulates thrombopoiesis through activation of TPO receptors on the megakaryocyte cell surface, resulting in increased platelet production. The TPO receptor agonists are novel treatments for patients with chronic ITP aimed at increasing platelet production through interactions with the TPO receptor on megakaryocytes. Two TPO receptor agonists, romiplostim and eltrombopag, have received regulatory approval. In patients with chronic ITP who remain at risk of bleeding following treatment with first-line therapies, these agents have been shown to increase platelet counts, decrease bleeding events and reduce the need for adjunctive or rescue treatments. The TPO receptor agonists are well-tolerated, though uncertainty remains regarding the risk of thromboembolism and bone marrow fibrosis. Comparative clinical trial data addressing the efficacy, safety, cost-effectiveness, and impact on health-related quality of life of TPO receptor agonists relative to other second-line treatment options are needed to guide treatment decisions in chronic ITP patients who fail first-line therapies.

Keywords

immune thrombocytopenia; ITP; thrombopoietin receptor agonists; eltrombopag; romiplostim

Introduction

Immune thrombocytopenia (ITP) is characterized by isolated thrombocytopenia secondary to immune-mediated platelet destruction and impaired platelet production¹. Primary ITP is diagnosed in the absence of secondary causes of immune-mediated thrombocytopenia including autoimmune diseases (e.g. systemic lupus erythematosus, antiphospholipid antibody syndrome), lymphoproliferative disorders (e.g. chronic lymphocytic leukemia), viral infections (e.g. hepatitis C virus, human immunodeficiency virus) and drugs¹. Historically, the treatment of ITP has been directed at inhibiting the production of anti-platelet autoantibodies or opsonization of antibody-coated platelets. However, impaired

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platelet production is increasingly recognized as a contributor to thrombocytopenia in patients with ITP².

Thrombopoietin (TPO) is a hormone constitutively produced by the liver which regulates platelet production by binding to and activating TPO receptors on the megakaryocyte cell surface, thereby inducing intracellular signalling cascades that lead to increased platelet production³. Plasma levels of TPO are regulated by binding of TPO to circulating platelets which results in its removal from circulation and subsequent degradation⁴. In patients with ITP, TPO plasma levels are inappropriately low as compared with individuals with hypoproliferative thrombocytopenias, an observation which led to the development of recombinant thrombopoietins, the first generation of exogenous thrombopoiesis-stimulating agents^{5,6}. These agents were discontinued after initial clinical trials in healthy volunteers showed development of thrombocytopenia secondary to drug-induced antibodies that cross-reacted with endogenous TPO⁷. Two second-generation TPO agonists (romiplostim and eltrombopag) are approved by the U.S. Food and Drug Administration for the treatment of patients with chronic ITP and insufficient response to corticosteroids, IVIg, or splenectomy, and are the subject of this review¹.

Romiplostim

Mechanism of Action

Romiplostim (Nplate, Amgen) is a recombinant fusion protein “peptibody” composed of 2 IgG1 constant regions (Fc fragments) linked to a peptide domain containing 4 binding sites for the TPO receptor⁸. Binding of romiplostim to the TPO receptor results in activation of intracellular signalling cascades (JAK-STAT and MAP kinase pathways) that lead to increased platelet production⁹. Romiplostim does not share sequence homology with endogenous TPO⁸. Following a single intravenous or subcutaneous dose, there is a dose-dependent increase in platelet count within 5 to 8 days which returns to baseline by day 28⁸.

Efficacy in Clinical Studies

Two parallel phase III randomized controlled trials evaluated the efficacy and safety of romiplostim (starting dose 1 µg/kg subcutaneously once weekly) compared to placebo in splenectomized and non-splenectomized patients with chronic ITP and mean platelet count 30,000/µL¹⁰. More patients in the romiplostim group had a durable platelet response (platelet count ≥ 50,000/µL during ≥ 6 of the final 8 weeks on study) compared to placebo (non-splenectomized: 56% vs. 5%, p<0.0001; splenectomized: 38% vs. 0%, p=0.0013). Concomitant treatments (e.g. corticosteroids) were discontinued or decreased more frequently in the romiplostim versus placebo group (87% vs. 38%). Romiplostim treatment resulted in improved health-related quality of life measured using the ITP Patient Assessment Questionnaire^{11,12}. A retrospective analysis showed a significant decrease in corticosteroid use from 35% to 20% after 3 years of treatment with romiplostim¹³. Patients with ITP who previously completed a romiplostim study were enrolled in an open-label extension study in which romiplostim was administered weekly for a median of 78 weeks¹⁴. A platelet count of ≥ 50,000/µL was achieved in 94.5% of patients during the study. More than 50% of patients had platelet counts of ≥ 50,000/µL on ≥ 90% of all visits.

In a 52-week open-label study, non-splenectomized patients with ITP were treated with romiplostim or standard of care¹⁵. Overall platelet response was 2.3 times higher in the romiplostim group than the standard of care group (95% CI 2.0 – 2.6). Treatment failure occurred less frequently in romiplostim-treated patients compared to those receiving standard of care (11% vs. 30%, OR 0.31 95% CI 0.08 – 0.35). A prospective study of ITP patients enrolled in a romiplostim compassionate release program in France reported a

primary platelet response ($> 50,000/\mu\text{L}$ and double baseline) in 74% of all patients¹⁶. Long-term responses at 2 years were observed in 65% patients.

Eltrombopag

Mechanism of Action

Eltrombopag (Promacta, Revolade GlaxoSmithKline) is an oral, small non-peptide molecule which binds to the TPO receptor via its transmembrane domain and activates the JAK-STAT and MAP kinase intracellular pathways to increase platelet production^{9, 17, 18}. Eltrombopag produces a sustained increase in platelet count after 8 days of repeat dosing which decreases to baseline 12 days following discontinuation with a half-life of approximately 12 hours¹⁹.

Efficacy in Clinical Studies

In a phase II dose-finding study, 118 patients with chronic ITP, platelet counts $< 30,000/\mu\text{L}$ and previous relapses or treatment failure received eltrombopag (30 to 75 mg/day) or placebo for 6 weeks²⁰. A greater proportion of eltrombopag treated patients (50 mg or 75 mg doses) achieved a platelet count $> 50,000/\mu\text{L}$ at 43 days compared to placebo.

A subsequent double-blind phase III clinical trial randomized patients with chronic ITP (platelet counts $< 30,000/\mu\text{L}$ and ≥ 1 prior treatments) to receive eltrombopag (50 mg/day initial dose) or placebo for 6 weeks²¹. A greater proportion of patients in the eltrombopag group achieved a platelet count $> 50,000/\mu\text{L}$ at 6 weeks compared to placebo (59% vs. 16%; OR 9.61, 95% CI 3.3 – 28). Patients in the eltrombopag group had less bleeding compared to those in the placebo group (OR 0.49, 95% CI 0.26–0.89).

Patients with chronic ITP and baseline platelet count $< 30,000/\mu\text{L}$ received eltrombopag (50 mg/day) or standard of care for 6 months in a double-blind phase III study²². The odds of a response to treatment (platelet count 50,000–400,000/ μL) was higher in eltrombopag-treated compared to placebo-treated patients (OR 9.2, 99% CI 3.59 – 18.73). Patients receiving eltrombopag were more likely to reduce concomitant treatment (59% vs. 32%) and less likely to need rescue treatment (18% vs. 40%) compared to patients receiving placebo. Clinically significant bleeding was reduced in patients treated with eltrombopag compared with placebo (OR 0.35, 95% CI 0.19 – 0.64).

Clinical Use of TPO Receptor Agonists in Primary ITP

The goal of treatment in ITP is to maintain a platelet count which reduces the risk of bleeding while minimizing treatment-related toxicity. The recently published American Society of Hematology guidelines on ITP suggest initiating treatment with TPO receptor agonists in patients at risk of bleeding who relapse following splenectomy or have a contraindication to splenectomy and previous treatment failure¹. Although remissions of ITP have been reported after TPO receptor agonist discontinuation, thrombocytopenia usually recurs following drug withdrawal. Thus, these agents are used indefinitely to maintain a platelet count that is likely to minimize bleeding. The recommended initial dose of romiplostim is 1 $\mu\text{g}/\text{kg}$ (actual body weight) administered subcutaneously once per week and then titrated to a maximum of 10 $\mu\text{g}/\text{kg}$ to achieve a platelet count $> 50,000/\mu\text{L}$ ²³. The recommended starting dose of eltrombopag is 50 mg per day administered orally and then adjusted to a maximum of 75 mg per day to maintain platelet count $> 50,000/\mu\text{L}$ ²⁴. A reduced dose of eltrombopag (25 mg per day) should be used in patients with hepatic dysfunction and those of East Asian ancestry. Eltrombopag should not be taken within 1 to 2 hours of a meal, and 4 hours of antacids, dairy products or polyvalent cations (calcium, magnesium, aluminum). TPO receptor agonists cross the placenta and their safety in pregnancy has not been demonstrated⁹.

Platelet count should be measured weekly until a stable platelet count that is associated with an absence of bleeding symptoms is achieved for 4 weeks without adjustment and then measured monthly thereafter⁹. Because treatment with eltrombopag can cause hepatic dysfunction (see below), levels of serum aspartate aminotransferase, alanine aminotransferase and bilirubin should be monitored every 2 weeks during the dose-adjustment phase and monthly thereafter²⁴.

Safety

TPO receptor agonists are generally well tolerated with the most common adverse effects including headache, fatigue, arthralgias, nausea and nasopharyngitis^{10, 15, 21, 25}. Eltrombopag use is associated with elevations in alanine aminotransferase and bilirubin which may resolve despite ongoing treatment²². Therapy should be discontinued if alanine aminotransferase levels reach 3 times the upper limit of normal and are progressive, persistent (4 weeks), associated with increased direct bilirubin, or associated with symptoms of liver injury or evidence of hepatic decompensation²⁴. Thromboembolic events have been reported in patients treated with TPO receptor agonists, the majority of whom had pre-existing cardiovascular or thromboembolic risk factors^{14, 16, 22, 25–27}. Twelve thrombotic or thromboembolic events were reported in 7 patients (4.9%) receiving extended duration romiplostim²⁵. In a study of extended eltrombopag treatment 21 thromboembolic events were reported in 16 patients (5%)²⁷.

Bone marrow fibrosis is also reported with use of TPO receptor agonists^{14, 25, 28–30}. However, the clinical importance of this observation is unknown. In EXTEND, an open-label extension study of eltrombopag in which bone marrow biopsies were conducted annually, increased bone marrow reticulin was described in 2.6% of bone marrow biopsies after a median 25 months of treatment³¹. The long-term consequences of increased bone marrow reticulin deposition are unclear, though it appears to be reversible with drug discontinuation⁹.

Summary

TPO receptor agonists are a safe, effective treatment option for patients with chronic ITP who are at risk of bleeding after failing first-line therapies. TPO receptor agonists are associated with increased platelet counts, decreased bleeding events and reduced need for adjunctive or rescue treatments. What remains unclear is where TPO receptor agonists fit along the spectrum of second-line treatment options for ITP. Some authorities favor splenectomy before TPO receptor agonist use in the absence of a contraindication to surgery¹. Others do not express a preference among second-line options³² and note a dearth of evidence necessary for prioritization of such options³³. High-quality comparative clinical trial data are needed to assess the relative efficacy, safety, cost-effectiveness, and impact on health-related quality of life of second-line treatment options. In the interim, treatment decisions should be individualized through discussion of established benefits and disadvantages and incorporation of patient values and preferences³³.

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