FRESH FROM THE PIPELINE

Romiplostim

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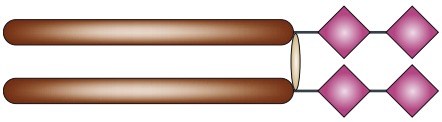

Romiplostim

In August 2008, romiplostim (Nplate; Amgen), a thrombopoietin receptor agonist, was approved by the US FDA for the treatment of thrombocytopaenia in patients with chronic immune thrombocytopaenic purpura who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.

Immune thrombocytopaenic purpura (ITP) is an autoimmune disorder characterized by low platelet counts and bleeding[1]. Thrombocytopaenia in patients with ITP has long been thought to result from accelerated platelet destruction mediated by tissue macrophages that ingest platelets coated with autoantibodies[1]. Treatment is typically initiated with corticosteroids, supplemented with intravenous immunoglobulin or intravenous anti-D immunoglobulin, which act primarily by interfering with platelet destruction[1].

However, primary ITP (defined by the absence of other disorders with a known association with immune thrombocytopaenia) persists in the vast majority of adults and ~20% of children, and the toxicities of corticosteroids, and the cost and inconvenience of parenteral management with immunoglobulins, are major limitations to their long-term use. Surgical removal of the spleen, which is the organ that clears ITP platelets most efficiently as well as a major site of autoantibody production, has historically been the standard treatment for chronic ITP[1]. Splenectomy can provide long-lasting benefit, but ~30–40% of adults undergoing splenectomy do not respond, or have a relapse[1]. So, there is a significant need for improved treatments for chronic ITP.

Basis of discovery

Although accelerated platelet destruction has traditionally been thought to underlie thrombocytopaenia in ITP, evidence has accumulated indicating that impaired platelet production is also an important contributor in a substantial proportion of patients[2]. Thrombopoietin (TPO), a growth factor that mediates its effects through the TPO receptor, is the primary physiological regulator of platelet production[3], and so the development of TPO receptor agonists has been pursued as a strategy for increasing platelet production.

A first-generation agent, recombinant human megakaryocyte growth and development factor (MGDF; a truncated non-glycosylated form of TPO) conjugated to polyethylene glycol (PEG–MGDF), increased platelet counts in patients with ITP in an initial clinical study[4]. However, clinical development of this agent was halted owing to the development of antibodies against PEG–MGDF that crossreacted with endogenous TPO, causing severe, persistent thrombocytopaenia[5]. Consequently, efforts have since focused on identifying TPO receptor agonists that do not pose this risk, and romiplostim is the first such agent to receive regulatory approval.

Drug properties

Romiplostim (previously known as AMG531) is a recombinant fusion protein that contains two identical single-chain subunits, each consisting of a human immunoglobulin IgG1 Fc domain (which prolongs the half-life of the protein) covalently linked at the C terminus to a peptide containing two TPO receptor-binding domains[6,7]. Romiplostim has no amino-acid-sequence homology to endogenous TPO[6,7]. Romiplostim increases platelet production through binding and activation of the TPO receptor[6,7], and increased platelet counts in healthy subjects and patients with ITP in initial clinical studies[8,9], supporting its further clinical evaluation.

Clinical data

The safety and efficacy of romiplostim were assessed in two double-blind, placebo-controlled clinical studies (studies 1 and 2) involving 125 patients with chronic ITP who had completed at least one prior treatment (including corticosteroids, immunoglobulins or rituximab) and had a platelet count of $\leq 30 \times 10^9$ per L before study entry[7,10]. Patients were randomized in a 2:1 ratio to receive either 24 weeks of romiplostim (1 μg per kg subcutaneously) or placebo[7,10]. Patients received single weekly doses of romiplostim, with individual dose adjustments to maintain platelet counts between 50×10^9 per L and 200×10^9 per L[7,10]. The primary efficacy end point was durable platelet response, defined as the achievement of a weekly platelet count $\geq 50 \times 10^9$ per L for any 6 of the last 8 weeks of the 24-week treatment period in the absence of any rescue medication[7,10].

Study 1 evaluated 62 patients who had not undergone a splenectomy[7,10]. In this study, a durable platelet response was achieved by 25 of the 41 (61%) non-splenectomized patients receiving romiplostim compared with one of 21 patients in the placebo group[7,10]. Patients receiving romiplostim achieved platelet counts of 50×10^9 per L or more on a mean of 15.2 weeks, compared with 1.3 weeks for those receiving placebo[7,10].

Study 2 evaluated 63 patients who had undergone a splenectomy[7,10]. In this study, 16 out of 42 (38%) of the splenectomized patients receiving romiplostim achieved a durable platelet response, compared with none of 21 patients in the placebo group[7,10]. Patients receiving romiplostim achieved platelet counts of 50×10^9 per L on a mean of 12.3 weeks, compared with 0.2 weeks in the placebo group[7,10].

Overall, 87% (20 out of 23) of patients receiving romiplostim (12 out of 12 splenectomized patients and 8 out of 11 non-splenectomized patients) reduced or discontinued concurrent therapy compared with 38% (6 out of 16) of those given placebo (1 out of 6 splenectomized, and 5 out of 10 non-splenectomized patients)[7,10]. Nine patients reported a serious bleeding event: five patients (6%) in the groups receiving romiplostim and four patients (10%) in the groups receiving placebo[7]. Bleeding events that were grade 2 severity or higher occurred in 15% of patients treated with romiplostim and 34% of patients treated with placebo[7]. No antibodies against romiplostim or TPO were detected[10].

Indications

Romiplostim is approved by the FDA for the treatment of thrombocytopaenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy[7]. Romiplostim should be used only in patients with ITP whose thrombocytopaenia and clinical condition increases the risk for bleeding[7]. Romiplostim should not be used in an attempt to normalize platelet counts[7]. ▸

ANALYSIS | IMMUNE THROMBOCYTOPAENIC PURPURA

Analysing issues in the treatment of ITP is Douglas B. Cines, M.D., Professor of Pathology and Laboratory Medicine at the Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA.

Historically, splenectomy has been the recommended second-line treatment for chronic ITP. Two-thirds of patients enter and maintain remission, but splenectomy is associated with a small life-long risk of overwhelming sepsis due to encapsulated organisms and potentially other long-term sequelae. Moreover, patients are increasingly reluctant to undergo splenectomy unless alternative approaches have failed.

Rituximab, a chimeric monoclonal antibody against CD20, produces durable (greater than 1 year) responses in ~30% of patients, with good tolerance and a reasonable safety profile to date[11,12], but there is a dearth of effective non-surgical alternatives for most patients. Moreover, ~25% of patients have severe disease refractory to splenectomy and rituximab. Combinations of non-selective immunosuppressants and other agents that impair platelet clearance are used in such patients who are at high risk of bleeding, but recent studies show poor quality of life and mortality rates approaching several percent per year that increase with age[13].

Romiplostim, which has recently become the first TPO receptor agonist to receive regulatory approval, raises platelet counts in most adults with chronic ITP. It is important to note that patients in the pivotal trials[10] had severe chronic disease, treatment with multiple agents had been unsuccessful and many had failed splenectomy, making the efficacy data especially relevant and compelling. Romiplostim is generally well tolerated, responses have been durable and there is no evidence to date of an increased risk of thrombosis or clonal evolution.

Romiplostim should be considered for use in patients with severe refractory ITP who have failed splenectomy, in those unable or unwilling to undergo the procedure, and to raise platelet counts prior to planned surgical procedures. Its place earlier in the treatment algorithm will evolve based on several considerations. ITP is a chronic condition, the agent is not inexpensive, it is not designed to be 'curative' and results from recent studies indicate that short courses of high-dose dexamethasone induce remission in a surprising proportion of patients, but these require confirmation. Although the natural history of ITP is not well defined because splenectomy is so effective, it is clear that some patients attain haemostatic platelet counts after discontinuing other forms of therapy if supported for several years.

Eltrombopag, an orally active small-molecule TPO receptor agonist, has been used with similar success on-study in patients with chronic ITP[14] and in those with chronic hepatitis C and thrombocytopaenia to enable use of antiviral therapies that impair platelet production[15]. Several other TPO receptor agonists are also in clinical trials. Ongoing studies to determine whether romiplostim, or this class of compounds, stimulate reticulin fibrosis in the marrow with prolonged use through release of profibrotic mediators from stimulated or damaged megakaryocytes or platelets may ultimately determine their role in initial and long-term management. Notwithstanding these caveats, romiplostim and other TPO receptor agonists represent a paradigm shift in the management of ITP and potentially other thrombocytopaenic disorders.

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Box 1 | Market for immune thrombocytopaenic purpura

Analysing the market for ITP is Uma Yasothan, IMS Health, London, UK.

The incidence and prevalence of ITP is not well documented, but in the US alone, it is estimated that there are currently 60,000 chronic ITP patients[16]. Owing to limitations of current treatments, there is a significant need for novel drugs. In August 2008, the FDA approved romiplostim (NPlate; Amgen), a first-in-class thrombopoietin receptor agonist, for chronic ITP patients who have had an insufficient response to established treatments. The US approval of romiplostim was based on a Risk Evaluation and Mitigation Strategy (REMS) developed by Amgen after the FDA expressed safety concerns with the drug. In the US, it will be made available through a special programme known as NEXUS (Network of EXperts Understanding and Supporting Nplate and Patients). Romiplostim is also approved in Australia, and Amgen has filed for regulatory approval in the EU, Canada and Switzerland.

In 2007, intravenous immunoglobulins for thrombocytopaenia had sales of US $3 billion[17]. The safety concerns, the first-in-class nature and lack of dependable epidemiological estimates for ITP makes it challenging to define the market potential of romiplostim. Analysts have estimated peak annual sales potential ranging from $300 million[16] to $400 million[18]. Another thrombopoietin receptor agonist, eltrombopag (Promacta; GSK), which is administered orally, is under FDA review at the time of writing, and if approved could represent significant competition to the subcutaneously administered romiplostim. Both the drugs are also being investigated for other indications, including chemotherapy-induced thrombocytopaenia and myelodysplastic syndrome.

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Competing financial interests
D.B.C. declares competing financial interests: see web version for details.