Romiplostim for the Treatment of Chronic Immune (Idiopathic) Thrombocytopenic Purpura

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On August 22, 2008, the US Food and Drug Administration (FDA) granted marketing approval (licensure) to romiplostim (Nplate, Amgen Inc) for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Abstract
Purpose: On August 22, 2008, Romiplostim (Nplate for Injection) received approval from the US Food and Drug Administration (FDA) for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. This report summarizes the FDA analyses of the clinical data supporting this approval.

Experimental Design: The FDA reviewed data from two double-blind, placebo-controlled clinical studies, an uncontrolled extension study, and supportive studies. In the controlled studies, enrolled patients had completed at least one prior treatment for chronic ITP and had a platelet count ≤ 30 × 10⁹/L. One study enrolled patients who had undergone splenectomy; the other enrolled patients who had not undergone splenectomy. The primary endpoint in both controlled studies was durable platelet response.

Results: Overall, 125 patients were randomized in the controlled studies. A durable platelet response was observed in 61% of nonsplenectomized patients and 38% of patients who had undergone splenectomy. One placebo group patient achieved a durable platelet response. Serious hemorrhage events were reported in 10% of placebo recipients and 6% of romiplostim recipients. In the extension study, patients received romiplostim for a median of 60 weeks and a maximum of 96 weeks; the majority of patients maintained platelet counts ≥ 50 × 10⁹/L throughout the study. Major safety findings pertained to a risk for bone marrow reticulin formation and worsened thrombocytopenia following romiplostim discontinuation.

Conclusions: The FDA approved romiplostim for use among certain patients with chronic ITP. This approval included a Risk Evaluation and Mitigation Strategy to ensure that the benefits of the drug outweigh its risks.

On August 22, 2008, the US Food and Drug Administration (FDA) granted marketing approval (licensure) to romiplostim (Nplate, Amgen Inc) for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Romiplostim is a recombinant protein, thrombopoietin (TPO) receptor agonist that stimulates bone marrow megakaryocytes to produce platelets. The marketing approval was based on demonstration of a favorable risk-benefit profile, where the major benefit pertained to demonstration of a sustained increase in blood platelets, an accepted surrogate for clinical benefit in the proposed clinical setting.

Clinical and Regulatory Background

Chronic ITP is an acquired autoimmune disorder that primarily affects adults, with a female-to-male ratio of approximately 2:1 and is characterized by a low platelet count, mainly secondary to accelerated platelet destruction.[1-3] In addition to accelerated platelet destruction, some patients appear to have impaired platelet production. Nevertheless, blood TPO levels are generally not increased in patients with chronic ITP.[1] The diagnosis of ITP is based on the detection of thrombocytopenia and the exclusion of “secondary” causes of the abnormally low platelet count.[4]
Hemorrhage is the major clinical complication of chronic ITP. In general, no treatment is necessary for asymptomatic patients with platelet counts in excess of $30 \times 10^9/L$ unless there are mitigating factors such as a planned surgical procedure or participation in contact sports that may increase the risk of bleeding. For patients requiring treatment, initial options include glucocorticoids, intravenous immunoglobulins (IVIG), and anti-D immunoglobulin. When ITP does not respond to these therapies, splenectomy results in improved platelet counts in approximately two-thirds of patients. Failure to respond to splenectomy and available medications may result in fatal hemorrhage if the patient continues to experience severe thrombocytopenia. The initial clinical experience with recombinant TPO molecules was complicated in some patients by the development of neutralizing antibodies that resulted in thrombocytopenia. Cross-reactivity between the drug-induced antibodies and intrinsic TPO was implicated in these reactions, and further development of TPO-sequence homologous molecules was halted. Because romiplostim lacks sequence homology with TPO, investigators proposed that it may have less potential for immunologic complications. Nevertheless, the detection of antibody formation to romiplostim and intrinsic TPO was a major focus throughout the product’s clinical development program. The initial clinical study of romiplostim showed that the product produced dose-related increases in platelet counts in healthy subjects, and clinical development proceeded in patients with chronic ITP. Because of the relative rarity of chronic ITP, the FDA designated romiplostim as an orphan drug (a product that treats a disease affecting fewer than 200,000 Americans). Subsequently, FDA reviewed the protocols for the two major romiplostim clinical studies under the Special Protocol Assessment process. By this process, if the protocol’s description of the study design is found to be appropriate, FDA provides an explicit agreement that the design and planned analyses of the study adequately address the objectives in support of a regulatory submission. FDA agreed that the primary endpoint for the two controlled romiplostim studies—durable platelet response—was an established surrogate endpoint for clinical benefit in chronic ITP. This determination was based on the well-accepted role of thrombocytopenia as the pathophysiologic basis for hemorrhagic complications in chronic ITP. Additionally, the endpoint was defined to establish that romiplostim therapy resulted in both the achievement as well as the maintenance of a prespecified platelet count goal.

On October 23, 2007, the manufacturer submitted a Biologics License Application for romiplostim seeking market approval. Following a detailed review of the clinical data and an FDA Advisory Committee recommendation, the FDA approved romiplostim with a Risk Evaluation and Mitigation Strategy (REMS). A REMS is an FDA-required risk management plan that utilizes tools beyond the approved package insert to mitigate serious risk(s). The Food and Drug Administration Amendments Act of 2007 provides the FDA with the authority to require a REMS if FDA determines that additional postmarketing strategies (beyond routine) are necessary to ensure that the benefits of a drug outweigh the risks. Serious risks identified during the romiplostim clinical development program (worsened thrombocytopenia after drug discontinuation), as well as signals of potentially serious risks (hematologic malignancy and progression of disease in patients with myelodysplastic syndromes [MDS], bone marrow reticulin formation leading to fibrosis, as well as thrombotic/thromboembolic complications), prompted the need to require a REMS.

**Phase III Clinical Studies**

The approval of romiplostim was based predominantly on findings of its efficacy and safety in two double-blind, placebo-controlled clinical studies.

**Study Design**

The two phase III investigations shared many design features. Both trials were designed as multicenter, double-blind, placebo-controlled studies in which patients were randomly assigned (in a 2:1, active:placebo ratio) and received treatment for 24 weeks, followed by 12 weeks when the study drug was not administered. Patients were evaluated at the end of 36 weeks of study. Eligible patients were adults with a diagnosis of ITP according to American Society of Hematology guidelines. The patients also had to have completed at least one previous treatment for ITP and have a mean of three platelet counts during screening and pretreatment that was $\leq 30 \times 10^9/L$, with no individual count $> 35 \times 10^9/L$.

One study enrolled patients who had undergone splenectomy, while the other study enrolled nonsplenectomized patients. Patients with splenectomy were required to have had the splenectomy procedure performed at least 4 weeks before study entry. Exclusion criteria also helped select for
patients who were receiving only stable doses of corticosteroids, azathioprine, or danazol. Patients receiving IVIG or anti-D immunoglobulin were excluded if they received the products less than 2 weeks prior to screening. Also excluded were patients treated with rituximab (Rituxan) within 14 weeks prior to screening, as well as those using various other platelet-stimulating agents prior to screening. **TABLE 1**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Romiplostim</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55%</td>
<td>57%</td>
</tr>
<tr>
<td>Female</td>
<td>54%</td>
<td>56%</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Baseline platelet count</td>
<td>101 ± 150</td>
<td>98 ± 150</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>8.9 ± 2.1</td>
<td>8.6 ± 2.0</td>
</tr>
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</table>

In both studies, romiplostim was administered subcutaneously once per week at a starting dose of 1 μg/kg. Dose adjustment was allowed throughout the 24-week treatment period to allow subjects to maintain platelet counts in the target range of 50 to 200 × 10^9/L. The maximum permitted dose was 15 μg/kg. Romiplostim was administered by health-care providers. After 24 weeks of treatment, romiplostim was withdrawn and the platelet count was monitored. Participation was completed once platelet counts were ≤ 50 ×10^9/L or the subject reached week 36 with a platelet count > 50 ×10^9/L, whichever occurred first.

The primary endpoint in both studies was a comparison of the rates of “durable platelet response,” defined as at least six weekly platelet counts ≥ 50 × 10^9/L during the last 8 weeks of study drug treatment, in the absence of “rescue medications” at any time during the 24-week treatment period. The major secondary endpoints involved comparisons of platelet count “responses” (defined as any weekly platelet count ≥ 50 × 10^9/L) and the use of thrombocytopenia “rescue medications.” **TABLE 2**

**TABLE 3**

**Efficacy Results From the Phase III Clinical Studies of Romiplostim**

Patients were assessed weekly for major study outcomes (including platelet counts) during the 24-week treatment period. Patients were also monitored for 12 weeks after the study medication had been discontinued. Patients in both arms were eligible to receive rescue medication throughout the study. Rescue medication was permitted for bleeding or wet purpura, or if the patient was at immediate risk of bleeding. Concurrent ITP therapies could be reduced during the first 12 weeks of treatment once platelet counts were > 100 × 10^9/L prior to dosing. Predose sampling for pharmacokinetic studies was performed once the patient reached a dose ≥ 10 μg/kg/wk.

**Results**

Overall, 125 patients underwent randomization in the two phase III clinical studies; 41 were in the placebo group and 84 in the romiplostim group. Major baseline characteristics are summarized in Table 1. In general, baseline characteristics were relatively balanced between the groups within each study. All patients had failed at least one prior ITP therapy, and most (77%) had received three or
more different types of prior ITP therapies. In general, patients who had undergone splenectomy had slightly lower baseline platelet counts as well as a more extensive history of prior ITP medication use compared to patients who had not undergone splenectomy. TABLE 4

Disposition within the two studies is summarized in Table 2. Overall, a relatively small number of patients (8%) failed to complete the studies. The major efficacy results are described in Table 3. Overall, the romiplostim group experienced increased platelet counts compared to the placebo group, with statistical success for all the platelet count endpoints. Additionally, fewer patients in the romiplostim group received “rescue medications” because of bleeding or marked decreases in platelet counts. In general, platelet count response rates were higher for patients who had not undergone splenectomy, compared to those who had undergone the procedure. Major safety findings were similar between the two phase III studies. The pooled, summarized results are shown in Table 4. The incidence of patients who experienced any bleeding event was similar in the romiplostim and placebo groups. Serious hemorrhages were uncommon and too few to definitively detect differences between the study groups. The most common adverse event in the studies was headache, which occurred among 35% of patients receiving romiplostim and 32% of those receiving placebo. The majority of adverse events were of mild to moderate severity. As summarized below, most of the serious risks for romiplostim were detected in the supportive studies and/or integrated analyses of the overall safety database.

Supportive Studies and Integrated Safety Findings

In addition to the phase III clinical trials, important safety data were obtained from an extension study of prolonged romiplostim administration to patients with ITP as well as an exploratory study of romiplostim administration to patients with myelodysplastic syndromes (MDS). Other studies contributed to the overall romiplostim exposure database. Patients With Chronic ITP

A total of 271 adult patients with chronic ITP received at least one dose of romiplostim. In this population, romiplostim was administered to 114 patients for at least 52 weeks and 53 patients for at least 96 weeks. Serious adverse events associated with romiplostim in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after romiplostim discontinuation. During the development of romiplostim, reticulin deposition within the bone marrow, as well as marrow fibrosis, was reported in some animals exposed to the product. Animal data from other TPO-mimetic agents also indicated a risk for marrow fibrosis. Among the 271 patients exposed to romiplostim, 4 discontinued the drug because of bone marrow reticulin deposition. In 6 additional patients, reticulin was observed on bone marrow biopsy. All 10 patients with bone marrow reticulin deposition had received romiplostim doses ≥ 5 µg/kg, and 6 had received doses ≥ 10 µg/kg. In the phase III studies, progression to marrow fibrosis with cytopenias was not reported. In the extension study, 1 patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during romiplostim therapy. Overall, the safety database did not exclude a risk for bone marrow fibrosis with cytopenias during romiplostim therapy.

Within the safety database, 57 patients had platelet counts monitored intensively during and following romiplostim discontinuation. When romiplostim was discontinued in four of these patients, severe thrombocytopenia developed, to a degree of even greater severity than was present at baseline. This worsened thrombocytopenia resolved (to baseline) over 14 days. One fatal intracranial hemorrhage occurred following romiplostim discontinuation. The basis for the worsening thrombocytopenia following romiplostim discontinuation is not known, although suppression of intrinsic TPO levels has been proposed as a possible mechanism.
Formation of antibodies to romiplostim as well as to intrinsic TPO was monitored closely in the clinical studies. These data showed that some patients had preexisting antibodies (8% to romiplostim and 5% to TPO). Binding antibodies to romiplostim developed in 10% of patients, and binding antibodies to TPO developed in 5% of patients. Neutralizing antibody formation to romiplostim was observed in one patient and no patients developed neutralizing antibodies to TPO. No correlation was observed between antibody development and clinical effectiveness or safety.

Patients With MDS

In an uncontrolled, exploratory clinical study, 44 patients with low-risk or intermediate-1-risk MDS (assessed according to the International Prognostic Scoring System, or IPSS) and thrombocytopenia were exposed to romiplostim. Twenty-two patients (50%) experienced MDS progression (increased blasts or worsening cytogenetics), acute myelogenous leukemia (AML), or a temporary increase in the number of blast cells (that improved with cessation of the drug). At least 7 of 44 patients developed acute leukemia or rapid MDS progression and death during or shortly after romiplostim administration. The uncontrolled nature of this study precluded conclusions regarding the role of romiplostim in MDS progression. However, the occurrence of disease progression or temporary blast count increases within 3 months in 15 of 22 patients appeared to be greater than would be expected in the general MDS population with low-risk or intermediate-1-risk MDS.

The TPO receptor has been detected on hematopoietic clones in some patients with MDS and AML, and in vitro studies have shown AML cell proliferation following exposure to TPO. The implications of these observations for patients with chronic ITP are unknown, but the findings signaled special concerns for the use of romiplostim among patients who do not have chronic ITP. In the phase III clinical trials of patients with chronic ITP, the incidence of hematologic malignancies was low and similar between romiplostim and placebo.

Discussion

Romiplostim, a TPO-mimetic agent, increased platelet counts in patients with chronic ITP, including patients who had previously undergone splenectomy. A “durable platelet response” was observed in 61% of nonsplenectomized patients and 38% of patients who had undergone splenectomy. The study population consisted primarily of patients who had received multiple prior therapies, and almost all patients had severe thrombocytopenia (platelet counts < 30 x 10^9/L) prior to the initiation of romiplostim. Achievement and maintenance of a platelet count in excess of 50 x 10^9/L was accepted by FDA as evidence of a clinical benefit, based on the general understanding that hemorrhage—the most clinically important consequence of ITP—is importantly correlated with platelet counts in patients with severe, chronic ITP. This contention was supported during the FDA’s advisory committee review of romiplostim.

The incidence of serious hemorrhage was low in the clinical studies and insufficient to detect differences between the romiplostim and placebo groups. Given the low rate of serious hemorrhage, the clinical studies would have had to include many more patients to establish a difference between the study groups. The rarity of severe, chronic ITP would likely preclude performance of a study that chose serious hemorrhage as the primary endpoint. Hence, the manufacturer of romiplostim chose a demonstration of platelet count responses as the main efficacy endpoint for the phase III clinical studies.

Several safety concerns emerged during the romiplostim development program, predominantly among patients with chronic ITP who would likely receive the product on a long-term basis. Additionally, an exploratory study in patients with MDS signaled safety concerns. The major safety risks shown in patients with chronic ITP were related to reticulin deposition within the bone marrow and a risk for worsened thrombocytopenia (compared to baseline) following romiplostim discontinuation. Other potential safety concerns for use of romiplostim among patients with chronic ITP include risks for thromboembolic complications due to excessive platelet count increases (as may occur with medication errors), bone marrow fibrosis with cytopenias, and possible worsening thrombocytopenia due to formation of antibodies to romiplostim or TPO. Of special concern for the postmarketing period was the observation of MDS progression and AML development among some patients who participated in a study of romiplostim treatment of thrombocytopenia due to MDS. The extent of these safety concerns for romiplostim prompted FDA to require a REMS, coincident with the licensure of romiplostim. The REMS involves special procedures to promote informed risk-benefit decision-making and to require periodic monitoring of all patients during romiplostim treatment. Specifically, romiplostim is to be supplied via participation in a program referred to as the
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Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program. This program requires health-care providers who wish to prescribe romiplostim to register by attesting to understanding the risks associated with romiplostim, safe use conditions, and program requirements. Institutions that wish to provide romiplostim must also register through the Nplate™ NEXUS Program.

In addition, any patient treated with romiplostim must be enrolled in the program. At the time a patient is identified for treatment, the prescriber must complete an enrollment form and baseline questionnaire. Every 6 months throughout romiplostim treatment, the prescriber must complete a form for each patient that documents certain adverse events and a determination of whether it is appropriate to continue romiplostim treatment. Prescribers must report when romiplostim treatment is discontinued and the reason for discontinuation.

The licensure of romiplostim was also accompanied by the FDA’s requirement for the conduct of clinical studies that would further assess the safety of the drug. These studies are intended to provide additional information pertaining to the development of antibodies to romiplostim and TPO, information related to use of the drug during pregnancy and lactation, and more data related to the risk for bone marrow fibrosis.

Conclusions

The licensure of romiplostim represented the first FDA approval of a product within the class of TPO-mimetic agents. Romiplostim was shown to have a favorable risk-benefit profile for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy, based on data from two adequate and well controlled clinical studies as well as other supportive studies. Licensure of the product included a requirement for additional clinical studies as well as a REMS intended to optimize the product’s safe use. These requirements should help refine the long-term assessment of romiplostim’s risk-benefit profile in a manner that will safely allow use of the product among patients with chronic ITP who have few other therapeutic options.

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