Romiplostim – A Thrombopoiesis-stimulating Peptibody for the Management of Chronic Immune Thrombocytopenic Purpura in Adults

a report by
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Romiplostim
Romiplostim (AMG 531, Amgen, Thousand Oaks, CA, US) is a novel recombinant thrombopoiesis-stimulating Fc-peptide fusion protein (‘peptibody’) that was developed for the treatment of ITP. Romiplostim was recently approved for the treatment of adults with chronic ITP in the US and Australia. In addition, the European Committee for Medicinal Products for Human Use has issued a positive opinion recommending marketing authorisation for romiplostim in the EU. The molecule has two domains: a peptide domain that binds to the TPO receptor and activates intracellular pathways, stimulating megakaryopoiesis, and a carrier antibody crystallisable (Fc) fragment that undergoes endothelial recirculation, thereby extending its circulating half-life. Romiplostim has no sequence homology with endogenous human TPO.

In vitro studies in human and murine megakaryocytes indicated that romiplostim binds the TPO receptor in a similar manner to endogenous TPO. This stimulates megakaryopoiesis via tyrosine phosphorylation and triggering of Janus kinase (JAK)-2 and signal transducers and activators of transcription (STAT)-5. In healthy volunteers, single intravenous or subcutaneous doses of romiplostim ranging from 0.3 to 10.0µg/kg and from 0.1 to 2.0µg/kg, respectively, were well-tolerated and induced dose-
Coagulation Disorders

| Table 2: Most Common Adverse Events* Reported During the Phase III Studies |
|---------------------------------|----------------|
|                                | Romiplostim (n=84) | Placebo (n=41) |
| Patients with any adverse event | 84 (100)          | 39 (95)        |
| Headache                        | 29 (35)           | 13 (32)        |
| Fatigue                         | 28 (33)           | 12 (29)        |
| Epistaxis                       | 27 (32)           | 10 (24)        |
| Arthralgia                      | 22 (26)           | 8 (20)         |
| Contusion                       | 21 (25)           | 10 (24)        |
| Peteciae                        | 14 (17)           | 9 (22)         |
| Diarrhoea                       | 14 (17)           | 6 (15)         |
| Upper respiratory tract infection| 14 (17)           | 5 (12)         |
| Dizziness                       | 14 (17)           | 0 (0)          |
| Insomnia                        | 13 (16)           | 3 (7)          |
| Myalgia                         | 12 (14)           | 1 (2)          |
| Back pain                       | 11 (13)           | 4 (10)         |
| Nausea                          | 11 (13)           | 4 (10)         |
| Pain in extremity               | 11 (13)           | 2 (5)          |
| Cough                           | 10 (12)           | 7 (17)         |
| Anxiety                         | 9 (11)            | 5 (12)         |
| Gingival bleeding               | 9 (11)            | 5 (12)         |
| Abdominal pain                  | 9 (11)            | 0 (0)          |
| Nasopharyngitis                 | 7 (8)             | 7 (17)         |
| Eczymosis                       | 6 (7)             | 6 (15)         |

*At least 10% of patients in either treatment group. Source: Kuter et al., 2008.22

**Tolerability**

Romiplostim was well tolerated during the two 24-week phase III clinical trials.22 Although adverse events were reported in almost all patients treated with either romiplostim (84/84 [100%]) or placebo (39/41 [95%]), most events were mild to moderate and may have been related to the underlying thrombocytopenia (see Table 2). Very few patients (3 [4%]) discontinued romiplostim because of adverse events. An increase in dizziness, insomnia, myalgia and pain in the extremities and abdomen were noted in the romiplostim-treated patients, the clinical significance of which could not be determined due to the small study size. Thromboembolic events are a concern in patients with ITP, but there was no evidence in the phase III studies that romiplostim treatment increased the risk of such events: the overall incidence of thromboembolic events was 2.4% in both the romiplostim (2/84) and placebo (1/42) patient groups.

Clinically significant bleeding adverse events (i.e. severity grade ≥2, where 2 = moderate, 3 = severe, 4 = life-threatening and 5 = fatal) were observed in 15% of romiplostim- and 34% of placebo-treated patients (p=0.018). The percentage of patients who had bleeding events of grade 3 severity or above was 7 and 12% in the romiplostim and placebo groups, respectively (p=0.36). None of the patients with bleeding events of grade 3 or above had achieved a durable platelet response during the study period.

Serious treatment-related adverse events occurred in two romiplostim-treated patients. After seven weeks of treatment, increased bone marrow reticulin (thought to result from increased transforming growth factor-β released from megakaryocytes within the bone marrow) was noted in one patient. This particular patient had bone marrow reticulin present at baseline and was unresponsive to romiplostim treatment. Reticulin returned to baseline 14 weeks after discontinuation of romiplostim. Similar reversible increases in bone marrow reticulin have been noted previously in animals and humans exposed to other thrombopoietic agents (rhTPO, interleukin [IL]-3 and IL-11).23 The second patient with a serious treatment-related adverse event was an 82-year-old man who experienced a right popliteal arterial embolism. This patient, who had a history of extensive peripheral vascular disease and atrial fibrillation, underwent successful embolectomy and anticoagulation treatment, and continued the study.

Other than abnormal platelet counts, no clinically significant treatment-related changes in vital signs or haematological or serum chemistry values were seen in any of the patients participating in the phase III studies. No antibodies against romiplostim or thrombopoietin were detected.

**Long-term Extension Study**

Patients from the phase III studies could enter a long-term open-label extension study.24 As of July 2007, 143 patients (60% splenectomised; median baseline platelet count 17x10⁹/l, range 1–50x10⁹/l) have been enrolled and 142 have been treated with romiplostim for up to three years (median 65 weeks).

**Efficacy**

A platelet response (>50x10⁹/l and double the baseline value) was observed in 87% (124/142) of the patients overall: 30% (42/138) of patients responded after the first dose, and 51% (71/138) after the third dose of romiplostim. Ad hoc analysis revealed that platelet counts above 50x10⁹/l were maintained for ≥25 and ≥52 consecutive weeks by 78% (102/131), 54% (66/122) and 35% (29/84) of patients, respectively. Altogether, 84% (27/32) of patients receiving concurrent ITP medications at baseline either discontinued these or reduced their dosage by >25%, and the use of rescue medications decreased from 23% (33/142) of patients during weeks one to 12 to 15% (18/124) during weeks 24–36.

**Tolerability**

In the long-term extension study, romiplostim was generally well tolerated by the patients, several of whom were treated for up to three years. Eight patients were found to have bone marrow reticulin present or increased.24 Six patients had mild to moderate reticulin reported (grade 2 or lower or within the normal range). Follow-up bone marrow biopsies in two patients revealed that one patient showed improvement in the amount of reticulin, while the other patient had no change. All of the affected patients continue to be monitored for clinical signs of any progressive bone marrow abnormalities, and to date there has been no evidence of progression to collagen fibrosis, myelofibrosis or clonal myeloproliferative disorder. The incidence and clinical significance of bone marrow reticulin, as well as the extent of regression that occurs following discontinuation of romiplostim treatment, will have to be followed closely in future studies of patients with ITP treated with romiplostim.

Thromboembolic events were reported in seven patients (5%), six of whom had pre-existing risk factors for thrombosis including congestive heart failure, antiphospholipid antibodies, coronary artery disease, hypertension, cancer and/or a history of thrombotic events. Five thromboembolic events were assessed as being serious treatment-related events: one patient with myocardial infarction, one patient with portal vein thrombosis and deep vein thrombosis, one patient with transverse sinus thrombosis and one patient with thrombosis. Thromboembolic events did not appear to be related to higher than normal platelet counts, with most events occurring at counts below the median peak platelet count (167x10⁹/l). All of the events resolved. One patient developed transient neutralising antibodies to romiplostim, but these did not cross-react to endogenous TPO or affect the platelet response.
dependent increases in platelet counts, with peak counts being achieved on days 12–16.\(^8\)

**Phase I–II Clinical Trials**

Two phase I–II trials conducted in the US\(^20\) and Europe\(^21\) in splenectomised patients with ITP found that romiplostim increased platelet counts in a dose-dependent manner. In the US study (n=24), a platelet count ≥50x10^9/l was achieved in seven of 12 patients treated with 3, 6 or 10µg/kg romiplostim. The platelet count was within the target range in four patients and above the target range (i.e. >450x10^9/l) in three patients. In the European study (n=16; romiplostim dose range 30–500µg administered on days one and 15), platelet responses were seen at all dose levels (30, 100 and 300µg). Treatment with the 500µg romiplostim dose was discontinued because of an excessively high platelet count measured in the first patient treated. It was calculated that doses equivalent to ≥1µg/kg induced platelet responses in eight of 11 patients. Transient rebound thrombocytopenia after discontinuation of romiplostim, possibly resulting from enhanced clearance of endogenous TPO by the increased number of megakaryocytes or from discontinuation of concurrent ITP medications during treatment with romiplostim, was reported in approximately 10% (4/41) of patients in a phase I–II study.\(^20\) This suggests that abrupt cessation of romiplostim without tapering or re-initiation of other ITP treatments might be inadvisable.

**Phase III Trials**

Two similarly designed, multicentre, randomised, placebo-controlled, double-blind phase III trials were conducted in parallel. These studies included 63 splenectomised and 62 non-splenectomised patients who had chronic ITP and a mean of three platelet counts ≥30x10^9/l despite treatment for ITP.\(^21\) Patient criteria were identical for both studies, with the exception of splenectomy status. The splenectomised patients had a longer duration of ITP (median eight years versus 2.1 years in non-splenectomised patients) and were more heavily pre-treated, with over 90% of splenectomised patients having received more than three previous treatments for ITP compared with 32% of non-splenectomised patients. Patients were randomised 2:1 to receive romiplostim (n=42 splenectomised; n=41 non-splenectomised) or placebo (n=21 in each study) once weekly for 24 weeks. Patients receiving concurrent ITP treatment with corticosteroids, azathioprine and danazol at a constant dose and schedule were permitted to enter the study. The starting dose of romiplostim or placebo was 1µg/kg and was adjusted to maintain platelet counts in a dose-dependent manner. A rigorous primary end-point was chosen: durable platelet response, defined as a platelet count ≥50x10^9/l during at least six of the last eight weeks of treatment in the absence of rescue medication at any time during the study. A transient response was defined as four or more weekly platelet responses without a durable response from weeks two to 25. Patients assessed as having had a transient response were not allowed to have received rescue medications within eight weeks of the response.

**Efficacy**

Romiplostim increased and sustained platelet counts in both splenectomised and non-splenectomised patients during the study period (see Figure 1). A platelet count ≥50x10^9/l was maintained for a mean (standard deviation (SD)) of 15.2 (7.5) and 12.3 (7.9) weeks for non-splenectomised and splenectomised patients, respectively, over the 24-week course of the study compared with 1.3 (3.5) or 0.2 (0.5) weeks, respectively, for placebo recipients. Durable and overall (durable plus transient) platelet response rates are shown in Table 1. Across both studies, 23 romiplostim- and 16 placebo-treated patients were receiving concomitant ITP medications at enrolment. Most of the romiplostim patients (20/23 [87%], 12/12 splenectomised, 8/11 non-splenectomised) were able to discontinue or substantially reduce (by >25%) these medications by the end of the study, compared with only 38% (6/16, 1/6 splenectomised, 5/10 non-splenectomised) of the placebo patients. Romiplostim also reduced the percentage of patients requiring rescue medications (immunoglobulins, corticosteroids, platelet transfusions) compared with placebo (26.2 versus 57.1% of splenectomised and 17.1 versus 61.9% of non-splenectomised patients; see Figure 2).
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Future Perspectives

In the past, for many adults who suffered continuous severe and symptomatic chronic ITP, splenectomy was almost inevitable if they did not respond to initial treatment with corticosteroids. Today, with the increasing number of alternative treatments, there is great interest in trying various therapies for at least 12 months before opting for splenectomy, and this new way of thinking is reflected in falling rates of this procedure.8 Platelet counts can be increased and sustained at satisfactory levels by romiplostim in a high proportion of patients who were intolerant of other therapies or for whom other treatments have failed. Indeed, the overall response rate of approximately 80% observed with romiplostim is higher than that seen with any other agent used to treat chronic refractory ITP.

What does this all mean for the patient? Patients with chronic ITP complain of fatigue, embarrassment about their appearance due to bruising and decreased ability to carry out their routine daily activities.25 A recent publication highlighted the impaired health-related quality of life (HRQoL) experienced by patients with ITP.26 Using the Short-Form 36 questionnaire, McMillan et al found that the HRQoL of 73 adults with ITP was significantly worse than that of patients with hypertension, arthritis or cancer. Data from studies using the specific ITP Patient Assessment Questionnaire (ITP-PAQ) to examine HRQoL changes in patients participating in the two phase III studies27 and the open-label romiplostim extension study28 indicated that treatment with romiplostim significantly improves HRQoL in this patient population.

Romiplostim appears to be generally well tolerated during prolonged treatment periods of up to three years, with few patients discontinuing treatment for adverse events. Most patients can reduce or discontinue the use of concomitant immunosuppressive treatments, including corticosteroids, azathioprine and danazol, as well as decreasing their need for rescue therapies such as immunoglobulins and corticosteroids. As romiplostim is not an immunosuppressive agent, the problems associated with immunosuppressive treatment can be avoided.

There are concerns about the potential increased long-term risk of malignancy or stimulation of solid tumour growth in patients treated with growth factors. Some myeloid haematopoietic malignant cells have been found to express c-Mpl, which is a member of the cytokine receptor superfamly encoded by the proto-oncogene c-mpl and the receptor to which endogenous TPO and romiplostim bind.29 Follow-up of patients participating in the ITP studies of romiplostim has shown no evidence of stimulation of tumour growth. However, patient safety is paramount and therefore vigilant monitoring by clinicians and regulatory bodies will help to ensure patient wellbeing and the rapid identification and corrective treatment of any possible side effects that appear with time.

In conclusion, romiplostim provides a novel option for the treatment of adults with chronic ITP and could change the way in which patients are treated in the future. Looking ahead, romiplostim is currently also being evaluated for the treatment of other conditions in which suboptimal platelet production contributes to thrombocytopenia, including myelodysplastic syndromes and certain chemotherapy-induced thrombocytopenias.

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