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

a report by
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Idiopathic or immune thrombocytopenic purpura (ITP) is an autoimmune condition characterised by an abnormally low number of platelets in the circulating blood. Initially, ITP was thought to be caused by antibody-mediated platelet destruction,[1] but better understanding of the pathogenesis of the condition has indicated that insufficient or inadequate platelet production also plays a role.[2] ITP can be acute or chronic. Acute ITP is normally seen in children between three and five years of age, often occurs after a viral infection and has a seasonal incidence. It usually presents, as the name suggests, with sudden onset of bruising and bleeding.[3] In contrast, chronic ITP is typically seen in adults, is usually more serious and has no seasonal variation. A proportion of patients with ITP may be diagnosed incidentally, but frequently there is a slow, insidious onset of symptoms. In contrast to acute ITP, where remission is seen in the majority of patients, fewer than 10% of patients with chronic ITP experience spontaneous remission and therefore these patients need long-term management.

Corticosteroids are typically used as initial treatment, but if platelet levels fall precipitously or the clinical situation is serious and there is a need to rapidly raise the count, intravenous immune globulins (including anti-D) may be administered. A variety of agents have been used when first-line treatments fail, but few of these are specifically licensed for use in ITP. These agents include steroids (dexamethasone), azathioprine and other cytotoxic agents such as cyclophosphamide, as well as immune-suppressive agents such as rituximab, cyclosporine and mycophenolate mofetil, which act primarily by interfering with autoantibody production or by blocking platelet destruction. These treatments may be associated with significant side effects, and the increased incidence of infection due to immune suppression is associated with up to 50% of the mortality seen in ITP.[4,5]

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The role of splenectomy in the treatment algorithm varies because the decision to perform splenectomy is often patient-specific. Approximately one-third of patients do not respond to splenectomy,[6,7] and in a recent meta-analysis a five-year relapse rate of 32% after splenectomy was reported in this patient population.[8] In addition, the risks and benefits of this surgical procedure to the patient must be carefully weighed. Increasingly, patients are opting out of surgery as they become more aware of the risk–benefit ratio and the alternative treatments available to them.[9]

It was recognised that platelet production is suboptimal in a substantial proportion of patients with ITP,[10,11] which prompted a search for treatments that enhance platelet production. Thrombopoietin (TPO; megapoietin; megakaryocyte growth and development factor; *c*-mpl ligand), the key regulator of megakaryopoiesis and platelet production, was identified in 1994.[12,13] The first studies with recombinant thrombopoietins (pegylated recombinant human megakaryocyte growth and development factor [PEG-rHuMGDF] and recombinant human TPO [rhTPO]) were discontinued because of problems with the development of cross-reacting antibodies, leading to severe, persistent thrombocytopenia.[14] Nevertheless, this research paved the way for the development of the next generation of thrombopoiesis-stimulating therapies, which produced romiplostim. Other products in development include the small-molecule TPO receptor agonists eltrombopag[15] and AKR-501.[16] These newer agents and their place in treatment strategies have recently been reviewed.[17]

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.[18]

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.[19] 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-

Table 2: Most Common Adverse Events* Reported During the Phase III Studies

	Romiplostim (n=84) n (%)	Placebo (n=41) n (%)
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)
Petechiae	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)
Ecchymosis	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 thrombopoetic 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 17x10^9/l, range 1–50x10^9/l) have been enrolled and 142 have been treated with romiplostim for up to three years (median 65 weeks).

Efficacy

A platelet response (>50x10^9/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 50x10^9/l were maintained for ≥10, ≥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 (167x10^9/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.[18]

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.

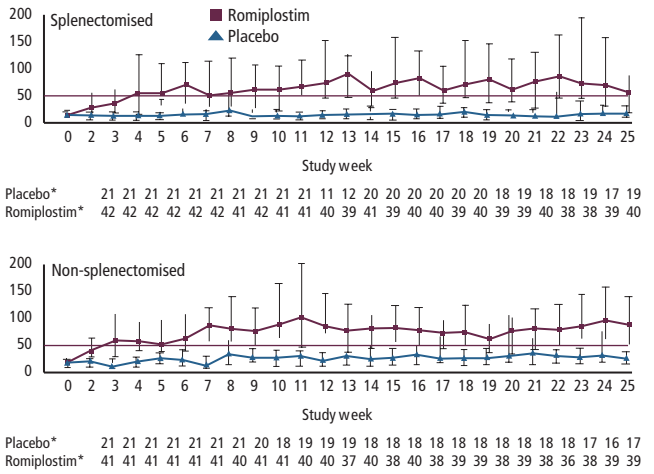
Phase III Trials

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 within a target range of 50–200x10^9/l. 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 week two to week 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

Figure 1: Increase and Maintenance of Weekly Platelet Counts in Splenectomised and Non-splenectomised Patients Treated with Romiplostim



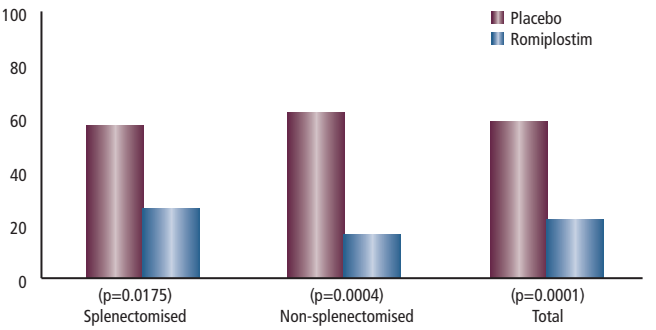
**Number available for measurement.*
Source: Kuter et al., 2008.[22]

Table 1: Incidence of Durable* and Overall† Platelet Response

	Splenectomised Patients n (%)			Non-splenectomised Patients n (%)		
	Romiplostim (n=42)	Placebo (n=21)	p-value‡	Romiplostim (n=41)	Placebo (n=21)	p-value‡
Durable response	16 (38)	0 (0)	0.0013	25 (61)	1 (5)	<0.0001
Overall response	33 (79)	0 (0)	<0.0001	36 (88)	3 (14)	<0.0001

**Durable 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.*
†Either durable or transient response where transient response defined as four or more weekly platelet responses without a durable response from weeks two to 25.
‡Cochran-Mantel-Haenszel test.

Figure 2: Proportion of Patients Receiving Rescue Medication (by Study and Integrated)



Source: Kuter et al., 2008.[22]

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*).

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.[9] 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 studies[27] and the open-label romiplostim extension study[28] 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 superfamily 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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