The Emergence of Thrombopoietin Receptor Agonists as a Novel Treatment for Immune Thrombocytopenia

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Abstract

Two thrombopoietin receptor agonists, romiplostim and eltrombopag, have completed phase III trials in patients with chronic immune thrombocytopenia and were shown to successfully improve platelet counts. Due to their proven efficacy and favourable side-effect profile, they have been granted marketing authorisation for use in this condition in the US, the EU and other countries. This article focuses on these two agents, their pre-clinical development and clinical trial results.

Keywords

Immune thrombocytopenic purpura (ITP), thrombopoietin receptor (TPO-R) agonists, romiplostim, eltrombopag, platelet response

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Primary immune thrombocytopenia (ITP), until recently referred to as idiopathic thrombocytopenic purpura (ITP), is an acquired autoimmune disorder defined by isolated thrombocytopenia (platelet count <100x 10^9/l) and the exclusion of other causes of thrombocytopenia.[1] The clinical manifestations of ITP are highly variable and range from the completely asymptomatic patient to frank haemorrhage from any site, the most serious of which is intracranial.[2] Several matters in terms of the optimal treatment of adult patients with chronic ITP remain unresolved. There is limited evidence based on randomised trials to guide management decisions and for some patients morbidity from the side effects of therapy may exceed any problems caused by the ITP.[2,3]

Currently, treatment is considered appropriate for symptomatic patients and for those at risk of bleeding.[4–8] Once the decision to treat a patient with ITP has been made, provided the patient's situation is not life-threatening, corticosteroids are the standard initial treatment.[4] Intravenous immunoglobulins are generally recommended for patients with critical bleeding and for those unresponsive to corticosteroids.[4] The platelet count also can be supported by anti-D immunoglobulin, which is active in 70–75% of Rh-positive patients only in the pre-splenectomy setting.[9] Splenectomy is traditionally considered to be the second-line treatment in adults with ITP in whom achieving a safe platelet count with initial prednisone therapy has failed. For those who are refractory or relapse after splenectomy, there is a long list of available approaches,[5] most of which have modest response rates.

Quite recently a new class of drugs, the thrombopoietin receptor (TPO-R) agonists, have shown remarkable efficacy. Recently published guidelines based on the highest level of evidence recommend the use of these agents for the treatment of patients with chronic ITP.[10] Two of these drugs, romiplostim and eltrombopag, have been approved for use in chronic refractory ITP in the US, the EU and in many other countries. This article discusses the rationale for megakaryocyte stimulation in ITP and presents the results of clinical trials with these new agents.

Pathophysiology of Immune Thrombocytopenia

For many years the prevailing view was that ITP resulted solely from excessive platelet clearance and destruction, mediated by autoreactive antibodies directed against platelet glycoproteins.[11] Kinetic studies conducted in the early 1970s using chromium-51 (^{51}Cr)-labelled allogeneic platelets demonstrated shortened platelet survival and increased platelet turnover in ITP patients,[12,13] consistent with this hypothesis. Interestingly, platelet survival was found to be inversely related to the quantity of bound antiplatelet antibodies.[14]

However, when autologous indium-111 (^{111}In)-labelled autologous platelets were studied in the 1980s it became evident that there was considerable heterogeneity in platelet turnover between patients.[15–19] Although the platelet lifespan is often markedly decreased, in some patients the lifespan is only mildly reduced; furthermore, platelet turnover (a measure of platelet production) is frequently suboptimal.

Table 1: Pharmacological Characteristics of Romiplostim and Eltrombopag

	Romiplostim*	Eltrombopag**
Chemical structure	Peptibody	Hydrazone organic compound
Molecular weight	29,542Da	564.6Da
Mechanism of binding to TPO-R	Similar to endogenous TPO	Different from endogenous TPO
Formulation	Powder for injection, 250 and 500µg	Tablets, 25 and 50mg
Route of administration	Subcutaneous†	Oral
Frequency of administration	Once weekly	Once daily
C_0 (pg/ml)	2,810±1,170 at 0.3µg/kg IV 12,900±1,800 at 1.0µg/kg IV 211,000±32,000 at 10µg/kg IV	–
C_{max}	–	7.3µg/ml at 75mg/day
AUC	964±1,310pg/hour/ml at 0.3µg/kg IV 26,700±19,100pg/hour/ml at 1.0µg/kg IV 1,530,000±260,000pg/hour/ml at 10µg/kg IV	79.0µg/hour/ml at 75mg/day
CL (ml/kg^{-1}/h^{-1})	754±435 at 0.3µg/kg IV 63±55.7 at 1.0µg/kg IV 6.69±1.03 at 10µg/kg IV	NR
Vc (ml/kg)	122±51 at 0.3µg/kg IV 78.8±10.7 at 1.0µg/kg IV 48.2±7.4 at 10µg/kg IV	NR
t½ (hour)	1.50±2.83 at 0.3µg/kg IV 2.41±1.56 at 1.0µg/kg IV 13.8±3.9 at 10µg/kg IV	>12
t_{max} (median)	13 days at 0.3µg/kg IV 12 days at 1.0µg/kg IV 15 days at 10µg/kg IV	15 days at 75mg/day

**In the phase I study, eligible subjects were randomised in a ratio of 2:1 to receive a single injection of romiplostin at escalating doses or placebo.[33]*
***In the phase I study, subjects received eltrombopag or placebo as oral capsules once daily for 10 days at doses of 5, 10, 20, 30, 50 or 75mg.[49]*
†Romiplostim was given intravenously to normal volunteers.
AUC = area under serum concentration-time curve; C_0 = maximum serum concentration at time 0 after intravenous (IV) bolus administration; CL = systemic clearance; C_{max} = maximum plasma concentration; NR = not reported; t½ = half-life; t_{max} = time when peak platelet count was observed; TPO = thrombopoietin; TPO-R = thrombopoietin receptor; Vc = central volume of distribution.

Overall, approximately 40% of patients with ITP have a reduced platelet turnover.[18–20] In keeping with this finding, autoantibodies against platelet glycoproteins have been shown to interfere with the maturation of megakaryocytes, resulting in reduced platelet production.[21,22] Furthermore, most megakaryocytes found in ITP show ultrastructural features of apoptosis or para-apoptosis and these morphological changes can be induced in cultured megakaryocytes with ITP plasma.[23] *In vitro* studies have shown that antibodies that target the platelet glycoprotein (GP) Ib-IX-V complex may induce thrombocytopenia by inhibiting megakaryopoiesis[22,24] and proplatelet formation.[25]

A Novel Therapeutic Approach – Thrombopoietic Agents

Most traditional treatments for ITP aim to suppress the production of autoantibodies and/or inhibit macrophage-mediated destruction of opsonised platelets. However, as discussed above, several patients have impaired platelet production rather than increased platelet destruction. Additionally, ITP patients have normal or slightly elevated TPO levels, whether measured in plasma or serum. The levels are always lower than the concentrations found in thrombocytopenias resulting from megakaryocytic hypoplasia.[26–28] The reasons for this finding have not been elucidated, but probably involve active TPO uptake and destruction by the expanded megakaryocyte mass in ITP.

On these grounds, growth factor stimulation of megakaryopoiesis was expected to increase the platelet count in patients with ITP and was investigated in clinical trials. First-generation TPOs included recombinant human TPO (rhTPO) and a non-glycosylated, truncated form of TPO coupled to polyethylene glycol. The recombinant protein – megakaryocyte growth and differentiation factor (MGDF) – had important differences compared with native TPO that probably explained its immunogenic potential.[29] When administered subcutaneously to platelet donors, some of the donors produced antibodies against MGDF that cross-reacted with endogenous TPO, thereby causing severe thrombocytopenia.[30] This adverse event led to the discontinuation of clinical research with both MGDF and the full-length form of TPO.

Despite this, early reports of the use of pegylated recombinant human MGDF suggested that megakaryocyte stimulation may actually be effective in ameliorating the thrombocytopenia associated with ITP.[31,32] This lent further support to the use of second-generation thrombopoietic agents. The theoretical advantage of the second-generation TPO-R agonists, also referred to as TPO-R agonists, is that they bear no structural similarity with native TPO and should not trigger auto-immune anti-TPO antibodies as is the case with pegylated-MGDF. These novel agents include TPO peptide agonists, TPO non-peptide agonists and TPO agonist antibodies. All of these bind to and activate the TPO receptor in different ways.[29] All have been engineered to have unique pharmacological attributes.

The molecules for which clinical trials in patients with chronic ITP have been completed are romiplostim – a subcutaneously administered TPO-R peptide agonist and eltrombopag – an orally bioavailable, non-peptide TPO-R agonist (see *Table 1*). Clinical trials investigating another non-peptide agonist, AKR-501, in chronic ITP patients have recently been initiated.

Romiplostim

Pharmacology

Romiplostim (formerly AMG 531), developed by Amgen, is a recombinant protein known as a 'peptibody'. It is made up of two disulphide-bonded immunoglobulin G1 (IgG1) heavy-chain and kappa light-chain constant regions (Fc fragments). Each of these is covalently bound at residue 228 of the heavy chain with two identical peptide sequences linked via polyglycine.[33] The carrier Fc component of the molecule binds to the FcRn salvage receptor and undergoes endothelial recirculation, resulting in a substantially longer half-life (t½) than the peptide alone.[34] The peptide component binds to and activates the human TPO-R in a similar manner to endogenous TPO via activation of signalling pathways, including tyrosine phosphorylation of TPO-R, janus kinase 2 and signal transducer and activator of transcription 5 (STAT5).[35]

The peptibody exerts a dose-dependent effect on the growth of megakaryocytic colony-forming units from murine marrow cells. It also increased megakaryocyte ploidy and maturation *in vitro*. Furthermore, it effectively competed with TPO for binding to human TPO-R *in vitro*.[35]

Phase I–II Clinical Trials

In healthy volunteers, single intravenous or subcutaneous doses of romiplostim ranging from 0.3 to 10.0µg/kg and from 0.3 to 2.0µg/kg, respectively, were well tolerated. The drug-induced dose-dependent increases in platelet counts, with peak counts being achieved on days 12–16.[33]

Two phase I–II clinical trials were conducted in the US[36] and Europe[37] in splenectomised adult patients with ITP. Platelet response was defined as a doubling of the baseline platelet count to between 50 and 450x10^9/l.

In phase I of the US study,[36] seven of 12 patients treated with romiplostim 3, 6 or 10µg/kg achieved platelet counts within the target range. Three of the patients achieved counts above the target range (i.e. >450x10^9/l). In phase II of the same trial, 21 patients were randomly assigned to receive six weekly subcutaneous injections of romiplostim (1, 3 or 6µg/kg) or placebo. However, the highest-dose cohort was closed after the platelet count increased to 520x10^9/l in one patient on day 21.

In the European study[37] (n=16, romiplostim dose range 30–500µg administered on days 1 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 out of 11 patients. Transient rebound thrombocytopenia (defined as a platelet count <10x10^9/l or below baseline) occurred after discontinuation of romiplostim in four patients (10%) in the US study and in one patient in the European study. This suggests that abrupt cessation of romiplostim without tapering or reinitiation of other ITP treatments should be avoided.

Phase III Studies

Two similarly designed, multicentre, randomised, placebo-controlled, double-blind phase III trials were conducted in parallel. One trial enrolled patients with a prior splenectomy (n=63) and the other enrolled patients who had not undergone splenectomy (n=62).[38] Both trials included adult patients who had chronic ITP, a mean of three platelet counts ≤30x10^9/l despite treatment for ITP and were over 18 years of age. 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.

The primary end-point was a durable platelet response. This was defined as a weekly platelet count of ≥50x10^9/l at a weekly study visit for six or more of the final eight weeks of treatment. Secondary objectives included:

- adverse events;
- proportion of transient responses (four or more weekly platelet responses without a durable platelet response from week 2 to 25);
- changes in concurrent ITP therapies;
- number of weekly platelet responses;
- proportion of patients receiving rescue medications; and
- overall platelet response (durable and transient responses).

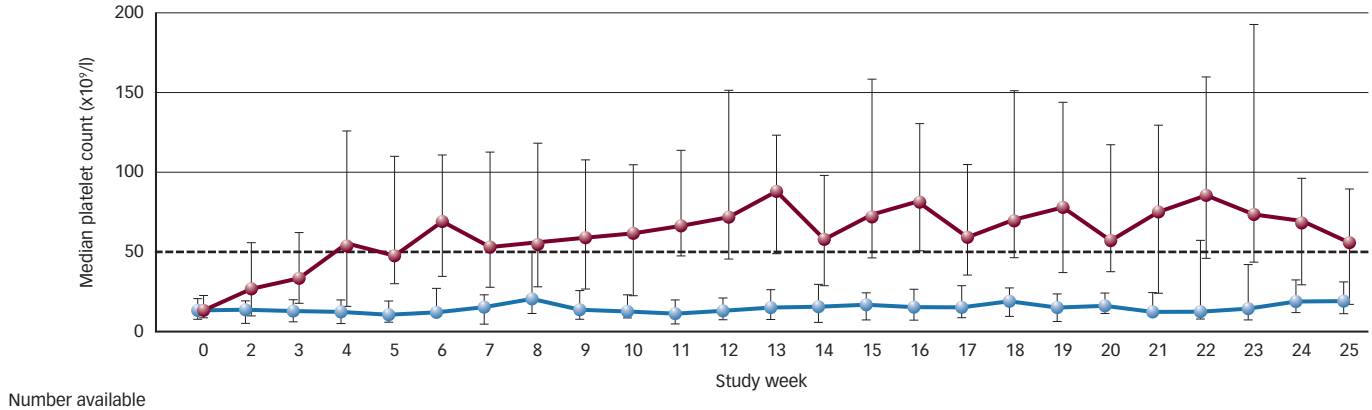
The splenectomised patients had a longer duration of ITP (median eight years versus 2.1 years in non-splenectomised patients) and were more heavily pre-treated. More than 90% of splenectomised patients had received more than three previous treatments for ITP compared with 32% of non-splenectomised patients. Patients receiving no current treatment or concurrent ITP treatment with corticosteroids, azathioprine or danazol at a constant dose and schedule were permitted to enter the study. The starting dose of romiplostim or placebo was 1µg/kg (with a maximum dose of 10µg/kg) and was adjusted to keep platelet counts within a target range of 50–200x10^9/l. 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 of 15.2 (standard deviation [SD] 7.5) and 12.3 (SD 7.9) weeks for non-splenectomised and splenectomised patients, respectively, over the 24-week course. This was compared with 1.3 (SD 3.5) or 0.2 (SD 0.5) weeks, for the non-splenectomised and splenectomised patients receiving placebo. Most of the romiplostim patients (20 out of 23 patients [87%], 12 out of 12 splenectomised and eight out of 11 non-splenectomised) were able to discontinue or substantially reduce concomitant ITP medications (by >25%) by the end of the study. This was compared with only 38% of the placebo patients (six out of 16 patients, one in six splenectomised and five in 10 non-splenectomised). Romiplostim also reduced the percentage of patients requiring rescue medications (immunoglobulins, corticosteroids and platelet transfusions) compared with placebo (26.2 versus 57.1% of splenectomised and 17.1 versus 61.9% of non-splenectomised patients).

Data pooled from the two trials mentioned above, adjusted for splenectomy status, showed significant improvement in health-related quality of life (HRQoL) in patients treated with romiplostim.[39]

In a recently-published trial, non-splenectomised patients with ITP were randomly assigned to either the standard care medications prescribed by their treating physicians or weekly romiplostim injections.[40] The study enrolled 234 adult ITP patients at 85 sites in North America, Europe and Australia. Treatment was considered to be ineffective if platelet levels remained low (≤20x10^9/l) for four consecutive weeks or if participants experienced major bleeding events or required changes in therapy, including splenectomy.

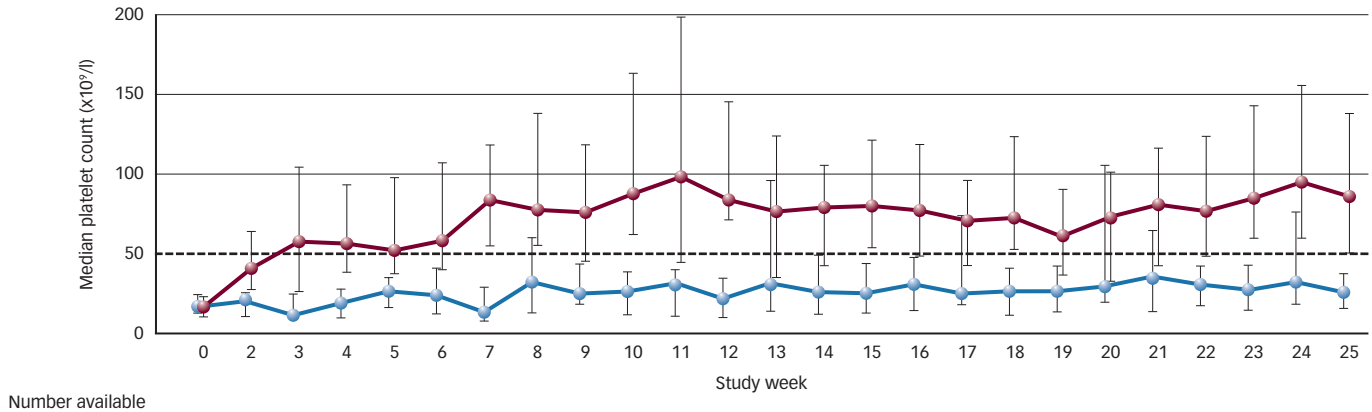
Figure 1: Platelet Responses of Patients Treated with Either Romiplostim or Placebo in the Randomised Phase III Study

A. Splenectomised



Number available for measurement																									
Placebo	21	21	21	21	21	21	21	21	21	21	11	12	20	20	20	20	20	20	18	19	18	18	19	17	19
Romiplostim	42	42	42	42	42	42	41	42	41	41	40	39	41	39	40	40	39	40	39	39	40	38	38	39	40

B. Non-splenectomised



Number available for measurement																									
Placebo	21	21	21	21	21	21	21	20	18	19	19	19	18	18	18	18	18	18	18	18	18	18	17	16	17
Romiplostim	41	41	41	41	41	41	40	41	41	40	40	37	40	38	40	38	39	39	38	39	38	36	38	39	39

Romiplostim Placebo

Median platelet count at every weekly study visit for splenectomised (A) and non-splenectomised (B) patients. Data include all patients, even those who received rescue drugs. Error bars indicate the range from the first to third quartiles. Dashed line indicates platelet count of 50x10⁹/l.
Source: Kuter et al., 2008.[38] Figures 1A and B reprinted with permission from Elsevier, The Lancet*, 2008;371:395–403.*

At the end of the 52-week study period, participants receiving romiplostim achieved and maintained desirable platelet levels at 2.3 times the rate of those on standard care.[40] Romiplostim treatment was at least three times as effective as other treatments and participants receiving the drug had a 90% reduction in the need for splenectomy. Serious adverse events occurred in 23% of patients receiving romiplostim and 37% of patients receiving standard care.[40]

Long-term Extension Study

Patients were eligible for the open-label, multicentre extension study if they had completed a prior study using romiplostim for the treatment of chronic ITP (regardless of whether they had received romiplostim or placebo) and had a platelet count ≤50x10⁹/l.[41] Those who had previously received romiplostim were initially given the same dosage of the drug as they received in the prior study. They were given 1µg/kg/week if >24 weeks had elapsed since their last dose or they had previously received placebo. The romiplostim dosage was adjusted throughout the study, depending on platelet response; the target platelet count range was 50–250x10⁹/l. Patients could continue to receive stable dosages of concurrent ITP medications (corticosteroids, azathioprine or danazol). The three-year update analysis included 143 enrolees, with a median age of 53 years, 60% splenectomised and 22% on concurrent ITP therapy at baseline. Of these patients, 142 were treated with romiplostim (mean duration 69 weeks).[41] Platelet responses (platelet count >50x10⁹/l and double baseline) were observed in 87% of all patients and occurred on average 67% of the time in responding patients. The mean (±SD) of the average weekly dose was 5.9±3.9µg/kg. In 77% of patients, the romiplostim dose remained within 2µg/kg of their most frequent dose at least 90% of the time. Ninety patients (63%) received treatment by self-administration.

Safety

In the phase I–II ITP studies, the most frequently reported event was mild to moderate headache.[42] In the phase III trials, serious

treatment-related adverse events occurred in two romiplostim-treated patients.[38] 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).[43] However, in a mouse model expression of a constitutively active mutant TPO-R, TPO-RW515A, resulted in the development of a myelofibrosis-like disease.[44]

The second patient with a serious treatment-related adverse event was a man 82 years of age 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.

In the long-term extension study, romiplostim was generally well tolerated by patients.[41] Eight patients were found to have bone marrow reticulin present or at increased levels. Six of these 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 present over time, while the other patient had no change. All of the patients affected continue to be monitored for clinical signs of any progressive bone marrow abnormalities.

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.

Twelve thromboembolic events were reported in seven patients (5%) on long-term treatment with romiplostim. Six of these 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 (thrombosed inflammatory fibrosis at the site of a central line).

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 with endogenous TPO or affect the platelet response. There were no clinically significant changes in laboratory parameters, blood coagulation or platelet aggregation in any of the studies.

Eltrombopag

Pharmacology

Eltrombopag (formerly SB497115) is a non-peptide TPO-R agonist developed by GlaxoSmithKline (see *Table 1*). It is administered as a daily oral tablet. In pre-clinical studies, eltrombopag was shown to stimulate human megakaryocyte differentiation and proliferation in a dose-dependent manner via stimulation of the TPO-R. Eltrombopag displays high receptor-specific and species-specific binding selectivity for human TPO-R. The response of normal human TPO-R has been elucidated by measuring growth and differentiation of human bone marrow *in vitro*: these studies demonstrated human and chimpanzee-specific activation of TPO-R-expressing cells via activation of STAT5.[45] By contrast, no eltrombopag-induced platelet activation was observed in other species tested, including cynomolgus macaques, rhesus monkeys, pigs, dogs, ferrets, rabbits, rats and mice.[46]

The mechanisms leading to activation of the TPO-R on eltrombopag binding are different from those of romiplostim. Eltrombopag interacts with the TPO-R at a binding site distant from that of TPO and appears to initiate signal transduction by a mechanism different from that of endogenous TPO. In fact, Erhardt et al. reported that eltrombopag induced the phosphorylation of STAT proteins, but not of AKT, whereas hrTPO induced the phosphorylation of AKT in addition to the STAT proteins.[47] Since eltrombopag and TPO do not bind to the same site, competitive binding is avoided and eltrombopag and TPO confer additive cell-signalling effects.[48]

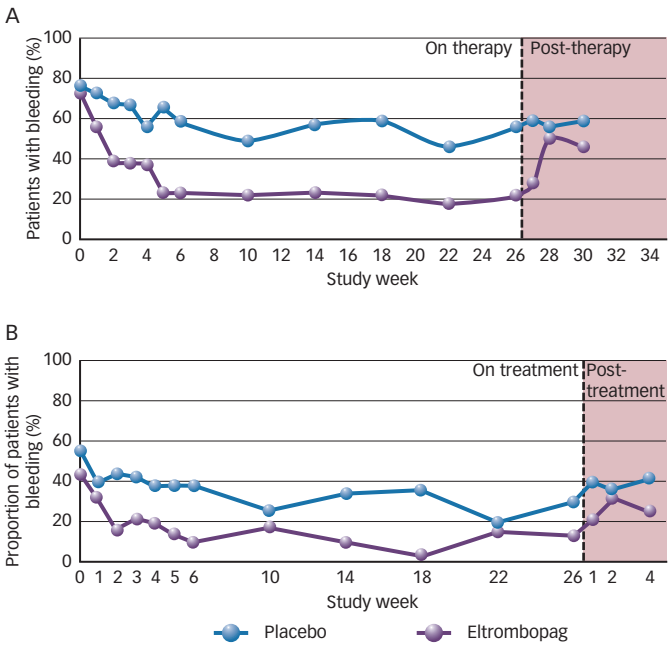
The pharmacokinetics of eltrombopag were studied in a phase I study in healthy volunteers and in ITP patients.[49,50] The terminal t½ averaged more than 12 hours on day 10 across all doses, with the exception of the 5mg dose (which had a t½ of nine hours). Limited pharmacology data suggest that in patients of East Asian ethnicity, exposure to eltrombopag expressed as area under the serum concentration-time curve was approximately 70–80% higher than in non-Asian patients who were predominantly Caucasian. An initial dose decrease to 25mg/day is therefore recommended in East Asian patients.[51]

Phase I–II Clinical Trials

Eltrombopag increased platelet counts in a dose-dependent manner in healthy, non-Asian adults, but the drug only appeared to be active at doses >20mg.[49] A consistent increase in platelet count started after eight days of repeat dosing with eltrombopag and the time from first dose to peak platelet count was 16 days. By day 22 (12 days after the last dose of eltrombopag) platelet counts had returned to baseline values, with no evidence of rebound thrombocytopenia following discontinuation of treatment. Eltrombopag did not prime platelets for activation and did not adversely affect platelet function.[52]

In a phase II, placebo-controlled, double-blind trial, the platelet counts of 118 patients with chronic ITP were analysed after six weeks of daily oral treatment with placebo or eltrombopag at doses of 30, 50 or 75mg.[53] There was a dose-dependent increase in the proportion of responders, with a statistically significant effect in the 50 and 75mg arms compared with placebo. The median platelet count on day 43 was 16x10^9/l in the placebo group and 26x10^9/l, 128x10^9/l and 183x10^9/l in the 30, 50 and 75mg groups, respectively. Furthermore, there were fewer bleeding events in those receiving the 50mg (7%) and 75mg (4%) doses than in those receiving placebo (14%) or 30mg eltrombopag (17%). The occurrence of bleeding symptoms gradually

Figure 2: Proportions of Patients with (A) Bleeding and (B) Clinically Significant Bleeding



A: World Health Organization (WHO) grades 1–4. Source: Cheng et al., presented at the American Society for Hematology Annual Meeting 2008; B: WHO grades 2–4. Source: Cheng et al., 2011.[55] Figure 2B: Reprinted with permission from Elsevier, The Lancet*, 2011;377: 393–402.*

returned to baseline levels during the six weeks of follow-up, as the platelet counts returned to near-baseline levels.[51]

Phase III Studies

The subsequent phase III trial (TRA100773B) demonstrated similarly positive results.[54] This randomised, double-blind, placebo-controlled study enrolled 114 adults with chronic ITP and baseline platelet counts of <30x10^9/l. These patients were randomised to standard care plus either placebo (38 patients) or eltrombopag 50mg (76 patients) once daily for six weeks. The eltrombopag dose could be increased to 75mg in patients not responding after the initial three weeks of treatment. All patients had received prior ITP treatment and 52% had received at least three prior therapies.

At the end of the trial, 16% of placebo patients and 59% of eltrombopag patients achieved the primary end-point (platelet count ≥50x10^9/l), with median counts of 18x10^9/l in the placebo arm and 69x10^9/l in the eltrombopag arm.[54] Importantly, there was a significantly lower incidence of bleeding events during treatment with eltrombopag compared with placebo (p=0.029), with clinically significant bleeding (World Health Organization [WHO] grades 2–4) observed in fewer eltrombopag patients (16%) than placebo patients (36%).[54]

The RAndomized placebo-controlled Idiopathic thrombocytopenic purpura Study with Eltrombopag (RAISE) phase III trial that assessed the safety, efficacy and tolerability of eltrombopag in a long-term treatment setting (up to six months) has been completed.[55] Adult patients with previously treated chronic ITP and who had baseline platelet counts <30x10^9/l were randomly allocated in a 2:1 ratio to eltrombopag (n=135) or placebo (n=62). The primary end-point was the odds of responding during the entire six-month treatment period.

Eltrombopag increased and maintained platelet counts during the study period irrespective of splenectomy status, baseline platelet counts and concomitant ITP medication.[55] By contrast, platelet counts remained low in patients receiving placebo, despite the use of rescue treatment in 40% of those participants. Patients assigned to eltrombopag were approximately eight times more likely to achieve target platelet counts ranging from 50–400x10^9/l (odds ratio [99% confidence interval] = 8.2 [3.59–18.73]; p<0.0001). In the eltrombopag group, the rates of bleeding (WHO grades 1–4) and clinically significant bleeding (WHO grades 2–4), see *Figure 2*, were reduced from baseline by roughly 50% from day 15 throughout the six-month treatment period. The rates returned to near baseline after discontinuation of eltrombopag.[55]

More than half of the eltrombopag-treated patients (37 out of 63 [59%]) were able to reduce concomitant treatment compared with 32% (10 out of 31) of the placebo patients (p=0.02). In addition, eltrombopag reduced the percentage of patients requiring rescue medications compared with placebo (18 versus 40%, respectively; p=0.001).[55]

Several other eltrombopag trials investigating the short- and long-term treatment of chronic ITP have been conducted, although results are only available in abstract form. Repeat ExPosure to Eltrombopag in Adults with Idiopathic Thrombocytopenic Purpura (REPEAT) was an open-label dose study involving three cycles of six weeks on treatment, followed by four weeks off treatment. This study assessed the safety and efficacy of repeated administration of eltrombopag.[56] In the REPEAT study, response was maintained during episodic use with multiple courses of eltrombopag. In particular, by days eight and 15 of each cycle, >50 and >75% of patients had responded, respectively.

The Eltrombopag eXTENded Dosing (EXTEND) study is an open-label study for patients who have participated in previous eltrombopag trials and wish to take eltrombopag for the long-term treatment of their chronic ITP. This study is still active (see http://clinicaltrials.gov/ct2/show/NCT00351468) and at the time of the latest analysis, 299 patients had received eltrombopag.[57] The median duration of eltrombopag treatment was 204 days (range: two to 861 days). At baseline, 33% of patients were receiving concomitant ITP medication and 38% had been splenectomised. Overall, 86% of patients (257 out of 299) had achieved platelet counts ≥50x10^9/l.[57]

Splenectomised and non-splenectomised patients responded equally well (89 and 82%, respectively) to eltrombopag. They responded regardless of baseline use of concomitant ITP medications. At baseline, 56% of patients reported bleeding symptoms (WHO grades 1–4) compared with 27, 21, 40 and 25% at six, 12, 18 and 24 months, respectively.[57]

Improvements in HRQoL in the RAISE (and EXTEND) studies have been assessed with various validated tools (the Short Form 36 version 2 [SF-36v2]; the Functional Assessment for Chronic Illness Therapy [FACIT]-Fatigue subscale and six-item subset of the Functional Assessment of Cancer Therapy-Thrombocytopenia [FACT-Th] scale).[58] In both trials, elevations in platelet counts and reductions in bleeding were associated with improvements in HRQoL across multiple domains, measures of fatigue and activities of daily living.

Safety

No serious adverse events were reported during the phase I study in healthy adults. Within the controlled clinical studies, adverse events were mostly mild to moderate.[49] The rate of serious adverse events was similar between the study groups (12% in the placebo group and 11% in the eltrombopag group).

Aggregate results from the placebo-controlled clinical trials reveal that patients in the eltrombopag arm were more likely to experience nausea (6 versus 4%), vomiting (4 versus 3%) and menorrhagia (4 versus 1%).[51] Headache was the most common adverse event in both groups (≥30%). A higher incidence of serum liver test abnormalities, more specifically alanine transferase (ALT) elevations, was reported in the eltrombopag group. Approximately 5% of eltrombopag-treated patients experienced ALT ≥3 times the upper limit of normal compared with 2% of placebo-treated patients.[59] Approximately 2% of patients withdrew from the study due to elevations in ALT or bilirubin.

Liver toxicities were typically mild, reversible and unaccompanied by clinical symptoms; some patients had more marked elevations and discontinued therapy. For this reason, it is prudent to monitor liver function tests periodically, every four weeks or so, even in patients on long-term eltrombopag.

In the controlled studies, one thrombotic/thromboembolic complication was reported within the groups that received eltrombopag and none within the placebo groups.[53] Seven patients experienced thrombotic/thromboembolic complications in the extension study.[60] Data collection across all ITP studies indicate that the frequency of thromboembolic events observed during eltrombopag treatment (3.8%) is similar to that reported in the literature and prior to enrolment in the eltrombopag programme (3.2%).[61] Importantly, no correlation has been observed between platelet count increases or maximum platelet counts and thromboembolic events.

Serious haemorrhages occurred in two patients receiving eltrombopag, one patient receiving placebo and five patients following discontinuation of eltrombopag. Most of these patients had developed rebound worsening of thrombocytopenia (platelet counts $<10x10^9$/l) prior to the serious haemorrhagic episode.[51] However, from a recent analysis of safety data from the ITP programme 8% of patients treated with eltrombopag (n=20) and 8% of patients treated with placebo (n=10) experienced drops in platelet counts to $<10x10^9$/l.[62] It is unclear at this time whether these decreases may be related to study medication or may represent normal fluctuations in platelet counts in patients with chronic ITP.

There were no clinical or laboratory symptoms suggestive of bone marrow fibrosis. Adverse reactions reported in the extension study occurred in a pattern similar to those reported in the placebo-controlled studies. There were no significant changes in blood coagulation, platelet aggregation, electrocardiographic findings or preliminary results of ophthalmic examinations in any of the studies.[51]

Conclusion

Stimulation of platelet production is a new approach to treating patients with chronic ITP, which has traditionally aimed to decrease platelet destruction. The rationale underlying this approach resides in the evidence of both impaired platelet production and low TPO levels. While the inhibitory role of platelet autoantibodies can account for the ineffective megakaryopoiesis, the reason why endogenous TPO levels are below adequate levels in ITP is not yet clear. There is a poor correlation with megakaryocyte mass. Despite this, it was hypothesised that the use of the new thrombopoietic agents could fix the disturbed balance of platelet destruction and platelet production.

The results of randomised clinical trials investigating romiplostim and eltrombopag provide compelling evidence supporting platelet production stimulation in chronic ITP. These novel agents appear to be very effective in a high percentage of refractory adult patients with chronic ITP. The drugs are well tolerated, at least in the first six months of treatment. Due to the efficacy data, both drugs have been approved by the US Food and Drug Administration (FDA) for use in adult patients with chronic ITP, although only available on a restricted programme called Risk Evaluation and Mitigation Strategies (REMS). REMS is the term used to identify drugs or biological products that require additional procedures or documentation to ensure their safe use. The Network of EXperts Understanding and Supporting Nplate and patients (NEXUS) programme for romiplostim and PROMACTA *CARES* for eltrombopag are multifaceted REMS programmes. They aim to provide comprehensive access, support and education for chronic ITP patients, their caregivers and healthcare providers.

The major concern about the use of these new drugs beyond six months is the lack of long-term safety data. As a matter of fact, the European Medicines Agency has restricted the use of these agents to patients refractory to splenectomy or in those with contraindications to splenectomy.

A recent consensus report on the diagnosis and management of ITP is the first official document trying to position these new drugs in therapy.[10] Eltrombopag and romiplostim are the only drugs for which efficacy has been demonstrated in randomised phase III trials. They are therefore recommended with the strongest level of evidence as medical second-line treatment options for adult ITP patients (as opposed to the surgical option, i.e. splenectomy). They are also recommended as the subsequent line of therapy for adult patients failing first- and second-line therapies.

Apart from their efficacy prior to and after splenectomy, the new thrombopoietic agents are appealing for a number of reasons. These include the fact that:

- they are not blood products, thereby avoiding the potential risk of infectious diseases;
- unlike most of the current conventional therapies they are not immunosuppressive; and
- they do not have the undesirable and often invalidating long-term side-effects of corticosteroids.

Several other TPO-R agonists are being developed. Ongoing studies will reveal how these agents actually impact the current management of patients with chronic ITP. The results of the studies are expected to lead to an expansion of the armamentarium of drugs available for ITP in the near future and may revolutionise the therapeutic approach to this autoimmune disorder. ■

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