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► To cite this version:

Hans Wadenvik, Bob Olsson. Moving towards a new era in the management of chronic immune thrombocytopenia. *Annals of Hematology*, 2010, 89 (s1), pp.87-93. 10.1007/s00277-009-0873-9 . hal-00535111

HAL Id: hal-00535111

<https://hal.science/hal-00535111>

Submitted on 11 Nov 2010

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Moving towards a new era in the management of chronic immune thrombocytopenia

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Received: 12 October 2009 / Accepted: 23 November 2009 / Published online: 26 March 2010
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Abstract Immune thrombocytopenia (ITP) is an organ-specific autoimmune disease in which a low concentration of plasma thrombopoietin (TPO) contributes to the thrombocytopenia. Functional thrombopoietin deficiency in response to thrombocytopenia is central to the pathophysiology of chronic ITP. Decreased platelet production in ITP patients has been described only in recent years, however. Following the development of TPO-mimetics, it has become clear that the augmentation of thrombopoiesis is a key therapeutic target. TPO mimetics are novel effective treatments providing durable platelet responses in ITP. Two agents have reached clinical practice, the ‘peptibody’ romiplostim (Nplate®) approved for treatment of thrombocytopenia in patients with chronic ITP in Europe, Canada, Australia and the USA and the non-peptide TPO mimetic, eltrombopag (Promacta®), approved in the USA. This review summarises the background to the development of these agents and presents an update on data from randomised phase III trials and open-label studies. These novel drugs provide a noteworthy treatment option for patients with chronic ITP, in whom thrombocytopenia and bleeding risk have not been controlled by standard treatments. The first candidates for treatment in clinical practice are undoubtedly refractory patients with lack of response to other therapies or at continued risk for bleeding despite treatment. Appropriate inclusion of TPO mimetics into the treatment paradigm will most likely have a positive impact on the long-term outcome of ITP and allow carefully

monitored patients to remain well controlled, with good tolerability for prolonged periods.

Keywords Thrombopoietin mimetics · Romiplostim · Eltrombopag · Chronic immune thrombocytopenia

Introduction

Chronic immune thrombocytopenia (ITP) is an acquired platelet-specific autoimmune disease characterised by low platelet counts, which can lead to life-threatening bleeding. In ITP, anti-platelet antibodies accelerate the destruction of platelets. In addition, bone marrow platelet production can be impaired [1–4], and cytotoxic T lymphocytes have been shown to lyse platelets in vitro and in vivo [5–7]. Although the thrombocytopenia in ITP can be profound, in the majority of adult patients, signs of bleeding are typically mild to moderate. However, persistently low platelet counts ($<20 \times 10^9/L$) can contribute to a risk of serious bleeding, such as gastrointestinal and intracranial haemorrhages [8–10]. When managing chronic ITP in adults, the ultimate goal is to maintain the platelet count at a haemostatically safe level to prevent bleeding with the least possible intervention and, therefore, low treatment-related toxicity [11].

Treatment remains challenging in many adult patients who relapse after therapy with corticosteroids and/or intravenous immunoglobulins and may ultimately require splenectomy [12–14]. Approximately a third of adult patients relapse after splenectomy [15]. While current treatment options for refractory patients post-splenectomy now include immunomodulatory/immunosuppressive agents, e.g. intermittent immunoglobulins (IVIg), corticosteroids, azathioprin, cyclophosphamide, mofetil mycophenolate, vinca alkaloids and the B cell depleting agent

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rituximab, these generally generate low long-term response rates and significant toxicity [16–19].

Progress in uncovering an impaired bone marrow response to low platelet count in chronic ITP has made the augmentation of platelet production a key therapeutic target [20], with the result that novel effective treatments providing high durable response rates in patients with chronic ITP are now approved.

Thrombopoietin

The term thrombopoietin (TPO) was first used in 1958 to describe the humoral regulator of platelet production. Doubts surrounding its existence remained until the molecule was cloned [21–23]. TPO, the ligand for the c-mpl proto-oncogene, is mainly expressed in liver and kidney [21, 22, 24] and has been shown to influence all aspects of megakaryocyte development and platelet production [25]. Animal model data suggest a feedback mechanism whereby circulating platelet mass and megakaryocyte mass are inversely related to TPO levels [26, 27]. Several studies showed that circulating TPO is selectively cleared by platelets through receptor-mediated endocytosis and destruction [28–32]. Paradoxically, TPO levels appear normal or only slightly elevated in ITP. These patients uniformly display normal megakaryocyte numbers in bone marrow biopsies, further supporting plasma TPO level regulation by circulating platelets and bone marrow megakaryocytes [33].

Early studies with pegylated and recombinant TPO in the late 1990s demonstrated platelet response in cancer patients with chemotherapy-induced thrombocytopenia [34, 35]. However, clinical evaluation of early TPO analogues, i.e. pegylated recombinant TPO, was halted because antibodies were formed that cross reacted with endogenous TPO, causing secondary and long-lasting thrombocytopenia and bleeding [36]. This setback stimulated research for second-generation c-mpl agonists including peptide and non-peptide agonists [37–41].

TPO mimetics

The search for second-generation TPO analogues has focussed on agents capable of binding to the TPO receptor as strongly as TPO, without having cross-reactive immunogenicity against native TPO.

Two agents have reached clinical practice, the ‘peptibody’ romiplostim (Nplate®) approved for treatment of thrombocytopenia in patients with chronic ITP in Europe, Canada, Australia and the USA and the non-peptide TPO mimetic, eltrombopag (Promacta®), approved in the USA.

Romiplostim

The romiplostim ‘peptibody’, administered subcutaneously, consists of two covalently linked carrier-Fc domains, each attached to a polypeptide containing two c-mpl-activating sequences [38, 40]. Lack of sequence homology to endogenous TPO is clinically relevant as this reduces the risk of development of cross-reacting anti-TPO antibodies that can compromise treatment efficacy. Early studies in healthy adults showed that single injections of romiplostim induced a dose-dependent increase in platelet count, with no serious adverse events [40, 42]. Platelet numbers peaked at 12–16 days, returning to baseline at 28 days [40]. Platelet response in adults with ITP and low platelet counts were first reported in a dose-finding assessment of romiplostim given as two injections separated by a 15-day interval [43].

A randomised, double-blind, placebo-controlled phase I/II US study investigating romiplostim in patients with ITP led to the establishment of individualised dosing based on platelet counts [44]. The phase II study population was 21 highly refractory adult ITP patients. Patients were randomised 4:1 to receive weekly doses of romiplostim (1, 3 or 6 µg/kg) or placebo, for 6 weeks, with follow-up (FU) up to day 78. No dose adjustments were allowed, although doses were withheld when platelet count was $>350 \times 10^9/L$. The primary objectives were to evaluate safety and to identify a weekly dose that would give a platelet count within the target range of $50\text{--}450 \times 10^9/L$ and that was at least twice the baseline count. Platelet targets were reached or exceeded in 12 of 16 patients assigned to receive romiplostim (1 or 3 µg/kg). Rates of adverse events were similar across treatment arms, and no neutralising antibodies against romiplostim or endogenous TPO were detected. Transient post-treatment worsening of thrombocytopenia was observed in four patients.

Two double-blinded phase III trials, carried out at 35 sites in the USA and Europe, have investigated 6-month treatment with romiplostim [45]. The trials were of identical design, except for splenectomy status. Both studies enrolled adults with previously treated ITP with a mean platelet count of $<30 \times 10^9/L$. Patients were randomised to romiplostim or placebo (2:1). Weekly romiplostim was given for 24 weeks. Follow-up was 12 weeks. Patients were allowed to enter an extension study after 4 weeks of follow-up, or once platelet count fell below $50 \times 10^9/L$. The starting dose was 1 µg/kg with subsequent dosing adjusted to achieve and maintain a target platelet count of $50\text{--}200 \times 10^9/L$. The maximum allowed dose was 15 µg/kg.

Patients were allowed to receive concurrent and rescue ITP medication. The primary endpoint was a durable platelet response (weekly platelet response of $50 \times 10^9/L$ or more, for at least six out of the last 8 weeks of the study without use of rescue medication). Platelet responses that occurred within

8 weeks after rescue medication was used were not included. Secondary endpoints included transient and overall platelet response, number of weekly platelet responses and the proportion of patients requiring rescue medication.

The incidence of durable platelet response was significantly higher in patients treated with romiplostim compared with placebo, in both splenectomised and non-splenectomised patients [45]. Of splenectomised patients, 38% (16/42) receiving romiplostim showed a durable platelet response, compared with none of the 21 patients in the placebo group ($p = 0.0013$). Similarly, of non-splenectomised patients, 61% (25/41) receiving romiplostim showed a durable platelet response, compared with 5% (1/21) in the placebo group ($p < 0.0001$). A wide dose range was administered to responding patients, particularly in patients who had failed to respond to splenectomy, which highlights the heterogeneity seen in chronic ITP.

Benefits were also seen in romiplostim patients not achieving a durable platelet response, with 40% (17/42) of splenectomised patients and 27% (11/41) of non-splenectomised patients achieving a transient platelet response (at least four weekly platelet responses from weeks 2–25). The overall platelet response rate was 79% in the splenectomised group and 88% in the non-splenectomised group, compared with 0% (splenectomised) and 14% (non-splenectomised) of patients in the placebo group (durable plus transient platelet response). Median weekly platelet counts were higher in romiplostim-treated patients than placebo controls, with platelet increases first observed within 1–2 weeks and sustained over 24 weeks of treatment.

Significantly fewer patients receiving romiplostim required rescue medications than those receiving placebo (19/83 (22.7%) vs 25/42 (59.5%); romiplostim vs placebo, respectively, $p < 0.0001$) [45] or needed intervention with intravenous immunoglobulins [46]. Decreasing concurrent ITP treatments is a desirable aim, to reduce treatment-related side effects and improve quality of life. Also, romiplostim enabled many patients to discontinue all concurrent ITP medication (12/23, 52%) or reduce doses of one concurrent ITP drug by >25% (8/23, 35%). However, it should be borne in mind that the number of patients able to discontinue concurrent medication was limited by trial protocol, which did not allow discontinuation after week 12 [45]. No patients tested positive for neutralising antibodies to romiplostim or TPO.

The incidence of adverse events was similar in the placebo and treatment arms, with 100% of patients receiving romiplostim reporting adverse events compared with 95% of patients receiving placebo. Most adverse events were mild to moderate and related to the underlying thrombocytopenia, being typical of events reported in the setting of chronic ITP (headache, fatigue, epistaxis, arthralgia and contusion bleedings). Two uncommon severe side effects were reported in the

romiplostim-treated patient groups, with one non-responding patient developing bone marrow reticulins, which reversed on treatment discontinuation, and two cases of thromboembolism. Increased reticulins deposits have been infrequently reported in romiplostim clinical studies [47]. The reversible nature of reticulins formation in response to romiplostim has also been observed by retrospective analysis across romiplostim clinical trials [47].

Bleeding events ($\geq$ grade 2) were less common in patients receiving romiplostim (14/84 vs 34/42, romiplostim vs placebo, respectively) [48]. Significant bleeding events (defined as severe, life-threatening or fatal events) were less common in the treatment arm, with events reported in 7% (6/84) of the romiplostim group compared with 12% (5/41) of patients in the placebo group [45]. Two of the patients receiving placebo died during the study due to bleeding events (cerebral haemorrhage and pulmonary embolism following an episode of severe gastrointestinal haemorrhage). Another patient in the placebo group died from pneumonia complications presenting after an intracranial haemorrhage due to trauma. One patient who had received romiplostim died 1 day after study completion as a result of intracranial haemorrhage, which occurred after commencing aspirin treatment for thrombosis following discontinuation of romiplostim [45].

Patients who had been enrolled in the phase III studies [45], and other studies assessing romiplostim for treatment of ITP [43, 44], were eligible for a long-term extension open-label trial, irrespective of whether they had received romiplostim or placebo [49]. The most recent reported data, (July 2008) is based on an Intent to Treat population of 223 patients; 99 of whom (44%) were splenectomised, and 34 patients (15%) were on concurrent ITP therapy at study entry [50, 51]. Previous treatment with romiplostim varied from no exposure to 24 weeks [43–45]. Dose adjustment was made according to platelet count, to a maximum of 10 $\mu\text{g/kg}$, weekly. In total, 215 patients received romiplostim, and 186 patients remain on study as of July 2008 [52]. The efficacy endpoint was platelet response (platelet count $\geq 50 \times 10^9/\text{L}$ and double baseline) in the absence of rescue medication within the preceding 8 weeks [52].

Thirty percent of patients (61/207) responded after the first dose and 74% of patients (160/215) overall. Among patients receiving concurrent ITP medications at baseline, 74% (25/34) discontinued or reduced their dose by >25% [50]. Use of rescue medications decreased over time. Bleeding of moderate or greater severity declined from 14% of patients during the first 24 weeks to 10%, 7% and 5% of patients during subsequent 24-week periods [50].

This study also provided important safety data in patients treated for up to 204 weeks, with exposure-adjusted incidence rates of adverse events showing no cumulative incidence and no cumulative toxicity [49, 51,

[52]. Retrospective analysis across clinical trials (to February 2008) shows that bone marrow reticulin was confirmed in ten bone marrow samples [47]. Reticulin was also examined over time in selected patients who participated in a supplemental prospective analysis designed to evaluate the effect of romiplostim treatment on bone marrow morphology [49]. Bone marrow biopsies were taken at baseline (before initiating romiplostim therapy) and after receiving romiplostim for 3 ($n = 4$) or 9 ($n = 5$) months. Of six patients with baseline and FU biopsies, reticulin staining following romiplostim treatment remained absent in five/six cases and in one patient treated with romiplostim for 3 months changed from none to mild.

Eltrombopag

The non-peptide, synthetic TPO-receptor agonist, eltrombopag (marketed as Promacta in the USA, but not licensed in the EU at the time of writing), is administered as a once daily oral tablet. Food interactions observed in pharmacokinetic studies indicate that eltrombopag should be administered to fasting patients or with low calcium foods [53]. It is a small non-peptide molecule and as such is unlikely to induce antibody formation. In a phase I clinical study, 73 healthy male subjects were randomised to receive eltrombopag (six dose groups of ~9 patients each) or placebo (18 patients) for 10 days at doses of 5–75 mg. The mean change in platelet count for the 30-, 50-, and 75-mg dose levels was 24.1% ($257.6 \times 10^9/L$ to $319.6 \times 10^9/L$), 42.9% ($254.3 \times 10^9/L$ to $363.4 \times 10^9/L$) and 50.4% ($235.9 \times 10^9/L$ to $354.9 \times 10^9/L$), respectively. The highest individual platelet count recorded was $457 \times 10^9/L$ [54]. A consistent increase in platelet count began after 8 days of repeat dosing with eltrombopag, and the interval from first dose to peak platelet count was 16 days. By day 22 (12 days after the last dose of eltrombopag), platelet count had returned to baseline values. These data are consistent with published platelet counts seen after the administration of recombinant TPO in humans [55]. In addition, there was no evidence of rebound thrombocytopenia. In a multicentre randomised trial, 118 adults with chronic ITP and platelet counts of less than $30 \times 10^9/L$ who had had relapses or whose platelet count was refractory to at least one standard treatment for ITP were randomly assigned to receive the oral thrombopoietin-receptor agonist eltrombopag (30, 50 or 75 mg daily) or placebo [56]. Of 109 patients receiving ≥ 1 dose, the primary endpoint (platelet count $\geq 50 \times 10^9/L$ on day 43) was achieved in 28%, 70% and 81% of patients for the respective 30, 50 and 75 mg doses compared with 11% for those receiving placebo. By day 15, more than 80% of patients on the 50 and 75 mg doses had a raised platelet count with the median platelet count approaching the normal range. Eltrombopag was discontinued in 28 patients

when platelet counts $>200 \times 10^9/L$ were reported, with median platelet counts returning near to baseline within 2 weeks without rebound thrombocytopenia.

In a phase III, randomised, double-blind, placebo-controlled study, previously treated adult patients from 63 sites in 23 countries with chronic ITP and platelet counts less than $30 \times 10^9/L$ received standard care plus once daily eltrombopag 50 mg ($n = 76$) or placebo ($n = 38$) for up to 6 weeks [57]. Forty-five patients (39%) had undergone splenectomy. Corticosteroid treatment was permitted, but other drugs for the disorder were stopped for at least 2 weeks before trial initiation. Patients were randomised (2:1, eltrombopag vs placebo). After 3 weeks, patients with platelet counts less than $50 \times 10^9/L$ could increase study drug to 75 mg, q.d. The primary endpoint was the proportion of patients achieving platelet counts $50 \times 10^9/L$ or more at day 43 [56]. Of 110 patients receiving ≥ 1 dose, 43/73 (59%) eltrombopag patients and 6/37 (16%) placebo patients responded (odds ratio 9.61 (95% CI 3.31–27.86); $p \leq 0.0001$). Patient response was independent of sex, age, the use of concomitant ITP drugs, splenectomy status, baseline platelet count and number of previous ITP therapies. Responses to eltrombopag were seen in 16/38 patients with

Fig. 1 It is not controversial that corticosteroids and/or IVIg are the first-line therapy for patients with newly diagnosed ITP and in need for treatment, and it will presumably be that over the foreseeable future. Splenectomy is still the second-line treatment for patients with ITP at many centres. However, spontaneous recovery can be seen during the first year after diagnosis, and splenectomy are usually postponed for several months to avoid unneeded surgical procedures. For patients who fail splenectomy, the therapy options are less uniform and include several treatment protocols with significant toxicity. The first candidates for treatment with TPO-mimetics in clinical practice are undoubtedly refractory ITP patients with lack of response to other therapies or at continued risk for bleeding despite treatment. It is likely that with increasing experience, these novel agents will be introduced earlier in the treatment algorithm, e.g. as steroid sparing agents pre-splenectomy

baseline platelet counts $15 \times 10^9/L$ or less. Eight of the remaining 22 patients had clinically significant platelet increases. Significantly fewer patients in the eltrombopag group than in the placebo group had bleeding symptoms, as measured by the WHO bleeding scale, at day43 (20 (39%) vs 18 (60%); $p = 0.029$) as well as at any point in time during the course of treatment (46 (61%) vs 30 (79%); $p = 0.021$). Mean scores for health-related quality of life were not affected by treatment.

An extended phase III study has treated 109 patients with ITP given eltrombopag at 50 mg daily, adjusted, when necessary, to 25 or 75 mg according to platelet counts [58, 59]. In this study, 78% of patients maintained a platelet count of $>50 \times 10^9/L$ for more than half their time in the study (mean 194 days), and 35% of patients requiring ITP medication at baseline were able to stop concomitant medication. Thromboembolic events were noted in four patients, all of whom had risk factors for thrombosis. After 12 weeks, $<5\%$ of patients reported clinically significant bleeding vs $>20\%$ at baseline.

Furthermore, eltrombopag has been investigated outside the context of primary chronic ITP in adults, with a report showing that eltrombopag administered to patients with hepatitis C-associated thrombocytopenia with cirrhosis produced a dose-dependent increase in platelet count [60].

Current status and future trends

Insufficient production of thrombopoietin in response to thrombocytopenia is central to the pathophysiology of ITP. Despite increased knowledge of disease pathophysiology and advances in molecular therapy, the treatment algorithm for ITP remains largely based on modalities aimed at correcting autoantibody-induced platelet destruction. In refractory patients, the treatment has mainly been “on demand” due to the toxicity profile of the second and third line therapies. Now, with the availability of thrombopoietic agents, it may be the time to apply close scrutiny to current treatment efficacy and toxicities. If the promising safety data for the TPO-mimetics hold true in the long term, we might move into ‘prophylactic treatment’ of these patients, as has been implemented in the current management of other bleeding disorders, e.g. hemophilias. However, given the 5-day lag time for a platelet effect of these agents, they are not a substitute for platelet transfusions in the acute treatment of thrombocytopenia.

TPO-mimetics provide a noteworthy treatment option for patients with chronic ITP, in whom platelet count and bleeding have not been controlled by standard treatments, and the first candidates for treatment in clinical practice are undoubtedly refractory ITP patients with lack of response to other therapies or at continued risk for bleeding despite treatment. However, the development of TPO mimetics also

has implications for the treatment algorithm in ITP (Fig. 1). In particular, TPO-mimetics could allow steroid-sparing treatment approaches to be implemented [61]. Ultimately, if use of these novel drugs were to be extended to non-splenectomised patients, this might allow surgical intervention to be postponed [62].

Recent guidelines are already helping to provide consistency across ITP terminology for disease diagnosis, response and outcome [12]. Currently, platelet counts are a surrogate marker for the risk of bleeding events and are the basis on which treatment decisions are made. Sustained improvement of platelet counts by TPO-mimetics is therefore of clinical importance [63] and can have additional quality-of-life implications for ITP patients [62, 64, 65]. For TPO-mimetics to be implemented routinely, early in the treatment algorithm, supportive long-term safety data are needed.

In this promising era for ITP treatment, many questions remain to be answered regarding which patients should receive TPO-mimetics and exactly when this should occur. As these questions are answered, more patients will be considered for therapy with TPO-mimetics. Appropriate inclusion of TPO mimetics into the treatment paradigm will most likely have a positive impact on the long-term outcome of ITP and allow carefully monitored patients to remain well controlled, with good tolerability for prolonged periods. Furthermore, there are other thrombocytopenic conditions where the risks of short-term exposure with TPO-mimetics appear acceptable, e.g. hepatitis C-related thrombocytopenia, liver failure patients awaiting transplantation, thrombocytopenia in myelodysplastic syndromes, thrombocytopenia in presurgical patients and chemotherapy-induced thrombocytopenia. Even platelet apheresis donors might benefit from TPO mimetics. Post-marketing surveillance of the novel TPO-mimetics and new studies in other thrombocytopenic conditions will increase our understanding of the correct use of these novel agents in haematology.

Acknowledgements This work was supported by grants from the Swedish Research Council (529-2004-6512; 521-2006-5103), the Swedish federal government under the LUA/ALF agreement, the Sahlgrenska University Hospital Foundation, the Foundations of the National Board of Health and Welfare, the Åke Wiberg Foundation, the Jeansson Foundations, the Tore Nilsson Foundation for Medical Research, the Magnus Bergvall Foundation and the Wilhelm and Martina Lundgren Science Foundation. Editorial support from Janet Stephenson of Bioscript Stirling Ltd., London, UK, was funded by Amgen.

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