Novel thrombopoietic agents: a new era for management of patients with thrombocytopenia

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After many decades of an orphan existence, immune thrombocytopenic purpura (ITP) is a central focus for the clinical development of multiple, novel thrombopoietic agents. These agents have the potential to transform the management of ITP and possibly other thrombocytopenic disorders. Now, with the approval of the first agents for clinical use, their role in patient care will become established and their potential risks may be more clearly revealed.

The availability of novel thrombopoietic agents for the treatment of patients with thrombocytopenia is remarkable both as a scientific achievement and also as an immediate benefit for patient care. The history of the isolation and characterization of thrombopoietin (TPO) in 1994 and the development of therapeutic thrombopoietic agents have been recently reviewed.[1] This year the first two agents, romiplostim (previously known as AMG 531) and eltrombopag, will be approved by the US Food and Drug Administration (FDA) for treatment of patients with ITP. The success of these thrombopoietic agents in clinical trials for treatment of ITP[2-4] has stimulated the development of multiple other compounds to enhance platelet production, including the novel small non-peptidyl molecule described in this issue of the journal by Nogami *et al*.[5] The molecular diversity of these agents, their therapeutic effectiveness, and their potential risks are an important story for hematologists. In this Perspective, we will describe [1] the evolution of understanding of the pathogenesis of ITP, that provided the insight for treatment with thrombopoietic agents; [2] the experience of individual patients with ITP who have received thrombopoietic agents; [3] the molecular spectrum of thrombopoietic agents that are currently in development; [4] the clinical spectrum of targeted thrombocytopenic disorders; and [5] the potential harm from these agents.

Immune thrombocytopenic purpura: a target for drug development

The clinical development of thrombopoietic agents has been intimately associated with ITP. The low prevalence of ITP, estimated at 9 patients per 10^5 population,[6] is a challenge for clinical trial accrual but also an opportunity for accelerated regulatory approval. ITP is classified by the US FDA as an *orphan* disease, defined as a condition that affects fewer than 200,000 persons in the United States. An advantage of ITP as a target for clinical trials is that patients are typically healthy, other than for thrombocytopenia, and platelet counts provide objective, accessible outcome measures. An important consideration for development of thrombopoietic agents was the unmet medical need for effective treatment for patients with chronic refractory ITP.[7]

Immune thrombocytopenic purpura: a disorder of both accelerated platelet destruction and insufficient platelet production

To understand why thrombopoietic agents may be effective for patients with ITP, we must go back to the beginning of our understanding of its pathogenesis.

First, in 1951, ITP was shown to be a disorder of accelerated platelet destruction by the legendary experiments of Harrington, Hollingsworth, and their colleagues.[8] They infused themselves with the blood of patients who had refractory ITP and severe thrombocytopenia; within two hours they became profoundly thrombocytopenic with overt bleeding. These experiments were extended by Shulman in 1962 who documented that the ITP factor was an immunoglobulin and that the titer of this factor, measured by the severity of thrombocytopenia in normal subjects following infusion of plasma from patients with ITP, was related to the severity of the donor's ITP.[9] These observations established the principle that ITP was a disorder caused by autoantibody-mediated platelet destruction. This principle, supported by the presence of normal – or perhaps increased – numbers of marrow megakaryocytes, became the paradigm of ITP.

A role for insufficient platelet production in the pathogenesis of ITP was suggested in 1987 by Ballem *et al*. who reported that almost all patients with untreated ITP had decreased or normal platelet production.[10] Other data suggesting insufficient platelet production in patients with ITP were observations that serum thrombopoietin (TPO) levels were normal or only minimally increased in patients with ITP, in contrast to the very high serum TPO levels in patients with aplastic anemia or amegakaryocytic thrombocytopenia.[11] This difference reflects the physiological clearance of TPO from plasma by its binding to platelets and megakaryocytes. In ITP, the normal numbers of marrow megakaryocytes continue to remove plasma TPO, apparently preventing maximal stimulation of platelet production.

Although the concept of insufficient platelet production in patients with ITP was acknowledged, the paradigm persisted that ITP was a disorder primarily of accelerated platelet destruction. The paradigm was supported by the fact that all treatments for ITP were focused on correcting autoantibody-mediated platelet destruction. Therefore, when thrombopoietic agents were proposed as a treatment for ITP, many hematologists were skeptical. If ever there was a need for proof of principle, this was the time. Now the principle has been proven many times over.

The development of novel thrombopoietic agents has brought ITP into the mainstream of clinical research. A systematic review in 2004 identified no randomized clinical trials comparing one treatment of ITP to another, or comparing treatment to no treatment.[12] Now multiple

placebo-controlled randomized clinical trials have been published[2-4] and more are in progress. These clinical trials have also facilitated the development and application of measures beyond platelet counts to assess clinical outcomes, including ITP-specific health-related quality-of-life questionnaires[13] and instruments that objectively and quantitatively document bleeding symptoms.[3]

Immune thrombocytopenic purpura: effective treatment with thrombopoietic agents

Thrombopoietic agents have been consistent in their ability to increase platelet counts of patients with ITP, even in patients who have persistent severe thrombocytopenia after failing multiple previous treatments.[2-4] Although group data suggest that platelet count responses are consistent at steady levels,[3,4] the responses of individual patients may be quite variable across time, requiring multiple dose adjustments. The clinical courses of two patients who are participating in the clinical trials of romiplostim illustrate two points that will be important for management of ITP patients with thrombopoietic agents (Figures 1 and 2): 1) these agents can be effective in patients who have chronic refractory ITP; 2) Even with a constant dose of romiplostim, platelet counts may appear to be cyclical or erratic. Sensitivity to these agents may appear to increase or decrease across time. Patients may appear to achieve transient remissions, maintaining their platelet counts in a safe range for several weeks with no treatment. These two patients illustrate the effectiveness of thrombopoietic agents but they also illustrate that the management of ITP patients with thrombopoietic agents may not be simple.

Immune thrombocytopenic purpura: when is treatment with thrombopoietic agents appropriate?

The patients who will receive the greatest benefit from the new thrombopoietic agents are those who have persistent severe and symptomatic thrombocytopenia following failure of previous treatments. These cases are not common, perhaps only 5% of adults[6] and even fewer children, but they have been extremely difficult to manage.

Beyond these few patients with great need, the appropriate use of thrombopoietic agents is less certain.

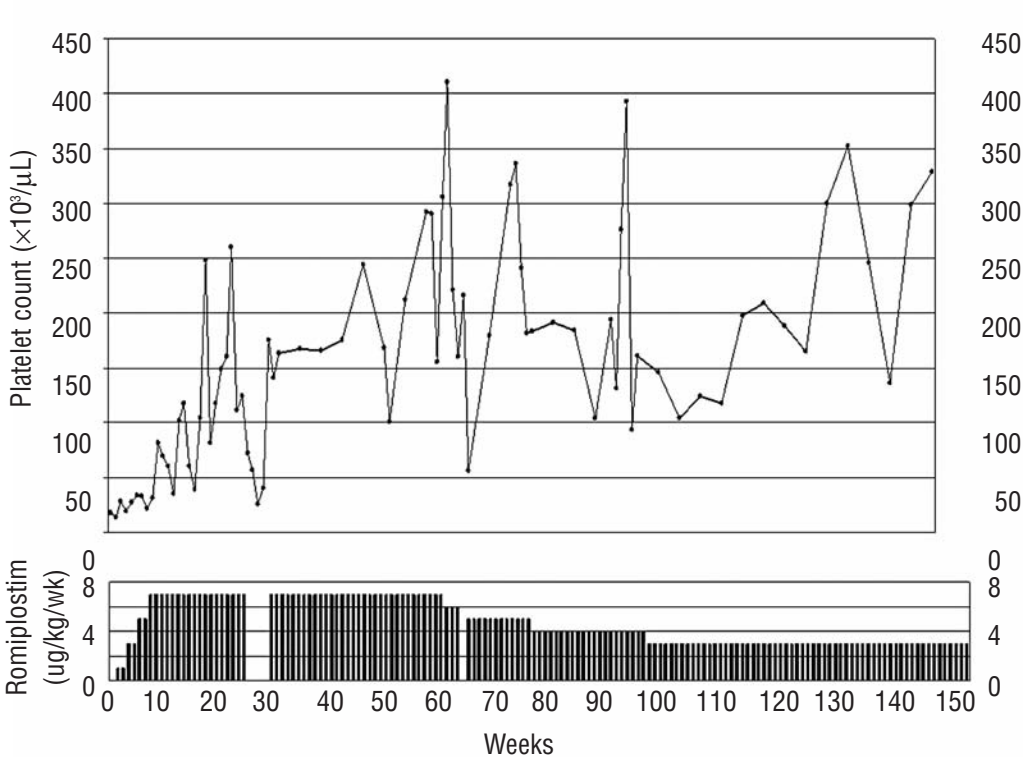

Figure 1. Platelet count response to romiplostim in a 37 year old woman diagnosed with ITP seven months previously. She initially presented with purpura, menorrhagia, and a platelet count of 7×10^9/L. Over seven months she had only transient responses to high-dose dexamethasone, intravenous immunoglobulin, seven infusions of rituximab, and splenectomy. The initial 26 weeks of romiplostim treatment were part of the clinical trial comparing romiplostim to placebo;[4] she received romiplostim. The target platelet count was 50-200×10⁹/L. The protocol required dose adjustments if two consecutive weekly platelet counts were less than 50×10^9/L or 200-400×10⁹/L; treatment was withheld if the platelet count exceeded 400×10^9/L. After the 26 week clinical trial, romiplostim treatment was stopped to determine if the platelet count would decrease, indicating a requirement for treatment.
When her platelet count fell below 50×10^9/L, romiplostim was resumed as part of a continuing open-label study. In the open-label study, the target platelet count was 50-250×10⁹/L. The protocol required dose adjustments if two consecutive weekly platelet counts were less than 50×10^9/L or 250-400×10⁹/L; treatment was withheld if the platelet count exceeded 400×10^9/L. Although she maintained her platelet count within the target range on a steady dose of 7 μg/kg/wk of romiplostim for 30 weeks, she then required a lower dose. The open-label study currently has a target range of 50-400×10⁹/L and she has now been within the target platelet count range for over one year on 3 μg/kg/week.

Glucocorticoids will continue to be the initial treatment for adults; they are effective and inexpensive. However, with the availability of thrombopoietic agents, there may be less reason to tolerate the disturbing emotional side effects of glucocorticoids if a durable remission is not soon achieved. Beyond initial glucocorticoids, splenectomy has been the standard second treatment option, as it offers the best opportunity for complete remission from ITP.[14] Now rituximab is increasingly used in patients with ITP who fail to achieve a durable response with initial glucocorticoid treatment.[15] Compared to these treatments, thrombopoietic agents may be described as *maintenance* therapy, rather than *remission induction* therapy, to be used if a remission with other treatments is not achieved or to defer a decision for potentially definitive treatment. The initial FDA approvals of romiplostim and eltrombopag will be restricted to adults. Clinical trials of thrombopoietic agents in children with ITP are only just beginning. In contrast to adults, most children spontaneously recover from ITP within 12 months.[16] However, initial treatment of children is important when severe bleeding occurs, and thrombopoietic agents may be better tolerated than the current treatments with glucocorticoids, intravenous immunoglobulin, or anti-Rh(D). For children who have persistent severe and symptomatic thrombocytopenia, thrombopoietic agents may defer the need for splenectomy or immunosuppressive treatments.

Beyond immune thrombocytopenic purpura, romiplostim and eltrombopag: other thrombocytopenic disorders, other thrombopoietic agents

The first thrombopoietic agents, PEG-rHuMGDF and recombinant human TPO (rhTPO), had no beneficial effect for patients undergoing high-dose chemotherapy and autologous stem cell transplant or treatment of acute leukemia.[1] These agents did increase the nadir platelet count and decreased the duration of thrombocytopenia in patients receiving non-myeloablative chemotherapy, and rhTPO was effective for increased mobilization of stem cells for donation.[1] The most effective result of clinical trials with PEG-rHuMGDF was the treatment of normal subjects who were apheresis platelet donors: a single dose could increase platelet yield by three-fold.[1] However, a few subjects developed profound and prolonged thrombocytopenia due to antibodies against PEG-rHuMGDF that cross-reacted with endogenous TPO,[1] causing abrupt discontinuation of PEG-rHuMGDF development. Although no adverse events had been reported in the clinical trials with rhTPO, its development was also stopped because of concerns for possible occurrence of cross-reacting antibodies to endogenous TPO.[1]

These critical complications only temporarily halted the development of thrombopoietic agents. Multiple new agents, all structurally distinct from endogenous TPO,[1] are currently in clinical trials for multiple new

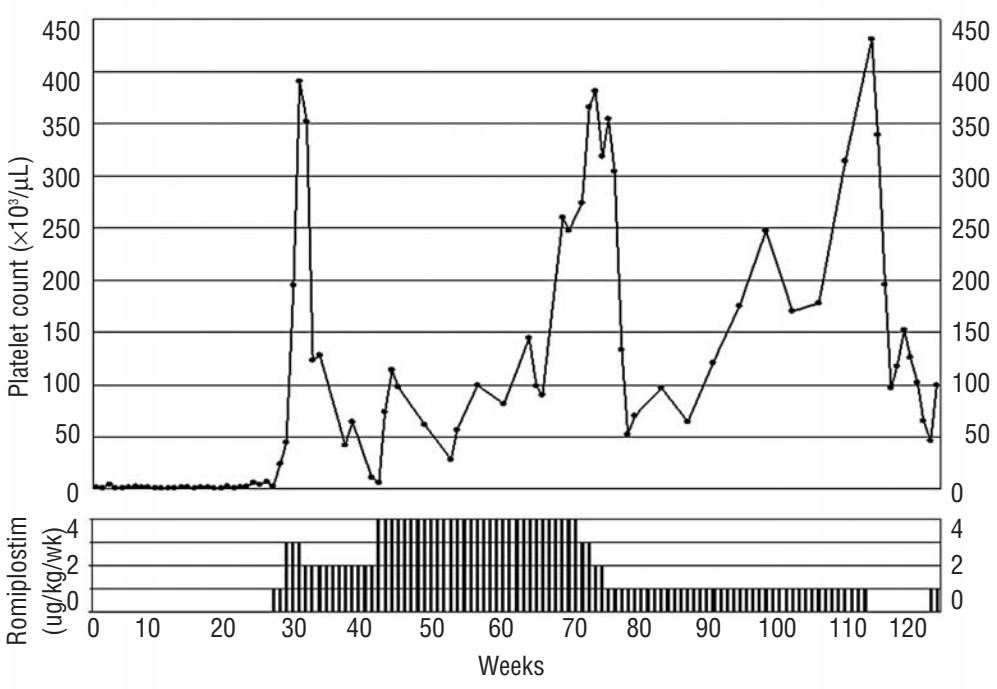

Figure 2. Platelet count response to romiplostim in a 63 year old man who had been diagnosed with ITP in 1991. He had transient responses to glucocorticoids, danazol and splenectomy. He felt best when he was on no treatment, however, without treatment his platelet count was always less than 10×10^9/L. The initial 26 weeks were part of the clinical trial comparing romiplostim to placebo;[4] he received placebo. On week 27 he began romiplostim treatment as part of a continuing open-label study, using the same target platelet count range and dose adjustment algorithm described in Figure 1. Although he required 4 μg/kg/week to maintain his platelet count above 50×10^9/L for over six months, he then required less romiplostim, and recently maintained a platelet count greater than 50×10^9/L on no treatment for eight weeks.

Table 1. Thrombopoietic agents currently in clinical development.

Agents	*Clinical development*
Peptides	
Romiplostim	Currently approved for ITP. Current clinical trials for myelodysplasia and chemotherapy-induced thrombocytopenia
Fab59	No human studies reported
PEG-TPOmp	No human studies reported
Non-peptide small molecules	
Eltrombopag	Currently approved for ITP. Phase 3 trial completed for thrombocytopenia associated with hepatitis C infection. Current clinical trials for chemotherapy-induced thrombocytopenia.
AKR-501	Current clinical trials for ITP, liver disease, and chemotherapy-induced thrombocytopenia
LGD-4665	Studies in normal subjects reported
Butyzamide	Described in this issue of Haematologica.[5] No human studies reported.
Monoclonal antibodies	
VB22B sc $(Fv)_2$	No human studies reported
MA01G4G344	No human studies reported

Data adapted from Kuter[1] and also from Kuter DJ, personal communication.

Table 2. Potential risks of thrombopoietic agents.

Adverse event	Clinical evidence
Rebound thrombocytopenia	Severe thrombocytopenia, with platelet counts below the patient's baseline level, may occur when thrombopoietic agents are stopped.
Thrombosis	There is no evidence for an increased risk for thrombosis from current clinical trials, but a risk could be revealed with long-term use.
Increased marrow reticulin	In a clinical trial of rhTPO in patients with AML, 8 of 9 patients had reversible increased marrow reticulin. Increased marrow reticulin has also been reported in patients in romiplostim clinical trials. It appears to be reversible. No increased collagen fibrosis has been reported.
Acceleration of hematologic malignancies	In a phase 1/2 clinical trial of romiplostim, 6 of 44 patients with MDS had increased myeloblasts and 1 patient progressed to AML

indications, in addition to ITP (Table 1). The number and variety of agents in Table 1 reflects current clinical needs and pharmaceutical commitment. The report of Nogami *et al.*[5] in this issue of the journal emphasizes that the discovery of novel agents continues. It can be anticipated that these agents may have distinct properties, one from another, because of their different structures and interactions with the TPO receptor. Because they have distinct properties, thrombopoietic agents may have different degrees of effectiveness for different thrombocytopenic disorders. It is possible that combinations of thrombopoietic agents may have enhanced effectiveness for some thrombocytopenic disorders. Current clinical trials with these agents are targeting disorders in addition to ITP, such as thrombocytopenia in patients with cirrhosis associated with hepatitis C[17] and chemotherapy-induced thrombocytopenia,

Potential risks of thrombopoietic agents

With the newer thrombopoietic agents described in Table 1, that have all been developed to sequence homology with TPO, there have been no reports of drug-dependent antibody formation that neutralized endogenous TPO.

When thrombopoietic agents are stopped, thrombocytopenia may be severe, below a patient's baseline level, because the higher platelet counts during treatment may have absorbed and thereby suppressed plasma levels of endogenous TPO. Thrombosis may be a potential risk, but clinical trials have not yet observed a difference in either arterial or venous thrombotic events between treatment and placebo groups. However, thrombosis may yet be a risk with longer use in more patients who may have greater susceptibility. A reversible increase of marrow reticulin associated with marked proliferation of megakaryocytes was observed in a trial of rhTPO to support induction therapy in 9 patients with AML.[18] Increased marrow reticulin has also been observed in a few patients in the clinical trials with romiplostim.[1,4] This may be a dose-dependent, physiological side effect as it appears to be reversible when the thrombopoietic agent is stopped and it has not been reported in more recent studies of romiplostim when dose escalation was stopped at 10 μg/kg/week. Because TPO promotes the viability of hematopoietic progenitor cells of all lineages and TPO receptors are present in hematologic malignancies, there is the potential risk that thrombopoietic agents may accelerate growth of malignant cells. This has been an issue in a single arm dose escalation study of romiplostim in patients with myelodysplasia. Six out of 44 patients had increased myeloblasts that decreased when romiplostim was stopped; 2 patients transformed to acute myelocytic leukemia.[19]

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Allogeneic hematopoietic stem cell transplantation for myelofibrosis

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Primary myelofibrosis (PMF) or myelofibrosis secondary to polycythemia vera (PV-MF) or essential thrombocythemia (ET-MF) can be cured only by means of allogeneic hematopoietic stem cell transplantation (HSCT).[1] However, the age of the patient, the number of circulating blasts, cytogenetic abnormalities, the type of conditioning regimen, previous splenectomy, or selection of an unrelated donor, are among the factors that have been reported to possibly affect the outcome of HSCT.[2] Patients with disease transforming into acute leukemia have no or little benefit from transplant. On the other hand, the indication for an allogeneic HSCT in patients with no adverse prognostic factors, such as anemia or an abnormal white cell count according to the Lille scoring system,[3] but with symptoms often due to enlarged splenomegaly is still debated. More recently, it has been proposed that a low number of circulating platelets or an increased number of monocytes[4] can be added to the parameters utilized in the Lille scoring system to better stratify patients with PMF with different degrees of risk. In addition, unfavorable cytogenetic abnormalities, such as those other than 13q- and 20q-, have been associated to adverse prognosis independently of blood cell counts in patients with secondary myelofibrosis.[5]

Recent retrospective analyses of series of patients transplanted with standard myeloablative or heterogeneous reduced intensity conditioning (RIC) regimens have encouraged many centers to consider a transplant option in the management of myelofibrosis patients. Nevertheless, these studies also raised different views on whether the conditioning regimen should be based on the patient's characteristics or not.

Another controversial point that has not yet been definitively solved is what role the presence of extramedullary hematopoiesis may have in the outcome of HSCT, in particular when it causes extremely enlarged splenomegaly.

What conditioning regimen?

Allogeneic HSCT can completely reverse the fibrosis in the bone marrow,[6] restore a normal hematopoiesis and cure patients with PMF or PV-MF, or ET-MF. Retrospective studies from single institutions or co-operative groups analyzed the outcome of HSCT utilizing myeloablative conditioning regimens. A first study[7,8] demonstrated that a myeloablative HSCT, mostly utilizing total body irradiation (TBI), was effective particularly in patients with low-risk disease (85% survival rate) as compared to high risk (35% survival rate), and in patients younger than 45 years (62% survival rate) as compared to older patients (14%). The same study also showed that T-cell depletion of the graft reduces the survival of transplanted patients, suggesting a graft-versus-myelofibrosis effect from donor lymphocytes. The same effect was then supported by the successful use of donor lymphocyte infusion (DLI) in patients relapsed after HSCT.[9] Another important retrospective study[10] demonstrated a significantly better outcome in patients condi-