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Thrombopoietin receptor agonists in the treatment of chronic immune thrombocytopenic purpura

Introduction

Understanding of the pathophysiology of immune thrombocytopenic purpura (ITP) has undergone substantial revision. Harrington and colleagues showed that infusing ITP plasma into healthy recipients caused acute thrombocytopenia. Subsequently, this activity was attributable to the IgG fraction with the effect mitigated by splenectomy or corticosteroids. Formal studies of platelet kinetics affirmed that platelet survival is shortened in ITP. It was inferred from these studies, the abundance of megakaryocytes in the bone marrow and the appearance of young megathrombocytes in the periphery, that increased platelet production compensates for platelet destruction, analogous to reticulocytosis in autoimmune hemolytic anemia. Corticosteroids, danazol, IV immune globulin or IV anti-D worked by reducing clearance of antibody-coated platelets by tissue macrophages.

In the mid 1980's, the issue of platelet production was revisited by several groups. The upshot of these studies is that platelet production is not increased or is actually reduced in most patients with ITP. This inference is supported by several findings, including: 1) Expression of platelet antigens relevant to ITP on megakaryocytes; 2) Impairment of megakaryocyte development *in vitro* by ITP-IgG; 3) Appearance of apoptotic ITP megakaryocytes on electron microscopy; and 4) "Normal" or minimally increased plasma levels of thrombopoietin (TPO) in ITP plasma.

The biochemistry and physiology of TPO and its receptor have been reviewed in detail elsewhere.[1] TPO production is not regulated primarily at the level of synthesis, as with erythropoietin. Rather, plasma TPO is cleared by binding to its receptor, cMPL. Receptor-bound TPO may be internalized and degraded by megakaryocytes and removed when antibody-coated platelets are destroyed. These studies provide rationale for the development of TPO-like agents for use in ITP.

First generation thrombopoietin receptor agonists

Studies were first performed with recombinant human TPO (rhTPO) and pegylated human megakaryocyte growth and development factor (PEG-rHuMGDF). Although these agents raised the platelet count in patients with ITP[2,3] and other disorders, development stopped when several normal volunteers paradoxically developed thrombocytopenia due to the development of antibodies

against the drug that neutralized endogenous TPO[4]. Thrombo-cytopenia was often severe and persisted for months after the drug was discontinued.[4] Therefore, efforts to develop agents to stimulate platelet production shifted to first generation thrombopoietin receptor agonists (TRAs) lacking resemblance to TPO.

Romiplostim: efficacy

Romiplostim is a recombinant protein composed of 2 identical polypeptide sequences, each covalently fused to a human Fc fragment. Each polypeptide contains 2 c-Mpl binding domains lacking sequence homology with human TPO. The Fc domains may recycle through the neonatal salvage receptor, prolonging drug half-life.[5] Romplostim competes with endogenous TPO for binding to c-Mpl.[6] Romiplostim is administered as a weekly subcutaneous injection at a starting dose of 1 µg/kg, with dose adjustments as necessary to attain a platelet count between 50 and 200×10^9/L.

Romiplostim has been studied in 3 randomized, double-blind, placebo-controlled trials of adults with chronic ITP.[7,8] Subjects had a baseline platelet count $<30\times10^9$/L and had undergone at least one previous ITP therapy. In the phase II trial, 21 patients were randomized to receive placebo or romiplostim at 1, 3, or 6 µg/kg weekly for a total of 6 weeks. Enrollment at highest dose was stopped because one patient developed thrombocytosis. Twelve of the 16 subjects in the other cohorts achieved a platelet count $\geq50\times10^9$/L.[8]

In 2 phase III trials, 125 adults with chronic ITP were randomized 2:1 to receive weekly romiplostim or placebo for 24 weeks. One study involved 63 patients who had undergone splenectomy; the other included 62 non-splenectomized subjects. Romiplostim was titrated to achieve a platelet count $\geq50\times10^9$/L. The primary efficacy endpoint, a platelet count $\geq50\times10^9$/L for at least 6 of the final 8 weeks of study drug in the absence of rescue therapy, was achieved in 61% of non-splenectomized and 38% of splenectomized patients receiving romiplostim, compared with 1 of 42 given placebo.[8] Subjects were allowed to enroll in a single arm, open label extension study. An analysis of 142 patients treated for a mean of 69 weeks (maximum duration 156 weeks) showed a platelet count of $\geq50\times10^9$/L and double baseline was achieved in 87%. Responses were sustained 67% of the time in responders. In 77% of patients, the dose remained within 2 µg/kg at least 90% of the time. Most (84%) patients reduced or discontinued concurrent medications with less need for rescue medications. Sixty three percent of the patients received the drug by self-administration.[9] Romiplostim as a splenectomy-sparing agent is under investigation.[10]

Eltrombopag: efficacy

Eltrombopag is a small, orally available, non-peptide organic molecule that may bind to human c-Mpl at a distance from TPO.[11] The recommended starting dose is 50 mg daily orally with adjustments as needed to achieve a platelet count of $50\text{-}200\times10^9$/L. Plasma levels were ~70% higher in some East Asian subjects in one analysis. Therefore, a starting dose of 25 mg daily is recommended in this population.[12]

Eltrombopag has been evaluated in 3 randomized, double-blind, placebo-controlled trials of adults with chronic ITP.[13-15] Subjects had baseline platelet counts $<30\times10^9$/L and had received at least one prior ITP therapy. In a phase II trial with subjects randomized to placebo or eltrombopag (30 mg, 50 mg, or 75 mg daily for 6 weeks), the median platelet counts at the end of the treatment period were 16×10^9/L, 26×10^9/L, 128×10^9/L, and

183×10⁹/L, respectively.[13] In a phase III trial of 6 weeks duration, 114 patients were randomized 2:1 to receive eltrombopag 50 mg daily or placebo.[15] In the third phase III RAndomized placebo-controlled ITP Study with Eltrombopag trial, 197 subjects were randomized 2:1 to eltrombopag 50 mg daily or placebo for 6 months.[14] In both phase III trials, the dose of eltrombopag could be increased to 75 mg if no response occurred after 3 weeks. In the 6-week study, the primary endpoint, a platelet count ≥50×10⁹/L at week 6, was achieved in 59% of eltrombopag-treated subjects compared with 16% of the placebo-treated cohort. In the 6 month study, the odds of achieving the primary endpoint, a platelet count ≥50×10⁹/L at any point during the study period, was 8-fold greater in the eltrombopag arm. In both phase III trials, patients receiving eltrombopag experienced less bleeding and required less rescue therapy.[14,15] In a recent interim analysis of 207 patients in an ongoing open-label extension study with a treatment duration of 3-523 days, 79% of subjects achieved a platelet count ≥50×10⁹/L at least once, responses were generally durable, patients experienced less bleeding on study than at baseline, and many responders saw reductions in concomitant medications and rescue therapy.[16,17]

Other thrombopoietin receptor agonists in clinical development

The efficacy and safety of other TRAs in ITP has not been reported. AKR-501 and LGD-4665 are orally available, non-peptide small molecules that induce a dose-dependent rise in platelet count in healthy volunteers[18,19] and are undergoing phase II testing.[20,21] RWJ-800088, a pegylated peptide with sequence homology to TPO, increased the platelet count in a single dose study in healthy volunteers.[22] Several other TRAs are currently in preclinical or early clinical testing.[23]

Table 1. Serious toxicities of the thrombopoietin receptor agonists.

TRA class toxicities	*Romiplostim-specific toxicities*	*Eltrombopag-specific toxicities*
Bone marrow fibrosis	Neutralizing antibody formation	Cataract formation
Thrombosis		Hepatotoxicity
Rebound thrombocytopenia		
Hematologic malignancy		

Toxicities

Safety information is available only for romiplostim and eltrombopag. Few serious adverse events have been observed; others remain of theoretical concern based on preclinical data or mechanism of action. Some toxicities might be associated with TRAs as a class; others may be specific to one or the other agent (Table 1).

Neutralizing antibodies

As mentioned, pegylated human megakaryocyte growth factor induced anti-drug antibodies that cross-reacted with endogenous TPO leading to severe protracted thrombocytopenia in 11 of 124 healthy volunteers.[4] Romiplostim shares no sequence homology with TPO and anti-TPO antibodies have not been detected to date. In the extension study, one patient transiently developed neutralizing anti-romiplostim antibodies after 79 weeks of therapy that did not cross-react with TPO[9]. Testing is available through Amgen[24] and should be considered in patients who have diminished response to romiplostim. Antibodies to eltrombopag have not been reported.

Bone marrow fibrosis

Bone marrow contains reticulin and collagen fibers that provide a structural network to support hematopoiesis. Reticulin is composed primarily of fibrils of type III collagen surrounding a core of type I collagen identified using silver stain. Increased reticulin may be associated with cytopenias and signify a serious bone marrow disorder, but mild to moderate reticulin fibrosis is also observed in normal healthy individuals[25,26] and in patients with ITP not treated with TRAs.[27] In contrast, collagen fibers are thicker, consist largely of collagen type I fibrils, are stained with trichrome[28] and are generally associated with cytopenias, most commonly in patients with myeloproliferative disorders or tumors metastatic to the bone marrow.[28]

Stimulated megakaryocytes release transforming growth factor-β and other cytokines that induce bone marrow fibroblasts to synthesize collagen.[29,30] In rodent models, injection of PEG-rMGDF[31,32] or genetic over-expression of TPO[33] induces marrow fibrosis. It is therefore not surprising that a reversible increase in reticulin was noted in 8 of the 9 subjects with acute leukemia given rhTPO.[34]

Reticulin fibrosis has also been observed in a few patients receiving romiplostim or eltrombopag. When data from all romiplostim trials were analyzed, 8 subjects had increased marrow reticulin while on therapy with biopsies performed at the discretion of the investigator, some due to loss of response or appearance of new abnormalities on the peripheral blood smear. In a retrospective central review of these specimens,[35] 4 showed occasional (grade 1) or diffuse fine fibers (grade 2) using a modified Bauermeister scale,[25] 3 demonstrated scattered coarse fibers (grade 3), and 1 showed collagen fibrosis (grade 4). Four of 6 patients with pre-treatment biopsies available for comparison showed increased reticulin from baseline. In 3 of 4 patients, follow-up biopsy performed 8-12 weeks after discontinuing romiplostim showed less reticulin, while one showed stable grade 2 fibrosis 68 weeks after stopping treatment. There was no evidence of dysplasia or a clonal disorder in any specimen. In the extension study, 1 of 6 patients with pre- and post treatment biopsies showed an increase in reticulin baseline (from grade 0 to 1), which not associated with clinical symptoms.[9]

Bone marrow biopsies were not routinely performed in the eltrombopag trials, and no cases of marrow fibrosis were identified based on clinical suspicion.[13,14,16] The extension study protocol has been amended to include bone marrow biopsy after 12 months on treatment.[16] In a recent interim analysis of patients treated for more than one year, 23 of 44 evaluable biopsies demonstrated some fibrosis based on the European consensus guidelines:[36] 18 with loose networks of reticulin (grade 1), 2 with diffuse and dense increase in reticulin (grade 2), and 3 with collagen fibrosis. Pre-treatment biopsies were available for very few patients. There were no reports of cytopenias or abnormalities on peripheral blood smear.[37]

Little is known about the incidence of bone marrow fibrosis in ITP. Immune-mediated injury to the expanded megakaryocyte mass may release TGF-β with an attendant increase in fibrosis. This hypothesis is supported by a retrospective survey of single bone marrow specimens from 40 ITP patients, two-thirds of whom demonstrated grade 1 or 2 reticulin.[27] Serial studies in treated or untreated patients are needed to: a) define the baseline and b) stratify for disease severity, duration, and therapy, before judging the impact of TRAs.

Clinically relevant cytopenias rarely develop within a year of initiating TRAs and may be reversible. However, incidence, severity, and clinical implications of TRA-induced bone marrow fibrosis are uncertain. Progression to myelofibrosis has not been reported. Nor is it clear whether marrow reticulin mandates dose-

reduction or stopping treatment or whether close monitoring of blood counts and the peripheral blood smear will suffice as a surrogate marker of risk, particularly in asplenic patients in whom abnormal erythrocyte morphology is common.

US Food and Drug Administration currently mandates monitoring of cell counts and the peripheral blood smear at least monthly in all patients receiving TRAs. If new morphologic blood smear abnormalities or cytopenias are noted or if there is loss of response, a bone marrow biopsy should be performed. If fibrosis is noted, strong consideration should be given to discontinuing TRA therapy and performing follow-up biopsies to assess response.

Thrombosis

There is limited evidence that ITP may be a prothrombotic disorder. In one descriptive analysis of 186 adults with chronic ITP, 5% had a history of arterial or venous thromboembolism (TE).[38] Intravenous immune globulin[39] and splenectomy[40,41] have also been associated with a small increase in risk. In theory, ITP patients with pre-existing atherosclerotic disease or prothrombotic risk factors may enjoy a measure of protection from thrombosis that is lost during a rapid, robust, and sustained response to any effective treatment.

In baboons with extravascular shunts given TPO, platelet deposition was increased.[42,43] There has been concern that TRAs may likewise increase the thrombotic risk by affecting platelet number or function. Although none of the TRAs activate platelets *in vitro* directly, rhTPO, PEG-rHuMGDF, and romiplostim reduce the threshold for activation by ADP, collagen, and thrombin receptor agonist peptide at concentrations substantially higher than those attained clinically.[43,44] Although not reported with eltrombopag, direct comparative studies are lacking.[1,45]

Clinical studies have been reassuring. Studies of first generation agents did not suggest response increased the rate of thrombosis, even in patients with cancer.[46-48]

In controlled trials, 2 patients who received romiplostim and 2 placebo-treated patients suffered TE.[7,8] In the romiplostim extension study, 12 thromboembolic events developed in 7 (4.9%) patients; 8 events occurred at platelet counts $<400\times10^9$/L[9] and 6 of the 7 patients had pre-existing risk factors. In a pooled analysis, the incidence of thrombosis did not differ between patients receiving romiplostim and those given placebo (8 *vs.* 10 events per 100 patient-years).[49]

In controlled clinical trials, 1 TE was reported among eltrombopag-treated subjects vs none given placebo.[12] The platelet count exceeded 400×10^9/L, in 15 patients, some of whom were treated briefly with an antithrombotic agent such as aspirin and none developed TE. TEs were observed in 7 subjects in the extension study, all of whom had one or multiple pre-existing risk factors; platelet counts at the time of TE ranged between 14 and 407×10^9/L.[16]

Based on these data, TRAs have not been shown to increase the risk of TE in patients with ITP, even in the setting of transient thrombocytosis. Nonetheless, platelet counts should be monitored regularly and the minimum dose needed to maintain a platelet count $\geq50\times10^9$/L should be used. Given that almost all TE occurred in those with pre-existing thrombotic risk factors, it would seem prudent to titrate the dose to achieve the minimal platelet count necessary to maintain hemostasis in such patients and to consider using aspirin or another antithrombotic agent if the platelet count exceeds the desired range. It should also be noted that patients at the highest thrombotic risk, e.g. those with pre-existing cardiovascular disease or history of venous thrombosis, were excluded from many studies. Therefore, safety in this population has not been established.

Rebound thrombocytopenia

Rebound thrombocytopenia, defined as a platelet count $<10\times10^9$/L and at least 10×10^9/L below the baseline within 4 weeks of stopping drug, was observed in the romiplostim and eltrombopag trials. This may be due to increased clearance of endogenous TPO by the expanded megakaryocyte and platelet mass. Moreover, some patients may have reduced or discontinued concurrent ITP treatment.

In the phase I/II trials, 4 of 41 romiplostim-treated patients developed rebound thrombocytopenia and two required rescue therapy. Platelet counts returned to baseline within 3 to 17 days.[7]

Rebound thrombocytopenia was observed in 10% of patients treated with eltrombopag and 6% given placebo.[13-15] Several patients experienced increased bleeding and required rescue therapy.[12] In an interim analysis of the extension study, rebound thrombocytopenia occurred in 3 of 35 subjects who withdrew from the study and in 6 of 54 patients who required treatment interruption.[16] Two patients experienced worsening bleeding and 3 required rescue therapy. In the REPEAT study, an open-label phase II trial to evaluate the safety and efficacy of repeated, intermittent dosing of eltrombopag for 3 cycles, rebound thrombocytopenia developed in 5 of 66 patients, 3 of whom noted increased bleeding;[50] in each case, the platelet count returned to baseline within 2 weeks.

In summary, rebound thrombocytopenia occurs in approximately 10% of patients who discontinue romiplostim or eltrombopag and appears to be associated with a heightened risk of bleeding. Platelet counts should be monitored on at least a weekly basis for at least 4 weeks after stopping a TRA. In theory, tapering the dose of a TRA prior to discontinuation may ameliorate rebound thrombocytopenia. In patients with severe thrombocytopenia and bleeding prior to treatment, it may be prudent to reintroduce or increase the doses of concomitant ITP medications prior to discontinuing TRAs.

Hematologic malignancy

Some hematopoietic malignancies express cMPL.[51] However, placebo-controlled studies of PEG-rHuMGDF as an adjunct to chemotherapy in patients with acute leukemia did not show increased blast counts.[52,53] In a single-arm study, 11 of 44 patients with myelodysplastic syndrome receiving romiplostim showed possible disease progression,[24] but placebo-controlled clinical trials are lacking. No such problem has emerged in patients with ITP. In the controlled trials of eltrombopag, no hematologic malignancies were reported.[13-15] In the extension study, one subject developed non-Hodgkin's lymphoma.[16] The incidence of hematologic malignancy in controlled trials of romiplostim was likewise low and similar to the placebo groups.[7,8] In the romiplostim extension study, a monoclonal gammopathy was identified in one patient.[9]

Cataracts

In preclinical toxicology studies of eltrombopag at doses ≥5-7 times the human clinical exposure, dose- and time-dependent development of cataracts was observed in rodents,[12] but did not develop in dogs after 52 weeks of exposure at 3 times the clinical dose. In the controlled clinical trials of eltrombopag, ophthalmic examinations were performed on all subjects at baseline, at the end of treatment, and 6 months after the last dose. Cataracts developed or worsened in 5% of patients receiving eltrombopag *vs.* 3% of patients given placebo.[13-15] Although examinations were not mandated, 4% of subjects participating in the eltrombopag extension study who underwent ocular examination prior to initiating therapy developed new or worsened cataracts.[16] Many patients with chronic ITP have well-estab-

lished risk factors for cataracts, particularly long-term corticosteroid use. Whether eltrombopag contributes to this risk will be addressed in LENS (Long-term Eltrombopag Observational Study), an ongoing assessment of ocular safety and lens changes over a follow-up period of 2.5 years in patients who participated in a phase II or phase III trial.[54] Until more is known, it is recommended that patients undergo ophthalmic examination prior to initiating eltrombopag and at least annually while treated.

Hepatotoxicity

The risk of hepatotoxicity is a boxed warning in the packaging insert for eltrombopag. In the phase II trial, one subject in the 50 mg cohort was hospitalized 2 weeks after starting eltrombopag with grade 4 (NCI terminology) elevations in alanine aminotransferase (ALT) and aspartate aminotransferase,[13] subsequenty attributed to sepsis and multi-organ failure.[55] Grade ≥3 elevations in liver function tests (LFTs) did not occur in any other subjects. Grade 1 and 2 abnormalities were observed in 10% and 8% of the eltrombopag and placebo arms, respectively.[13-15] Two patients (1%) in the eltrombopag arm and 2 patients (3%) in the placebo group discontinued treatment due to abnormal LFTs.[12] To date, 15 (7%) patients in the extension study have experienced hepatobiliary events on therapy, most grade ≤2. Two percent of subjects developed an ALT ≥3 times the upper limit of normal (ULN) and 3% developed a total bilirubin >1.5 times the ULN.[16] Six of 7 eltrombopag-treated patients who developed abnormal LFTs in the controlled clinical trials developed recurrent abnormalities 8-330 days after re-exposure in the extension study, which lasted an average of 39 days. Most events resolved on or after discontinuing treatment. On the other hand, eltrombopag was well tolerated in a phase II study of patients with thrombocytopenia secondary to hepatitis C-related cirrhosis.[56]

Nonetheless, eltrombopag should be used cautiously in patients with pre-existing liver disease. A reduced starting dose of 25 mg daily is recommended for those with moderate to severe hepatic impairment. LFTs should be monitored in all patients prior to initiating eltrombopag, every 2 weeks during dose titration, and monthly once a stable dose is attained. The drug should be discontinued if the ALT increases to ≥3 times the ULN or if clinical symptoms develop.[12]

Although hepatotoxicity has not been recognized as an adverse event in clinical trials of romiplostim, the drug has not been tested in patients with hepatic impairment.[24]

Common adverse events

Romiplostim and eltrombopag have been well tolerated in clinical trials of ITP. The most common non-bleeding adverse events and their incidences in clinical trials of romiplostim[7,8] and eltrombopag[13-15] are shown in Tables 2 and 3 respectively. In general, reactions other than headaches and myalgias occurred at a similar frequency in the treatment and placebo-controlled groups, were mild, and did not require stopping therapy.

Clinical perspective

Romplostim and eltrombopag are highly effective novel treatments for patients with ITP at every stage of the disease, inducing durable hemostatic responses in up to 80% of patients. Both are well tolerated and have good safety profiles. It is clear that nuisance bleeding is reduced in most patients, major bleeding is quite rare when patients attain platelet counts above 30,000/μL, and concurrent medications can be reduced or discontinued in most recipients. The major unresolved question is whether the incidence of clinically sig-

Table 2. Common non-bleeding adverse events in trials of romiplostim.

	Phase II		*Phase III*		*Extension*
	Romiplostim (n = 17)	*Placebo (n = 4)*	*Romiplostim (n = 84)*	*Placebo (n = 41)*	*Romiplostim (n = 142)*
Headache	4.9 (5)	0	1.4 (29)	1.3 (13)	1.8 (177)
Fatigue	1.0 (1)	0	1.4 (28)	1.2 (12)	0.8 (80)
Nasopharyngitis	0	0	0.3 (7)	0.7 (7)	0.8 (76)
Arthralgia	0	4.2 (1)	1.1 (22)	0.8 (8)	0.7 (72)
Diarrhea	2.9 (3)	4.2 (1)	0.7 (14)	0.6 (6)	0.6 (63)
Upper respiratory tract infection	0	0	0.7 (14)	0.5 (5)	0.5 (52)
Cough	0	0	0.5 (10)	0.7 (7)	0.5 (50)
Nausea	2.0 (2)	4.2 (1)	0.5 (11)	0.4 (4)	0.4 (44)
Pain in extremity	1.0 (1)	0	0.5 (11)	0.2 (2)	0.4 (38)
Dizziness	2.0 (2)	4.2 (1)	0.7 (14)	0	0.3 (31)
Back pain	1.0 (1)	8.3 (2)	0.5 (11)	0.4 (4)	0.3 (28)
Abdominal pain	2.0 (2)	4.2 (1)	0.4 (9)	0	0.3 (26)

Estimated events per 100 patient-weeks based on published literature are shown with number of events in parentheses.

Table 3. Common non-bleeding adverse events in trials of eltrombopag.

	Phase II/III[a]		*Extension*
	Eltrombopag 50 mg (n=106) n (%)	Placebo (n=67) n (%)	Eltrombopag (n=207) n (%)
Headache	9 (8)	10 (15)	31 (15)
Nasopharyngitis	6 (6)	3 (4)	19 (9)
Nausea	6 (6)	0	19 (9)
Fatigue	4 (4)	5 (7)	20 (10)
Arthralgia	2 (2)	4 (6)	16 (8)

[a]*Includes a pooled analysis of the eltrombopag 50 mg and placebo groups from the phase II trial and the 6-week phase III trial. Complete safety data from the 6-month phase III trial has not been reported yet, and is therefore not included in the table.*

nificant reticulin fibrosis will develop with long-term use. There is some concern as to whether eltrombopag causes transient transaminitis in a small number of patients.

Based on available data, TRAs are suitable in post-splenectomy patients who require treatment. TRAs are also indicated to produce a temporary rise in platelet counts prior to planned procedures, although IVIG and anti-D are needed in urgent settings. A more complex issue is whether TRAs should be used in an attempt to forestall splenectomy. Splenectomy remains the treatment option with the highest proportion of durable long-term responses. The benefits and risks of splenectomy are relatively well established after decades of use, including the peri-surgical complications and known risk of sepsis, but recent concerns about thrombosis, coronary artery disease and pulmonary hypertension have been raised. Moreover, patients are increasingly reluctant to agree even to laparascopic splenectomy until non-surgical modalities have been tried. Rituximab induces complete responses lasting

a year in 25-35% of patients and 15-25% remain in remission for 4-6 years. Patients with durable responses often respond to repeat administration, but the long-term sequelae of repetitive administration on immune reconstitution, especially in young patients, is unknown. TRAs induce responses in a higher proportion of patients, but require protracted, potentially indefinite, treatment and knowledge about the long-term toxicity, while acceptable at present, is based on fewer patients followed for a shorter period of time. Inconvenience involved in weekly visits to the doctor with romiplostim and dietary and drug-drug interactions with eltrombopag, may influence prioritization as do issues surrounding cost and reimbursement.

Lastly, and unresolved, is whether TRAs should now become part of first-line therapy to reduce reliance on corticosteroids. Alternatives for ITP on presentation include: 1) A standard several week course of prednisone to identify the occasional adult with transient disease; 2) Dexamethasone, which in some studies induces more durable responses than prednisone; 3) Dexamethasone and rituximab based on one preliminary report; or 4) Initiation of therapy with prednisone (or dexamethasone) and a TRA under the assumption that even standard doses and durations of corticosteroids are toxic and their withdrawal will be followed by relapse in a high proportion of patients. Additional experience with the safety profile of TRAs upon long-term use in larger number of patients will help to address these questions.

Conclusions

TRAs provide an important new option to manage chronic ITP. To date, clinical experience has demonstrated impressive efficacy and tolerability. This experience is limited to a small number of patients with relatively short-term follow-up. The incidence and clinical implications of recognized toxicities such as bone marrow fibrosis is uncertain. Assiduous surveillance for rare adverse reactions and cumulative toxicities associated with long-term use is imperative as clinical experience with these compounds accumulates. Ongoing extension studies of romiplostim and eltrombopag and mandatory safety reporting programs linked to the restricted distribution programs will help in this regard.

There is a great need for effective and safe alternative treatments for chronic ITP. Most therapies cause immunosuppression and diverse agent-specific cumulative toxicities, which impact quality of life. Treatment-related morbidity may be comparable to that caused by the disease itself.[57] From this has emerged the central principle that therapy should be administered only when the risk of bleeding outweighs the risk of treatment-related toxicity. More information on the safety and efficacy of the TRAs, particularly with long-term use, through meticulous safety surveillance and pharmacovigilance will help determine the optimal place for this class of drugs.

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