Clinical Medicine Reviews in Therapeutics

Libertas Academica
FREEDOM TO RESEARCH

CMR
Clinical Medicine Reviews

REVIEW

Pharmacotherapy of Chronic Immune Thrombocytopenic Purpura (ITP) with Romiplostim

Michelle Perugini[1], Herman Lee[2], Simon McRae[3] and Richard J. D'Andrea[1,2,4]

[1]The Division of Haematology and the Centre for Cancer Biology, Hanson Institute and SA Pathology, Adelaide, South Australia. [2]The Division of Haematology and Oncology, The Queen Elizabeth Hospital, Woodville, South Australia. [3]Department of Haematology, SA Pathology, The Royal Adelaide Hospital, Adelaide, South Australia. [4]Women's and Children's Health Research Institute, North Adelaide, South Australia. Email: michelle.perugini@health.sa.gov.au; richard.dandrea@health.sa.gov.au

Abstract: Immune Thrombocytopenic Purpura (ITP) has long been thought to result predominantly from immune mediated acceleration of platelet destruction. As a result, immunosuppressive therapy has traditionally played a central role in the treatment of the disorder. Despite many advances in treatment options chronic ITP that is refractory to available therapy remains a difficult clinical problem. Impaired platelet production is now accepted as a hallmark of ITP providing alternate avenues for therapeutic development. Romiplostim is a second generation Thrombopoietin (TPO) mimetic that was approved in 2008 by the US Food and Drug Administration (FDA) for the treatment of patients with chronic ITP that have an insufficient response to corticosteroids, immunoglobulins, or splenectomy, and an increased risk of bleeding. FDA approval was based on pivotal clinical trials that demonstrated romiplostim to be effective in the treatment of chronic ITP in adults, with limited serious side effects reported. Thus romiplostim now provides an option for management of ITP patients refractory to first-line treatments.

Keywords: romiplostim, cytokine mimetic, thrombopoietin, immune thrombocytopenia

Clinical Medicine Reviews in Therapeutics 2010:2 129-135

This article is available from http://www.la-press.com.

Introduction

First described in 1735 by the German physician Paul Gottlieb Werlhof, immune thrombocytopenic purpura (ITP) is characterized by the presence of either transient or persistent acquired thrombocytopenia.[1] There is no specific diagnostic test for ITP and the diagnosis is therefore one of exclusion, as indicated by the previous use of the term "idiopathic" to describe the condition. Patients with ITP typically only develop bleeding symptoms when the platelet counts drop to below 50×10^9 cells/L, with major bleeding uncommon unless the platelet counts fall to less than 10×10^9 cells/L. The incidence of acute ITP in children has been estimated at 1.9–6.4 per 100,000 and the incidence of adult ITP has been estimated at 3.3 per 100,000. (Reviewed in[2]).

Thrombocytopenia in ITP was long thought to result from accelerated platelet destruction, however, it is now clear that impaired platelet production is also an important contributor to the disease and this has provided alternate avenues for therapeutic development.[3,4] Despite many advances in treatment options for ITP, a significant proportion of patients with chronic ITP fail to achieve a sustained remission with currently available therapy. Corticosteroid treatments are effective for acute ITP but show cumulative toxicity when administered long-term.[5] Immunoglobulin (IVIg) and anti-Rh(D) treatments are also effective but the inconvenience of regular intravenous (IV) infusion delivery precludes their long-term use. Splenectomy has long been the recommended treatment for chronic ITP, however, 30%–40% of patients show no response or relapse following the procedure.[5] Therefore, there remains a clinical need for a practical and effective treatment option for the long-term management of patients with chronic ITP.

Thrombopoietin (TPO) is a cytokine that regulates platelet production by binding to, and activating the TPO receptor.[6] Patients with ITP display disproportionately low serum TPO levels and thus TPO receptor agonists/mimetics represent a potential strategy for treatment of chronic ITP (Reviewed in[7]). Based on the discovery of TPO, first generation recombinant TPOs were developed for treatment of ITP. Results were encouraging in early studies but a subsequent large safety study reported that 13 subjects developed anti-TPO antibody with associated severe thrombocytopenia. Development of this class of drug has since been discontinued.[8] Subsequent efforts have identified second generation TPO mimetics that bear no structural resemblance to TPO and therefore avoid the risk of antibody response, but that are still able to bind to and activate the TPO receptor. In 2008, romiplostim became the first TPO mimetic to be approved by the US Food and Drug Administration (FDA) for the treatment of chronic ITP.[9]

This review follows the journey of romiplostim through clinical trials, summarizing key clinical trial outcomes, safety and efficacy. In particular we discuss quality of life considerations and patient preferences for management of chronic ITP.

Mechanism of Action

Romiplostim overcomes the issue of cross-reacting anti-TPO antibodies as it is based on random peptides with binding affinity for the TPO receptor that bear no sequence homology to endogenous TPO. The presence of the F_c fragment in the romiplostim peptibody structure enables F_c binding to the F_cRn salvage receptor, resulting in endothelial recirculation and a substantially longer half-life than the peptide alone[10] (Fig. 1). Romiplostim is subsequently removed by reticuloendothelial elimination.[11]

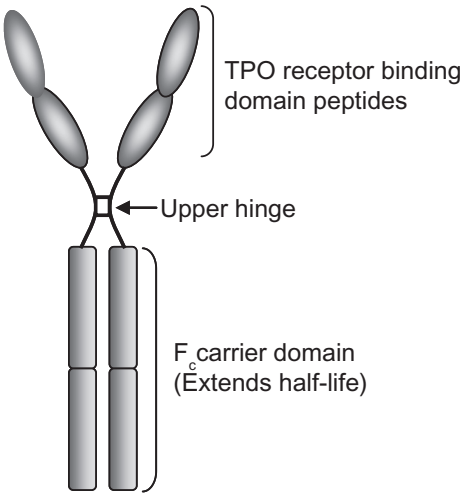

Figure 1. Schematic showing the peptibody structure of romiplostim. The TPO receptor binding domain peptides stimulate megakaryopoiesis through induced dimerisation and activation of the TPO receptor. The F_c carrier domains bind to the F_cRn salvage receptor to extend the half-life of the molecule.

Romiplostim acts similarly to naturally occurring TPO by binding to and inducing dimerisation of the TPO receptor, initiating intracellular signal transduction, and stimulating megakaryopoiesis and platelet production.[12] Romiplostim was initially tested in a number of TPO-dependent cell lines. It was shown to compete with naturally occurring TPO for binding to the TPO receptor, and to activate JAK2/STAT5 signalling pathways promoting *in vitro* cell growth. TPO-dependent cell lines also showed increased megakaryocyte differentiation *in vitro* when treated with romiplostim.[13]

Pharmacokinetic and Pharmacodynamic Data

Initial pharmacokinetic profiling studies in Rhesus monkeys showed that a single dose of romiplostim gave a dose-dependent rise in platelet count even with concentrations as low as 0.5 mg/kg, with a circulatory half life ranging from 110–160 hours.[11] This prompted an initial human phase I study involving 48 healthy volunteers. A starting dose of 10 µg/kg of romiplostim was administered intravenously.[10] Elevation of platelet counts was used as a measure of pharmacodynamic response and a biologically active dose was determined as a dose that increased platelet counts 2-fold. An unexpectedly high platelet increase was observed with the 10 µg/kg dose likely owing to the higher affinity of the drug for the human TPO receptor than the Rhesus monkey receptor. Lower doses of romiplostim were found to induce a dose-dependent rise in platelets, with a dose of 1 µg/kg resulting in a 2-fold increase in platelet count following both intravenous (IV) and subcutaneous (SC) delivery. IV delivery resulted in a more rapid increase in platelet counts (between 1 to 3 days) compared with 4 to 9 days for SC administration. This is consistent with the slow absorption of romiplostim via SC injection with peak serum concentrations achieved between 24–36 hours after dosing.[10] Peak platelet counts were achieved between 12–16 days following administration, and returned to baseline by 28 days. Importantly no subjects developed autoantibody responses to TPO at this concentration and both IV and SC injections produced similar rises in platelet counts.[11] The pharmacokinetic profile of romiplostim was shown to be nonlinear with dose.

Phase II Trials

In an intial phase II study 21 patients received weekly SC injections of romiplostim for 6 weeks at varying doses (1, 3, and 6 µg/kg) or placebo.[12] The drug was found to be effective in 12 out of 16 (75%) patients, where the target platelet range ($\geq 50 \times 10^9$ cells/L) was either reached or exceeded. No major adverse events were reported. Increases in platelet count were dose dependent, with the 6 µg/kg cohort being closed after the enrolment of only one patient due to the targeted platelet count being exceeded. Similar clinical responses were observed in a subsequent Phase II, open-label, sequential-cohort dose-escalation study in 12 Japanese men.[14] Doses of 1, 3 and 6 µg/kg were assessed in this study and showed platelet responses of 0%, 50% and 100% respectively. No severe or life-threatening adverse effects were identified in this study.[14] Based on these findings, a starting dose of 3 µg/kg was recommended for follow-on Phase III trials. Most recently a Phase I/II study was conducted to assess the safety and efficacy of romiplostim in children aged 12 months to 18 years suffering from chronic ITP.[15] Overall, 15 out of 17 (88.2%) patients in the romiplostim treatment arm achieved efficacy endpoints during the treatment period compared with 0 out of 5 (0%) of the placebo group.[15] This study showed that romiplostim was well tolerated and effective for the treatment of pediatric ITP and identified no new safety concerns over those previously identified.

Phase III Clinical Studies

Following the above findings from Phase II studies, two large Phase III multi-centre, double-blind, randomized placebo controlled trials of splenectomised and non-splenectomised ITP patients were conducted in parallel.

A total of 125 patients (63 splenectomised and 62 non-splenectomised) were enrolled in the Phase III trials over a 6 month test period.[16] Eligibility criteria for these trials included: at least one prior treatment for ITP; a platelet count less than 30×10^9/L; >18 years of age; no malignancy or history of a stem cell disorder; creatinine concentration >176.8 µmol/L; Bilirubin <1.5 times higher than normal; and >90 g/L haemoglobin. Romiplostim or placebo

was administered by SC injection at a ratio of 2:1 respectively. An initial dose of 1 μg/kg was used, with the dose increased to achieve a target platelet count of between 50×10^9/L and 200×10^9/L. The maximum allowed dose was 15 μg/kg weekly. Treatment was administered for 24 weeks, with platelet counts monitored weekly. The trial was concluded after 36 weeks or when platelet counts dropped below 50×10^9/L.

Efficacy

The primary efficacy endpoint of clinical studies with romiplostim was defined as the achievement of a weekly platelet count of $\geq 50 \times 10^9$/L for 6 of the last 8 weeks of the 24 week treatment period (Table 1). The proportion of patients that achieved a durable platelet response when treated with romiplostim, compared to placebo groups, was 38% of splenectomised patients and 56% of non-splenectomised patients. An additional 40% of splenectomised and 27% of non-splenectomised patients achieved a transient (>4 weeks) platelet response. The primary efficacy endpoint was achieved in 79% of splenectomised and 88% of non-splenectomised patients treated with romiplostim compared with 14% of non-splenectomised and 0% of splenectomised patients who received placebo.[16] This overall response rate is similar to that observed with first line treatments including corticosteroids and IV immunoglobulin, and better than response rates observed with other treatments including anti-D, azathioprine, danazol and splenectomy.[17]

Safety

Romiplostim was well-tolerated by the majority of patients in Phase III clinical trials.[16,18] Although adverse events were reported in the majority of patients, they were not severe and occurred at similar frequency in both treatment and placebo groups. Significant bleeding events were reported in 12% of patients within the placebo group and 7% in the romiplostim treatment group. Two patients within the placebo group died during the trial period, one from cerebral haemorrhage, and one from pulmonary embolism. A single patient in the treatment group died from intracranial haemorrhage a day after the study completed. Three thrombotic complications were also reported, two in the romiplostim arm (one popliteal artery thrombosis and one cerebrovascular disease), while one patient receiving placebo developed a fatal pulmonary embolism as mentioned above.

A significant side effect identified in the Phase III trials, was the development of increased bone marrow reticulin formation. Kuter et al have recently reported an overview of bone marrow reticulin formation in patients with ITP treated in the romiplostim clinical trial program.[19] From the combined total of 271 ITP patients treated with romiplostim between June 2002 and February 2008, only 11 patients underwent bone marrow biopsy, with 10 of these biopsies testing positive for reticulin. Reticulin formation was grade 4 (with collagen) in only one patient. In those patients with follow up biopsies after cessation of treatment, the level of reticulin appeared to improve or disappear in the majority of patients. A small prospective analysis of reticulin formation was reported in the same paper.[19] In this study patients had baseline bone marrow biopsies performed up to 1 year prior to study enrollment, and then follow up studies at 3, 6, and 9 months of romiplostim treatment. Of the

Table 1. Efficacy results from Phase III clinical trials of romiplostim.

Outcome	Splenectomised patients		Non-splenectomised patients	
	Romiplostim (n = 42)	Placebo (n = 21)	Romiplostim (n = 41)	Placebo (n = 21)
Durable platelet response, n (%)	16 (38%)	0 (0%)	25 (61%)	1 (5%)
Overall platelet response n (%)	33 (79%)	0 (0%)	36 (88%)	3 (14%)
Mean number of weeks with platelet counts $\geq 50 \times 10^9$/L	12	0	15	1

Data within Table 1 was derived from two combined Phase III trials described by Kuter et al.[16]

8 patients with evaluable samples only one patient had an increase in reticulin formation at a median follow up of 8.6 months. A dose-dependent increase in bone marrow fibrosis in rats that resolved following conclusion of the treatment, was also reported in the same study.[19] Therefore the initial evidence from these studies suggest that reticulin formation may be increased by romiplostim treatment, but that this is reversible and decreases upon treatment cessation.

Rebound thrombocytopenia is another potentially serious adverse side effect that has been documented in patients following romiplostim treatment cessation. In Phase I/II studies, 4 of 56 patients had platelet counts that fell below their pre-treatment levels.[12] This is thought to be a result of therapy-induced transient expansion of the megakaryocyte pool and increased clearance of endogenous TPO leading to temporary TPO deficiency and on occasion, a drop in platelet counts below pre-treatment levels.[20] Severe bleeding events may occur during this period and it may be possible to mitigate the risk of this platelet drop through gradual reduction in romiplostim rather than instant cessation of treatment.

The completion of the Phase III studies raised a number of safety concerns relating to the tolerability of romiplostim that were subsequently cited by the FDA in 2008 on the announcement of romiplostim approval. These included the potential risk for fibrous deposits in the bone marrow, depressed platelet counts on treatment cessation, thrombotic events due to elevated platelet counts, and acute leukemia (in patients with myelodysplastic syndrome).[21] In light of these concerns a Risk Evaluation and Mitigation Strategy (REMS) was devised that restricts the distribution of romiplostim to prescribers and patients that are enrolled in a tracking program called NEXUS (Network of Experts Understanding and Supporting Nplate and Patients).[22] Patients in the program are given a medication guide before each treatment and are counseled on the risks and benefits of treatment with romiplostim. Health care providers must provide long-term follow-up for adverse effects every 6 months while the patient is receiving treatment.[21] The FDA recommended initial dose is 1 μg/kg with weekly increases of 1 μg/kg until the target platelet count of $\geq 50 \times 10^9$cells/L is achieved up to a maximum dose of 10 μg/kg.

Ongoing studies

An ongoing, long-term open-label, single-arm study which began in June 2004 has investigated the safety and efficacy of romiplostim in the long-term treatment of chronic ITP.[23,24] As of May 2009, 219 patients from the Phase III trials have been enrolled to assess the effects of long-term treatment with romiplostim.[23] This study has enabled home administration of romiplostim by SC injection. Results thus far (almost 5 years), indicate that 94% of patients achieved $\geq 50 \times 10^9$/L platelet counts at some time during the study period, and that greater than 50% of patients had platelet counts $\geq 50 \times 10^9$/L at 95% of all study visits. Of the patients receiving concurrent ITP medication at baseline, 78% were able to discontinue or reduce their dose by >25%.[23] Side effects were similar in nature to those identified in the Phase III trials (see below) and their frequency and severity did not increase over time. Similarly, there was no increase in bleeding events over time.

Patient Preference and Quality of Life

The symptoms associated with ITP and its treatment can impact heavily on the quality of life of patients. Current standard treatment for ITP involves corticosteroid use supplemented by IVIg, which act by preventing platelet destruction.[5] As well as a high degree of disease persistence, there is also significant toxicity associated with steroid use, and the high cost, resource issues and the inconvenience of parenteral management precludes the long-term use of IVIg. Splenectomy is the historical treatment option for patients with chronic ITP. Removal of the spleen, however, is often viewed as more serious than the disease symptoms, and with a poor response rate of 60%–70% it is not always a favourable treatment option. Given the limited durable response and substantial side effects associated with many treatments, quality of life and patient-preference for treatments are important considerations when managing these patients.

A recent study assessed the impact of romiplostim treatment on health-related quality of life (HRQoL) on patients involved in the Phase III clinical trials.[25] The study involved dissemination of an ITP Patient Assessment Questionnaire (ITP-PAQ) to patients comprising 44 questions with 10 scales measuring: physical health, emotional health, work, social

activity, women's reproductive heath, and overall quality of life.[25] A total of 125 patients participated in the study (84 romiplostim, 41 placebo). Placebo and romiplostim treated groups had comparable (ITP-PAQ) scores prior to treatment initiation. Splenectomised patients had a significantly lower ITP-PAQ score compared with non-splenectomised patients, and ITP-PAQ scores improved significantly in splenectomised patients after receiving romiplostim treatment. When data from splenectomised and non-splenectomised patients were combined there was a significant increase in ITP-PAQ scores following romiplostim treatment, suggesting an improved quality of life for romiplostim treated patients.

Thus, in the climate of limited treatment options for chronic ITP sufferers, thrombopoietin mimetics such as romiplostim, have provided a much needed treatment alternative that promises high response rates and little toxicity. In addition to its favourable pharmacokinetic and pharmacodynamic profile the ease of administration via SC injection is also favourable over IV methods of administration, providing the opportunity for self-administration.

Place in Therapy

Unfortunately, given the nature of the mechanism of action of romiplostim, effects of treatment are transient and only persist until treatment is ceased. Thus long-term use is required for maintenance of adequate platelet count. Data relating to the effect of long-term use of romiplostim treatment, and in particular the risk of marrow fibrosis, is at present insufficient to recommend its use other than for patients refractory to other treatments. As more trials are conducted and long-term trials are completed, a place for romiplostim in the treatment of acute ITP or as a first-line treatment for chronic ITP may be justified. As such, the FDA approval for romiplostim has indicated its use only for patients that are susceptible to bleeding and that are refractory to other treatments.[9] Optimal monitoring regimes for reticulin deposition throughout the therapy are still to be determined.[26]

The uptake of new drugs into clinical use is heavily reliant on ease of administration and good cost-benefit ratio. The cost for each 250 mg single-use vial of romiplostim is $1275 and for 500 µg is $2550.[26,27] An alternative small molecule TPO mimetic that works via a different mechanism provides oral availability (Eltrombopag) has undergone extensive clinical testing (Reviewed in[7,20]). This agent was also approved in 2008 for second-line treatment of ITP. Ultimately the best option for long-term treatment will depend on both the efficacy and side-effects of these alternative agents.

Conclusions

The approval of romiplostim by the FDA in 2008 was the first of its kind within the class of TPO-mimetic agents. Extensive clinical studies of romiplostim have identified a favourable risk-benefit profile for patients with chronic ITP that is refractory to other conventional treatments including corticosteroids, immunoglobulins, or splenectomy. The availability of additional on-going, long-term safety and efficacy data will allow for informed decisions regarding the safety of long-term use of romiplostim for patients with chronic ITP.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Nakhoul IN, Kozuch P, Varma M. Management of adult idiopathic thrombocytopenic purpura. *Clin Adv Hematol Oncol*. 2006;4(2):136–44, 53.
2. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. *Am J Hematol*. 2009.
3. Ballem PJ, Segal GM, Stratton JR, Gernsheimer T, Adamson JW, Slichter SJ. Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. *J Clin Invest*. 1987;80(1):33–40.
4. Chang M, Nakagawa PA, Williams SA, et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. *Blood*. 2003;102(3):887–95.
5. Cines DB, Yasothan U, Kirkpatrick P. Romiplostim. *Nat Rev Drug Discov*. 2008;7(11):887–8.
6. Kaushansky K. Historical review: megakaryopoiesis and thrombopoiesis. *Blood*. 2008;111(3):981–6.
7. Perugini M, Varelias A, Sadlon T, D'Andrea RJ. Hematopoietic growth factor mimetics: from concept to clinic. *Cytokine Growth Factor Rev*. 2009;20(1):87–94.
8. Li J, Yang C, Xia Y, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. *Blood*. 2001;98(12):3241–8.
9. *Food and Drug Administration FDA labelling information FDA web site (online)*. 2008; http://www.fda.gov/cder/foi/label/2008/125268 lbl.pdf.
10. Wang B, Nichol JL, Sullivan JT. Pharmacodynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand. *Clin Pharmacol Ther*. 2004;76(6):628–38.

11. Kuter DJ. New thrombopoietic growth factors. *Blood*. 2007;109(11): 4607–16.
12. Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med*. 2006;355(16):1672–81.
13. Broudy VC, Lin NL. AMG531stimulates megakaryopoiesis in vitro by binding to Mpl. *Cytokine*. 2004;25(2):52–60.
14. Shirasugi Y, Ando K, Hashino S, et al. A phase II, open-label, sequential-cohort, dose-escalation study of romiplostim in Japanese patients with chronic immune thrombocytopenic purpura. *Int J Hematol*. 2009;90(2):157–65.
15. Buchanan GR, Bomgaars L, Bussel JB, et al. A randomized, double-blind, placebo-controlled phase 1/2 study to determine the safety and efficacy of romiplostim in children with chronic immune (Idiopathic) thrombocytopenic purpura (ITP). *In: Proceedings of the ASH Annual Meeting Abstracts*. 2009:680.
16. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet*. 2008;371(9610):395–403.
17. Newland A. Romiplostim: a breakthrough treatment for the management of immune thrombocytopenic purpura. *Eur J Haematol Suppl*. 2009;(71):20–5.
18. Weitz IC, Sanz MA, Henry DH, et al. Evaluation of bleeding-related episodes in patients with chronic immune thrombocytopenia (ITP) treated with romiplostim in two phase III placebo-controlled clinical trials. *In: Proceedings of the ASH Annual Meeting Abstracts*. 2009:891.
19. Kuter DJ, Mufti GJ, Bain BJ, Hasserjian RP, Davis W, Rutstein M. Evaluation of bone marrow reticulin formation in chronic immune thrombocytopenia patients treated with romiplostim. *Blood*. 2009;114(18):3748–56.
20. Kuter DJ. Thrombopoietin and thrombopoietin mimetics in the treatment of thrombocytopenia. *Annu Rev Med*. 2008;60:33.31–3.14.
21. (FDA) USFaDA. Romiplostim. *http://wwwfdagov/AboutFDA/Centers Offices/CDER/ucm129224htm*; Accessed February 24, 2010.
22. Romiplostim N. The Nplate Network of Experts Understanding and Supporting Nplate and Patients (NEXUS) Program. *wwwnplatenexuscom*; Accessed Feburary 24, 2010.
23. Bussel JB, Kuter DJ, Newland A, et al. Long term efficacy and safety of romiplostim for the treatment of patients with chronic immune thrombocytopenia (ITP): 5-Year update from an open-label extension study. *In: Proceedings of the ASH Annual Meeting Abstracts*. 2009:681.
24. Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood*. 2008.
25. George JN, Mathias SD, Go RS, et al. Improved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: results from two randomized, placebo-controlled trials. *Br J Haematol*. 2009;144(3):409–15.
26. Ipema HJ, Jung MY, Lodolce AE. Romiplostim management of immune thrombocytopenic purpura. *Ann Pharmacother*. 2009;43(5):914–9.
27. Drug topics red book (Update). *Montvale, NJ: Thromson Reuters*. April 2009; 28(4):56.