


Romiplostim in adult patients with newly diagnosed or persistent immune thrombocytopenia (ITP) for up to 1 year and in those with chronic ITP for more than 1 year: a subgroup analysis of integrated data from completed romiplostim studies

David J. Kuter,¹  Adrian Newland,²
Beng H. Chong,³ Francesco
Rodeghiero,^{4,5} Monica T. Romero,⁶
Ingrid Pabinger,⁷ Yuqi Chen,⁸
Kejia Wang,⁸ Bhakti Mehta⁸ and
Melissa Eisen⁸

¹Department of Hematology, Massachusetts General Hospital, Boston, MA, USA, ²The Pathology Clinical Academic Group, the Royal London Hospital, London, UK, ³University of New South Wales and St. George Hospital, Sydney, Australia, ⁴Hematology Project Foundation, ⁵San Bortolo Hospital, Vicenza, Italy, ⁶Hospital Juárez de México, México City, México, ⁷Medizinische Universität Wien, Vienna, Austria and ⁸Amgen Inc., Thousand Oaks, CA, USA

Received 19 September 2018; accepted for publication 18 December 2018

Correspondence: David J. Kuter, Department of Hematology, Massachusetts General Hospital, Yawkey 7940, 55 Fruit Street, Boston, MA, USA.

E-mail: dkuter@partners.org

Summary

The thrombopoietin receptor agonist romiplostim is approved for second-line use in chronic immune thrombocytopenia (ITP), but its effects in patients with ITP for ≤ 1 year are not well characterized. This analysis of pooled data from 9 studies included patients with ITP for ≤ 1 year ($n = 311$) or > 1 year ($n = 726$) who failed first-line treatments and received romiplostim, placebo or standard of care. In subgroup analysis by ITP duration, patient incidences for platelet response at $\geq 75\%$ of measurements were higher for romiplostim [ITP ≤ 1 year: 74% (204/277); ITP > 1 year: 71% (450/634)] than for placebo/standard of care [ITP ≤ 1 year: 18% (6/34); ITP > 1 year: 9% (8/92)]. Of patients with ≥ 9 months on study, 16% with ITP ≤ 1 year and 6% with ITP > 1 year discontinued romiplostim and maintained platelet counts $\geq 50 \times 10^9/l$ for ≥ 6 months without ITP treatment (treatment-free remission). Independent of ITP duration, rates of serious adverse events and bleeding were lower with romiplostim than placebo/standard of care and thrombotic events occurred at similar rates. In this analysis, romiplostim and placebo/standard of care had similar safety profiles and romiplostim increased platelet counts in patients with either ITP ≤ 1 year or ITP > 1 year, with more treatment-free remission in those with ITP ≤ 1 year.

Keywords: immune thrombocytopenia, newly diagnosed, persistent, thrombopoietin, romiplostim.

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by platelet counts $< 100 \times 10^9/l$ in the absence of other blood count abnormalities (Rodeghiero *et al*, 2009). This disorder is associated not only with an increased risk of bleeding but also with a mildly increased risk of thrombosis (Sarpawari *et al*, 2010; Rodeghiero, 2016, 2017), which can be further increased with splenectomy (Boyle *et al*, 2013; Ruggeri *et al*, 2014; Doobaree *et al*, 2016; Rodeghiero, 2018). The thrombocytopenia in ITP has long been attributed to increased destruction of opsonized platelets by the spleen (Harrington *et al*, 1951), but is now understood to also be a problem of inadequate platelet production, with both cellular and antibody-mediated immune mechanisms inhibiting platelet production in the bone marrow (Gernsheimer *et al*,

1989; Olsson *et al*, 2003; McMillan *et al*, 2004; Stasi *et al*, 2008).

The clinical course of an adult ITP patient may be assessed during three separate phases (Rodeghiero *et al*, 2009). The first is the newly diagnosed phase (< 3 months) in which the patient initially presents with thrombocytopenia and is assessed for the need for acute treatment depending on the severity of bleeding. For many, the thrombocytopenia continues despite initial therapy and enters a persistent phase (3–12 months). Finally, ITP is considered chronic when it lasts for > 12 months (Rodeghiero *et al*, 2009). It is not established whether these three chronological stages reflect any differences in pathophysiology, treatment response or likelihood of remission.

There is suggestive evidence that disease progression may occur over 1 year due to “epitope spreading” (McMillan, 2007), and there remains discussion as to whether more aggressive earlier therapy might mitigate the conversion to chronic disease (Zaja *et al*, 2010).

The initial therapy for symptomatic, newly diagnosed ITP has long been corticosteroids supplemented with intravenous gamma globulin (IVIg) for those patients with more serious bleeding (Neunert *et al*, 2011). Up to 80% of patients respond with a rise in platelet counts, but the majority relapse upon corticosteroid discontinuation or dose reduction, necessitating the need for other therapies. Subsequent second-line treatments are either surgical (e.g. splenectomy) or medical [e.g. thrombopoietin (TPO) receptor agonists, rituximab, azathioprine, mycophenolate mofetil, ciclosporin or danazol]. Regarding newer therapies for ITP, the SYK inhibitor, fostamatinib, has been approved by the United States Food and Drug Administration for use in chronic ITP (Bussel *et al*, 2018; Newland *et al*, 2018; <https://tavalisse.com/downloads/pdf/Tavalisse-Full-Prescribing-Information.pdf>), while other TPO receptor agonists, such as avatrombopag (Bussel *et al*, 2014) and lusutrombopag (Katsube *et al*, 2016), and agents with other mechanisms of action are under development.

TPO receptor agonists increase platelet production and have demonstrated marked benefit in treating patients with chronic ITP. Extensive studies with romiplostim and eltrombopag in chronic ITP patients have shown a response rate over 60%, long-term efficacy, reduced bleeding, minimal side effects, improved quality of life and reduced the need for rescue therapy, and have allowed most patients to discontinue other forms of ITP treatment, such as corticosteroids (https://www.pi.amgen.com/~media/amgen/repositorysites/pi-amgen-com/nplate/nplate_pi_hcp_english.pdf; <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/promacta.pdf>). TPO receptor agonists are currently approved by regulatory agencies in the United States and elsewhere only for second-line treatment of patients with chronic ITP not responsive to corticosteroids, immunoglobulins or splenectomy.

While most attention has been focused on the use of TPO receptor agonists in patients with chronic ITP (currently defined as >1 year, previously ≥ 6 months), it remains to be clarified whether similar treatment benefits will occur in patients with ITP for ≤ 1 year, including newly diagnosed or persistent ITP. No prospective, randomized, placebo-controlled study has examined TPO receptor agonist therapy specifically in patients with ITP ≤ 1 year, but these patients were allowed to enrol in a number of clinical studies. In this retrospective analysis, we examined the efficacy and safety of romiplostim treatment in adult patients with ITP ≤ 1 year, compared with those with ITP >1 year, who had failed first-line treatments and subsequently received romiplostim, placebo or standard of care in romiplostim ITP studies. Specifically, we assessed the effect of romiplostim in each

ITP duration subgroup for platelet response, bleeding and adverse events, including thrombosis.

Methods

Study design and patients

Data were integrated from nine romiplostim studies conducted from 2002 to 2014 that included patients with ITP ≤ 1 year (Table SI). Three were placebo-controlled studies (Kuter *et al*, 2008; Shirasugi *et al*, 2011), one had a standard-of-care control group (Kuter *et al*, 2010), and three had no control group (Janssens *et al*, 2015, 2016; Newland *et al*, 2016). After completing the parent studies, many patients had the option to enter one of two extension studies (Shirasugi *et al*, 2012; Kuter *et al*, 2013). One of the single-arm parent studies enrolled only patients with ITP ≤ 1 year (Newland *et al*, 2016); the other studies enrolled patients with either ITP ≤ 1 year or ITP >1 year. Four dose-finding studies of romiplostim (Bussel *et al*, 2006; Newland *et al*, 2006; Shirasugi *et al*, 2009) were not included in this analysis.

Outcomes

Platelet response was defined as a platelet count $\geq 50 \times 10^9/l$, excluding platelet counts obtained in the 8 weeks after rescue medication use. Durable platelet response was defined as a platelet response for ≥ 6 weeks during weeks 17–24 (to allow time for dose titration and effects on thrombopoiesis to be captured), including the studies with a duration of >24 weeks (Kuter *et al*, 2010; Janssens *et al*, 2015; Newland *et al*, 2016). For romiplostim-treated patients, rescue medications were added per investigator to treat or prevent bleeding and could include newly introduced ITP medications and dose or frequency increase of baseline ITP medications other than romiplostim. Most of the patients in the control group (27/34) received standard of care in a study that did not report those types of changes as rescue medications because they were considered part of the standard of care (Kuter *et al*, 2010).

By definition, serious adverse events could include adverse events of any grade that required or prolonged hospitalization, including nonspecific conditions, such as bleeding (e.g. contusion, purpura) as well as general symptoms (e.g. dehydration, pyrexia), whereas grade ≥ 4 adverse events were life-threatening conditions, such as cancer (e.g. liver, rectal) or organ failure (e.g. cardio-respiratory arrest, respiratory failure).

Statistical analyses

Results were summarized by ITP duration subgroups of ITP ≤ 1 year (demographics and baseline disease characteristics were further summarized by ITP duration of <3 months or 3–12 months) or ITP >1 year. For categorical variables, the

number and percentage of subjects in each category were summarized. Continuous variables were summarized by Q1 (25th percentile), median, and Q3 (75th percentile). Safety data were adjusted for exposure to reflect the longer exposure to romiplostim (e.g. in extension studies). Duration-adjusted event rates were obtained by using the total number of events divided by the total patient-years on study.

Data for placebo and standard of care were pooled because, for those with ITP ≤ 1 year, there were too few patients in each category (7 placebo and 27 standard of care) to analyse separately. For patients who received placebo/standard of care in the parent study and romiplostim in an extension study, only placebo/standard of care data from the parent study were used. For patients who received romiplostim in both the parent and extension studies, data from the extension study were also included (Shirasugi *et al*, 2012; Kuter *et al*, 2013). Exact binomial confidence intervals (CIs) were used to calculate 95% CIs of incidence rate. For the thrombotic event by platelet count analysis, if a given patient had multiple thrombotic events at different platelet counts, then that patient could be counted in multiple platelet count categories. Due to the post-hoc nature of these analyses, *P* values were not provided. Instead, the 95% CIs on event rates were used to compare ITP subgroups.

Results

Patient demographics, characteristics, and disposition

This integrated analysis included 1037 patients from nine clinical studies (Table SI): 311 patients had ITP ≤ 1 year and 726 had ITP > 1 year. Most patients came from three open-

label studies of romiplostim: a large compassionate use study ($n = 405$) (Janssens *et al*, 2015), a 3-year bone marrow study ($n = 169$) (Janssens *et al*, 2016), and a platelet response and remission study ($n = 75$) (Newland *et al*, 2016). Patients with ITP ≤ 1 year were primarily from Europe ($n = 191$) or North America ($n = 93$).

Of the 311 patients with ITP ≤ 1 year, 155 (50%) had newly diagnosed ITP (< 3 months) and 156 (50%) had persistent ITP (3–12 months) (Table I). In none of these studies was romiplostim used as an initial or rescue therapy. Most patients were Caucasian, with median age in the 50s. The median duration of ITP was 3 months for those with ITP ≤ 1 year and 72 months (6 years) for those with ITP > 1 year. Patients with ITP ≤ 1 year were less likely to have prior splenectomy (8% vs. 44%) or rituximab use (7% vs. 18%) than the patients with ITP > 1 year. Median baseline platelet counts were $18 \times 10^9/l$ in both ITP duration subgroups.

Of the 911 patients who received romiplostim in the parent studies, 680 (75%) completed those studies, with withdrawal of consent being the most common reason for discontinuing (Fig 1). Of the 223 patients who had the option to enter extension studies and chose to do so, 160 (72%) completed those extension studies.

Efficacy: platelet response

The romiplostim group included 277 patients with ITP ≤ 1 year and 634 with ITP > 1 year (Fig 1). The placebo/standard of care group included 34 patients with ITP ≤ 1 year and 92 with ITP > 1 year. Platelet counts rose in most patients who received romiplostim and remained stably elevated (Fig 2A). The ITP duration subgroups had

Table I. Patient demographics and disease characteristics by ITP duration.

	ITP ≤ 1 year			ITP > 1 year ($n = 726$)
	< 3 months ($n = 155$)	3–12 months ($n = 156$)	Total ($n = 311$)	
Sex, female, n (%)	77 (50)	88 (56)	165 (53)	470 (65)
Race, n (%)				
Asian	1 (0.6)	7 (5)	8 (3)	46 (6)
African American	5 (3)	2 (1)	7 (2)	16 (2)
Hispanic or Latino	7 (5)	6 (4)	13 (4)	29 (4)
Caucasian	141 (91)	141 (90)	282 (91)	628 (87)
Age (years), median (Q1, Q3)	52 (32, 69)	52 (35, 68)	52 (34, 68)	54 (42, 67)
Baseline platelet count ($\times 10^9/l$), median (Q1, Q3)	15 (8, 27)	20 (12, 29)	18 (10, 28)	18 (10, 29)
ITP duration (months), median (Q1, Q3)	1.2 (0.7, 2.0)	5.8 (4.2, 8.4)	3.0 (1.2, 5.8)	72 (34, 160)
Prior therapies, n (%)				
≤ 3	104 (67)	98 (63)	202 (65)	251 (35)
> 3	6 (4)	11 (7)	17 (5)	162 (22)
Not collected	45 (29)	47 (30)	92 (30)	313 (43)
Prior splenectomy, n (%)	6 (4)	19 (12)	25 (8)	320 (44)
Prior rituximab, n (%)	5 (3)	16 (10)	21 (7)	134 (18)

ITP, immune thrombocytopenia; Q1, quartile 1; Q3, quartile 3.

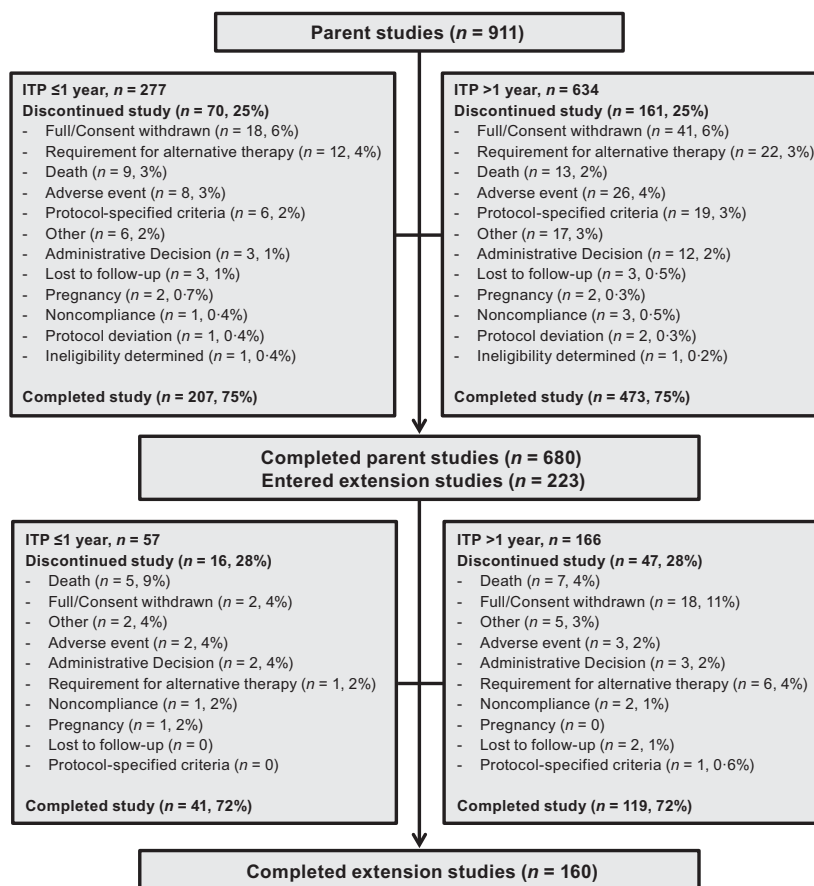


Fig 1. Patient disposition by ITP duration. Patient flow is shown by ITP duration through both the parent study and extension study (for those patients who entered an extension study) with reasons for discontinuation. ITP, immune thrombocytopenia.

similar median platelet counts and similar platelet responses over time with romiplostim treatment (Fig 2A–B). The median time to first platelet response for romiplostim-treated patients was 2 weeks in each ITP duration subgroup. For placebo/standard of care, the median time to first response was 4 weeks for patients with ITP ≤1 year and 12 weeks for those with ITP >1 year, but the 95% CIs overlapped. For patients with ITP ≤1 year, platelet response rates were 86% for romiplostim and 62% for placebo/standard of care; for patients with ITP >1 year, platelet response rates were 87% for romiplostim and 33% for placebo/standard of care (Table II). Response rates were notably higher for romiplostim than for placebo/standard of care for more stringent measures such as responding ≥75% or ≥90% of the time or having a durable platelet response (Fig 2B; Table II).

In the examination of how many patients with ≥9 months on study were able to discontinue romiplostim and maintain platelet counts $\geq 50 \times 10^9/l$ without any ITP treatments for ≥6 months (i.e. remission), the rate was greater for those with ITP ≤1 year (16%; 95% CI: 11–21%) than for those with ITP >1 year (6%; 95% CI: 4–8%) (Table II). Nine months on study (not necessarily 9 months of exposure) was

chosen as an appropriate period to assess for these treatment-free periods as it allowed sufficient time to escalate to a stable romiplostim dose and for the effects of romiplostim to be observed (i.e. a few months titrating the dose and ≥6 months off romiplostim).

Efficacy: rescue medication use

For romiplostim-treated patients, rescue medications were used in 44% of those with ITP ≤1 year and 50% of those with ITP >1 year (Table II). Use of rescue medication decreased over time irrespective of ITP duration, with roughly comparable rates between the ITP duration subgroups, and appeared to be higher in the first few weeks when the romiplostim dose was being titrated and other ITP therapies were being reduced or discontinued (Fig 3A). When examined by type of rescue medication, the use of corticosteroids (~60% of rescue medication use) decreased after the first few months and then fluctuated, dropping by approximately 75% over time (Fig 3B). Use of IVIg (~20% of rescue medication use) decreased somewhat over time (Fig 3C). The rate of decline of corticosteroid or IVIg use was similar between the two ITP duration subgroups.

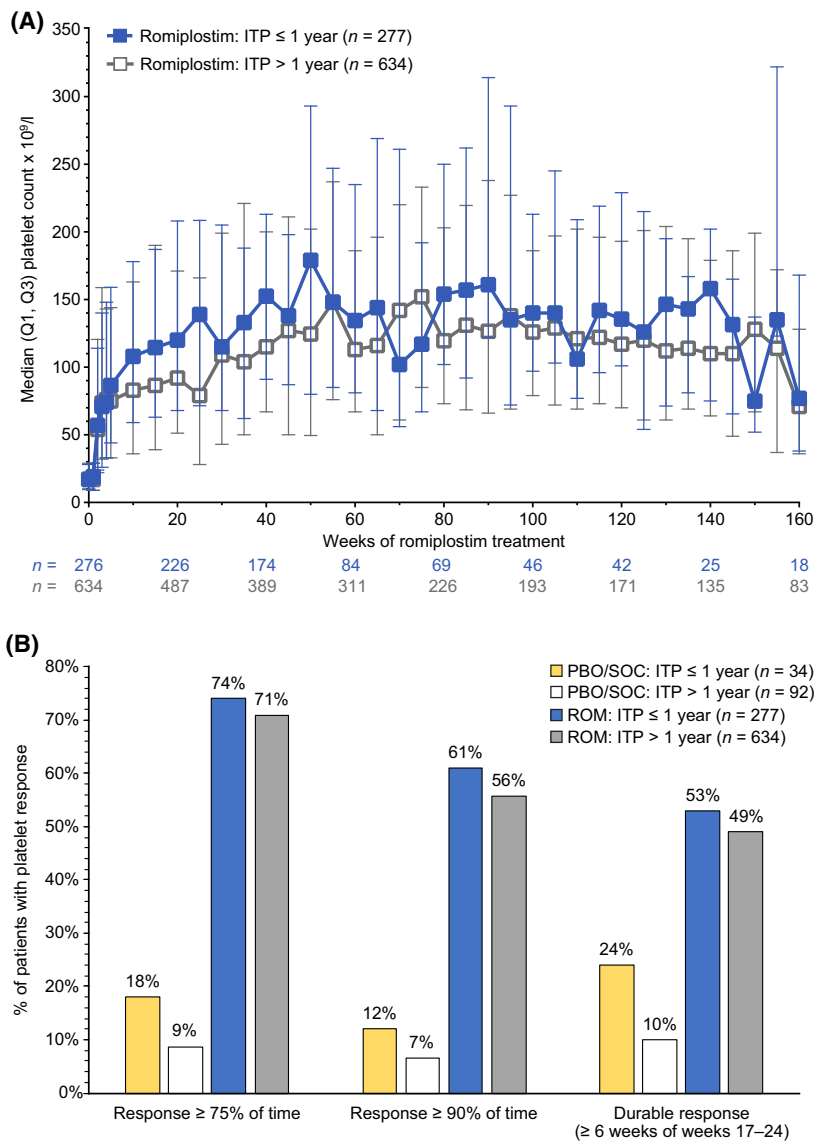


Fig 2. Platelet count over time (A) and platelet response (B) by ITP duration. (A) Median (Q1, Q3) platelet counts are shown for romiplostim-treated patients by ITP duration at study baseline. (B) Proportion of patients meeting various platelet response measures by ITP duration at study baseline. Platelet response was defined as platelet counts $\geq 50 \times 10^9/l$, excluding platelet counts obtained in the 8 weeks after rescue medication use. Durable platelet response is defined as having a platelet response for ≥ 6 weeks of weeks 17–24 so as to allow time for dose titration and effects on thrombopoiesis. ITP, immune thrombocytopenia; PBO, placebo; ROM, romiplostim; Q1, quartile 1; Q3, quartile 3; SOC, standard of care.

Bleeding

Although the patient incidence of bleeding varied modestly between groups (Table II), after adjustment for time on study, exposure-adjusted rates of bleeding in both ITP duration subgroups were lower for romiplostim than placebo/standard of care, with non-overlapping 95% confidence intervals (Table III). In both treatment groups, exposure-adjusted bleeding rates were higher in patients with ITP >1 year than in those with ITP ≤ 1 year. In the romiplostim group, overall bleeding and grade ≥ 2 bleeding decreased over time to similar extents in both ITP duration subgroups (Fig 4).

Safety

The median average weekly romiplostim dose was similar for both ITP duration subgroups (Table SII), did not vary much over time, and generally was $\sim 3\text{--}4 \mu\text{g/kg}$ per week. Compared with what was already known about the use of romiplostim in chronic ITP (Kuter *et al*, 2008, 2010, 2013), the safety profile was as expected (Tables III and SIII–SV). Overall, the safety of romiplostim was comparable for the two ITP duration subgroups and event rates were low for romiplostim relative to placebo/standard of care (Tables III and SIII). Serious adverse event rates were similar between

Table II. Efficacy summary by ITP duration.

	ITP ≤ 1 year		ITP > 1 year	
	PBO/SOC (<i>n</i> = 34)	Romiplostim (<i>n</i> = 277)	PBO/SOC (<i>n</i> = 92)	Romiplostim (<i>n</i> = 634)
Any platelet response	62%	86%	33%	87%
Responding $\geq 75\%$ of the time	18%	74%	9%	71%
Responding $\geq 90\%$ of the time	12%	61%	7%	56%
Durable platelet response (≥ 6 weeks of weeks 17–24)	24%	53%	10%	49%
Treatment-free remission (95% CI)*	NA	16% (11–21%)	NA	6% (4–8%)
Rescue medication use	NA	44%	NA	50%
Bleeding (95% CI)	62% (44–78%)	52% (46–58%)	59% (48–69%)	60% (56–63%)

CI, confidence interval; ITP, immune thrombocytopenia; NA, not available; PBO, placebo; SOC, standard of care.

*Treatment-free remission defined as maintaining platelet counts $\geq 50 \times 10^9/l$ without any ITP treatments for ≥ 6 months. The denominator was chosen to be patients with 9 months on study (not necessarily 9 months of exposure) as an appropriate duration to escalate to a stable dose, titrate off, and then have 6+ months off romiplostim.

patients with ITP ≤ 1 year or ITP > 1 year, and generally lower for romiplostim than placebo/standard of care in both ITP duration subgroups. All fatal adverse events that the investigator considered to be related to romiplostim treatment occurred in the subgroup with ITP > 1 year: (i) aplastic anaemia in a 75-year-old woman at study week 26 who died 6 weeks later; (ii) intestinal ischaemia in a 78-year-old woman at study week 27; (iii) unstable angina in a 77-year-old woman at extension study week 38; (iv) myocardial infarction in a 61-year-old man at extension study week 14; and (v) haemolysis secondary to a refractory urinary tract infection that led to disseminated intravascular coagulation in a 61-year-old woman at study week 5.

Bone marrow fibrosis or increased reticulin was reported for 3 patients in the romiplostim group and no patients in the placebo/standard of care group; however, the significance of this is unclear as bone marrow biopsies were not performed in most patients. Of the 3 patients, 1 had presence of collagen and 2 had a 2-grade increase in reticulin (per modified Bauermeister score); all 3 were from the bone marrow study with regularly scheduled bone marrow biopsies (i.e. biopsies were not due to concerns on peripheral smears or other findings) (Janssens *et al*, 2016).

In the romiplostim group, thrombotic/thromboembolic events occurred across a wide range of platelet counts and were independent of platelet count (Fig 5); there were too few thrombotic events with placebo/standard of care to analyse them by platelet count. Thrombosis rates were similar between the romiplostim and placebo/standard of care groups (Table SIV). There was a numerical increase in the rates of thrombotic/thromboembolic events overall for romiplostim-treated patients with ITP > 1 year *versus* those with ITP ≤ 1 year (6.1 vs. 4.4 per 100 patient-years) but the 95% CIs overlapped. Rates of thrombotic events for romiplostim-treated patients increased with age (Figure S1), as has been reported previously (Ruggeri *et al*, 2014). Thrombotic events occurring in ≥ 5 romiplostim-treated patients

were only seen in patients with ITP > 1 year and included deep vein thrombosis, pulmonary embolism, myocardial infarction and superficial thrombophlebitis (Table SV). Thrombosis rates were similar between the two ITP duration subgroups. No differences were seen by prior splenectomy status or in arterial *versus* venous thromboses. While placebo/standard of care data are provided for reference, the small number of patients in this subgroup limits comparison.

Discussion

The results of these analyses demonstrate that romiplostim therapy is as effective in patients with either newly diagnosed or persistent ITP (≤ 1 year), as it is in those who have already developed chronic ITP (> 1 year). With romiplostim treatment, time to platelet response, platelet counts, height of platelet count rise, reduction in use of rescue medications, and reduction in bleeding were all similar between patients with ITP ≤ 1 year and those with ITP > 1 year. Romiplostim appears to work in ITP by increasing the rate of platelet production (Meyer *et al*, 2012), as supported by studies in which TPO prevented megakaryocyte apoptosis and thereby increased platelet production (Harker *et al*, 1998). Based on the beneficial effect of romiplostim in patients with ITP (Kuter *et al*, 2008, 2010, 2013; Shirasugi *et al*, 2011, 2012; Janssens *et al*, 2015, 2016; Newland *et al*, 2016), romiplostim is approved by many regulatory agencies for the treatment of chronic ITP that has not responded to corticosteroids, IVIg or splenectomy, but not for patients with ITP ≤ 1 year. It remains to be clarified whether patients with ITP for ≤ 1 year, including either newly diagnosed ITP (< 3 months) or persistent ITP (3–12 months) (Rodeghiero *et al*, 2009), differ in a pathophysiological way from chronic ITP. In all ITP phases, platelet kinetic studies have demonstrated an increased rate of platelet destruction, as well as inhibition of platelet production (Heyns Adu *et al*, 1986; Ballem *et al*, 1987;

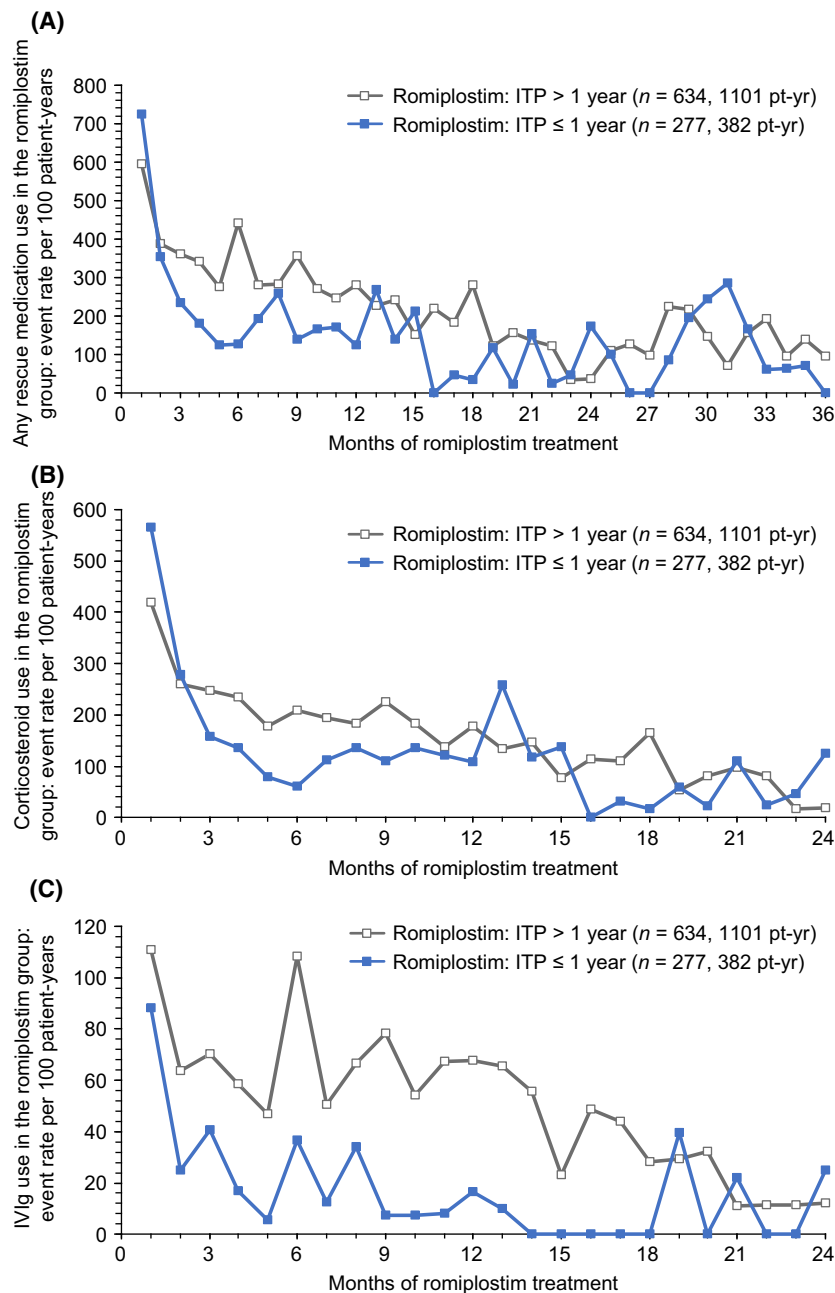


Fig 3. Rescue medication use by ITP duration. Duration-adjusted event rate of rescue medication use (per 100 patient-years) is shown by ITP duration at study baseline for any rescue medication (A), corticosteroid rescue medication (B), and IVIg rescue medication (C). Rescue medications were ITP medications added by the investigator to treat or prevent bleeding and could include newly introduced ITP medications and dose/frequency increase of baseline ITP medications other than romiplostim. ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; pt-yr, patient-year(s).

Gernsheimer *et al*, 1989). This study shows that by increasing platelet production with romiplostim, platelet responses are similar between patients with ITP ≤ 1 year and those with ITP that has become chronic.

The limitations of this exploratory retrospective analysis are clear. The individual studies had varying study designs (Table SI). We attempted to adjust for this by evaluating all patients with uniform diagnosis and outcome definitions and

we presented the data as a function of exposure time. Additionally, non-responders are typically more likely to leave studies early, which would select for those who respond well. Approximately 25% of patients discontinued from the parent studies, so hopefully that factor does not unduly affect our conclusions. The placebo/standard of care group in the integrated analysis was too small to make any major statements beyond that it showed a higher rate of adverse events and

Table III. Safety summary by ITP duration.

	ITP ≤1 year		ITP >1 year	
	PBO/SOC (n = 34) 37 pt-yr	Romiplostim (n = 277) 382 pt-yr	PBO/SOC (n = 92) 71 pt-yr	Romiplostim (n = 634) 1101 pt-yr
Grade ≥3	101 (71–140)	76 (67–85)	134 (109–164)	84 (79–90)
Grade ≥4	16 (6–36)	11 (8–15)	24 (14–38)	15 (13–17)
Serious AEs	90 (62–127)	51 (44–59)	99 (77–125)	56 (52–61)
Treatment-related serious AEs	33 (17–57)	4 (2–7)	8 (3–18)	7 (6–9)
AEs leading to D/C study drug	14 (4–32)	7 (5–11)	3 (0.3–10)	6 (5–8)
Fatal AEs	5 (1–20)	3 (2–6)	8 (3–18)	2 (1–3)
Treatment-related fatal AEs	0	0	0	0.5 (0.1–1)
Thrombotic/thromboembolic events	8 (2–24)	4 (3–7)	3 (0.3–10)	6 (5–8)
Bleeding	192 (150–242)	130 (118–142)	266 (229–306)	182 (174–190)

All data expressed as AE per 100 patient-years (95% CI). **Bolded** = 95% CI non-overlapping for PBO/SOC and romiplostim. A serious AE was fatal, life-threatening, required (or prolonged) hospitalization, resulted in significant disability/incapacity, or was another significant complication. AE, adverse event; CI, confidence interval; D/C, discontinuation of; ITP, immune thrombocytopenia; PBO, placebo; pt-yr, patient-year(s); SOC, standard of care.

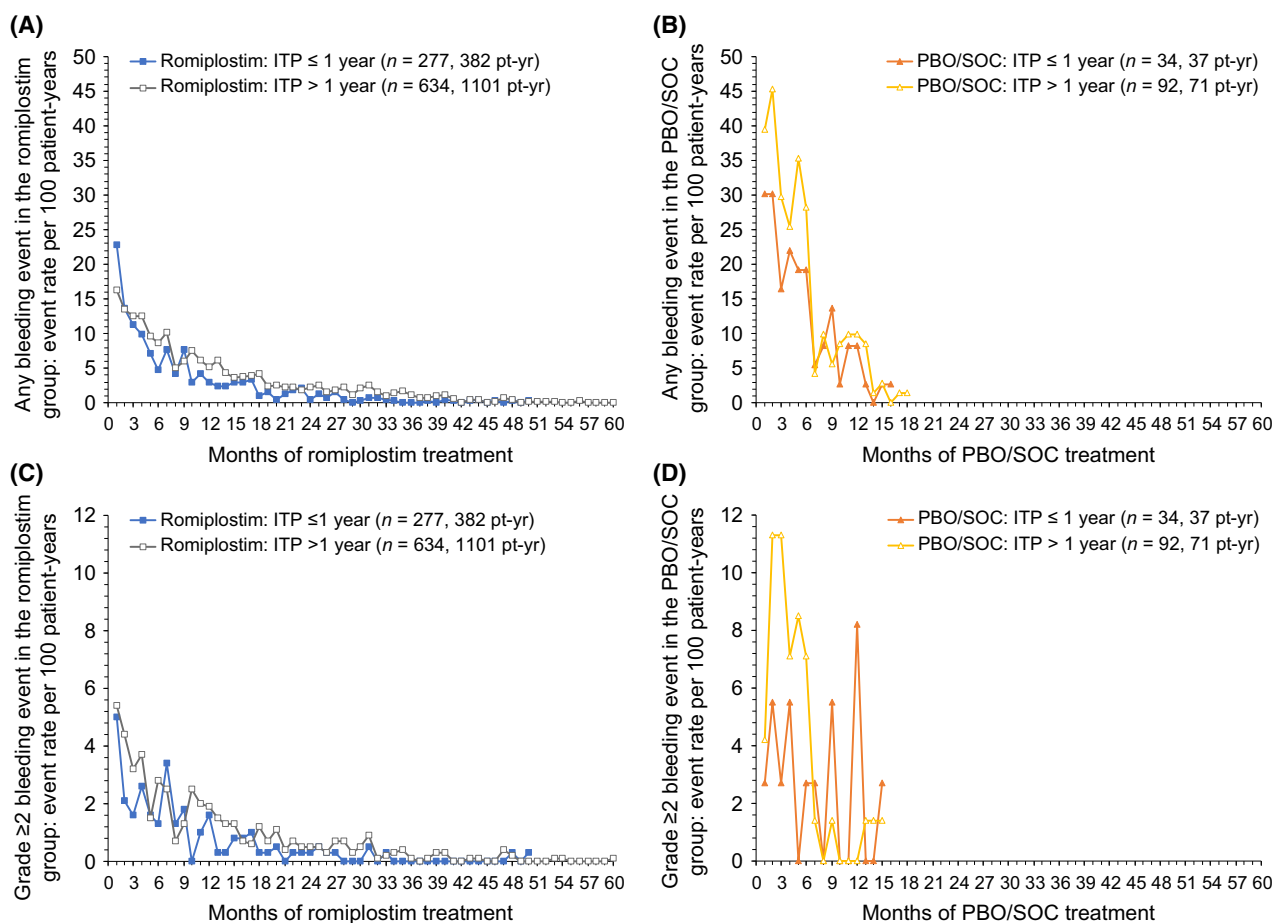


Fig 4. Bleeding over time by ITP duration. Duration-adjusted bleeding (per 100 patient-years) over time for romiplostim-treated patients (A, C) and PBO/SOC patients (B, D) by ITP duration at baseline for both all-grade (A, B) and grade ≥ 2 (C, D) bleeding. ITP, immune thrombocytopenia; PBO, placebo; PBO, placebo; pt-yr, patient-years; SOC, standard of care.

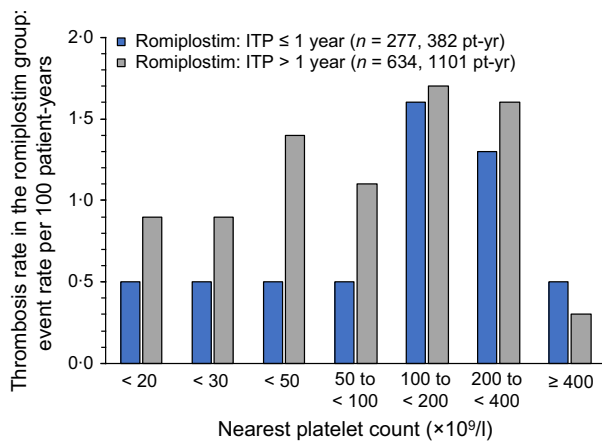


Fig 5. Thrombotic events in the romiplostim group by platelet count and ITP duration. Duration-adjusted rates (per 100 patient-years) are shown for thrombotic events by nearest previous platelet count in the previous 3 months. If a given patient had multiple thrombotic events at different platelet counts, then that patient could be counted in multiple platelet count categories. ITP, immune thrombocytopenia; pt-yr, patient-year(s).

bleeding than the romiplostim group in each ITP duration subgroup. Nonetheless, the marked treatment effect of romiplostim as compared with placebo or standard of care has been shown in other prior studies (Kuter *et al*, 2008, 2010), and one can infer that the large treatment effects seen there apply to patients with either ITP ≤ 1 year or ITP > 1 year. A major caveat is that comparisons between ITP duration subgroups are limited because patients with ITP > 1 year may have more severe disease that is refractory to other therapies, as was seen in the greater number of prior ITP therapies in this subgroup of the analysis. Further, there were relatively few patients with ITP ≤ 1 year who received placebo or standard of care, and most of those patients did not have rescue medication use recorded (due to the standard of care study design), making comparisons across the treatment groups problematic.

Comment should be made regarding some other comparisons between patients with ITP ≤ 1 year and those with ITP > 1 year. Remission, defined as a treatment-free period of ≥ 6 months, was numerically more frequent in patients with ITP ≤ 1 year than in those with ITP > 1 year (16% vs. 6%), which may reflect more severe and refractory disease for those with ITP > 1 year. These rates may underestimate the true occurrence of remission because most of the studies followed standard dosing rules without a forced taper of romiplostim treatment. Only one study had a dose-tapering scheme that was designed to detect remission (Newland *et al*, 2016). In that study, which included only patients with ITP ≤ 1 year, 32% achieved remission after discontinuation of romiplostim treatment.

In each ITP duration subgroup, rates of adverse events and serious adverse events were lower for romiplostim than placebo/standard of care, and rates of thrombotic

events were similar between the treatment groups. These findings are consistent with the identical rate of thrombotic events previously reported for romiplostim and placebo/standard of care overall (5.5 per 100 patient-years for both groups) (Cines *et al*, 2015). Patients with ITP > 1 year had a numerically higher rate of thrombotic/thromboembolic events than patients with ITP ≤ 1 year, but the 95% CIs overlapped. This increase could reflect greater disease severity in patients with chronic ITP. Other factors (e.g. age, gender, splenectomy status and other therapies, such as corticosteroids) could also influence the rate of thrombosis. In this analysis, rates of thrombotic events for romiplostim-treated patients increased with age, as has been reported previously (Ruggeri *et al*, 2014). Thrombotic events in romiplostim-treated patients were independent of platelet count, which may reflect both an increased risk of thrombosis in ITP and increased monitoring for adverse events in clinical trials as compared with epidemiological studies (Ruggeri *et al*, 2014).

In both treatment groups, bleeding rates were higher in patients with ITP > 1 year than in those with ITP ≤ 1 year, possibly because patients with ITP > 1 year had more severe disease that was refractory to other therapies. In both ITP duration subgroups, exposure-adjusted rates of bleeding were lower for romiplostim than for placebo/standard of care. As it was longer before patients receiving placebo or standard of care achieved a platelet response, most likely in response to standard of care (which was given to more patients than placebo), they also had a longer window in which they could have developed bleeding. We cannot exclude a preferential dropout from studies for romiplostim-treated patients experiencing bleeding, which may reflect the convergence of bleeding rates over time. Assessment of bone marrow fibrosis (collagen and reticulin) was hampered by the fact that most patients did not undergo bone marrow biopsy as part of the study protocol. However, a prospective bone marrow study showed a low rate (7%) of bone marrow reticulin in patients treated with romiplostim (Janssens *et al*, 2016).

In this post-hoc, retrospective analysis of patients with either ITP ≤ 1 year or ITP > 1 year across nine clinical studies of romiplostim, the efficacy and safety profile of romiplostim was similar in both ITP duration subgroups. Romiplostim is approved for use in patients with chronic ITP, but the data presented here suggest that patients with ITP ≤ 1 year, including either newly diagnosed ITP (< 3 months) or persistent ITP (3–12 months), are as responsive to romiplostim as are patients with chronic ITP (> 1 year). Earlier treatment with romiplostim may also be associated with a reduced exposure to corticosteroids. Further confirmatory studies would be helpful to assess the effects of romiplostim treatment as first-line and/or combination therapy with corticosteroids or rituximab to reduce corticosteroid use, avoid splenectomy, and achieve remission in patients with newly diagnosed or persistent ITP before it becomes chronic.

Disclosures

All studies and analyses were conducted and funded by Amgen Inc. Qualified researchers may request data from Amgen clinical studies. Complete details are available at <http://www.amgen.com/datasharing>. DJK has received research funding from Syntimmune, Bristol-Myers Squibb, Rigel, Principia, and Protalex; is a consultant for Amgen Inc., Novartis, Pfizer, Genzyme, Zafgen, Syntimmune, Fujifilm, Argenx, Alnylam, Shionogi, Dova, ONO, 3SBio, CRICO, Shire, Protalex, Principia, Shionogi and Rigel. AN was a consultant for Amgen Inc., Angle, Argenx, Rigel and Shionogi; was on advisory boards and/or a speaker at medical education events sponsored by Amgen Inc., Argenx and Novartis; has received research funding from Amgen Inc., GlaxoSmithKline, and Novartis. BHC has received research funding from Novartis and GlaxoSmithKline and honorarium from Novartis for participation in speakers' forum. FR is/was on advisory boards for Amgen Inc., GlaxoSmithKline/Novartis, LFB, MedImmune, Argenx and UCB. MTR has no disclosures. IP has received research funding from CSL Behring and Novo Nordisk; has received honoraria from CSL Behring, Amgen Inc., Boehringer Ingelheim, Bayer, Baxter

and Pfizer; is a speaker and on advisory boards for CSL Behring, Amgen Inc., Boehringer Ingelheim, Bayer, Baxter, Novartis and Pfizer. YC, KW, BM, and ME are employees of and stockholders in Amgen Inc. Medical writing support was provided by Susanna Mac, an employee of Amgen Inc., and Jonathan Latham (on behalf of Amgen Inc.).

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Thrombotic events by age and ITP duration in the romiplostim group.

Table SI. Parent studies included in the analysis by ITP duration.

Table SII. Baseline platelet count and romiplostim exposure by ITP duration.

Table SIII. Duration-adjusted AE rates to first event by ITP duration.

Table SIV. Duration-adjusted incidences of thrombotic/thromboembolic events by ITP duration.

Table SV. Types of thrombotic/thromboembolic events with romiplostim by ITP duration.

References

- Ballem, P.J., Segal, G.M., Stratton, J.R., Gernsheimer, T., Adamson, J.W. & Slichter, S.J. (1987) Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. *Journal of Clinical Investigation*, **80**, 33–40.
- Boyle, S., White, R.H., Brunson, A. & Wun, T. (2013) Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia. *Blood*, **121**, 4782–4790.
- Bussel, J.B., Kuter, D.J., George, J.N., McMillan, R., Aledort, L.M., Conklin, G.T., Lichtin, A.E., Lyons, R.M., Nieva, J., Wasser, J.S., Wiznitzer, I., Kelly, R., Chen, C.F. & Nichol, J.L. (2006) AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *New England Journal of Medicine*, **355**, 1672–1681.
- Bussel, J.B., Kuter, D.J., Aledort, L.M., Kessler, C.M., Cuker, A., Pendergrass, K.B., Tang, S. & McIntosh, J. (2014) A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia. *Blood*, **123**, 3887–3894.
- Bussel, J., Arnold, D.M., Grossbard, E., Mayer, J., Trellinski, J., Homenda, W., Hellmann, A., Windyga, J., Sivcheva, L., Khalafallah, A.A., Zaja, F., Cooper, N., Markovtsov, V., Zayed, H. & Duliege, A.M. (2018) Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. *American Journal of Hematology*, **93**, 921–930.
- Cines, D.B., Gernsheimer, T., Wasser, J.S., Godeau, B., Provan, D., Lyons, R., Altomare, I., Wang, X. & Lopez, A. (2015) Integrated analysis of long-term safety in patients with chronic immune thrombocytopenia (ITP) treated with the thrombopoietin (TPO) receptor agonist romiplostim. *International Journal of Hematology*, **102**, 259–270.
- Doobaree, I.U., Nandigam, R., Bennett, D., Newland, A. & Provan, D. (2016) Thromboembolism in adults with primary immune thrombocytopenia: a systematic literature review and meta-analysis. *European Journal of Haematology*, **97**, 321–330.
- Gernsheimer, T., Stratton, J., Ballem, P.J. & Slichter, S.J. (1989) Mechanisms of response to treatment in autoimmune thrombocytopenic purpura. *New England Journal of Medicine*, **320**, 974–980.
- Harker, L.A., Carter, R.A., Marzec, U.M., Cherry, J.K., Gunthel, C.J., Lennox, J.L., Sheridan, W. & Stead, R.B. (1998) Correction of thrombocytopenia and ineffective platelet production in patients infected with human immunodeficiency virus (HIV) by PEG-rHuMGDF therapy. *Blood*, **92**, 707a.
- Harrington, W.J., Minnich, V., Hollingsworth, J.W. & Moore, C.V. (1951) Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. *Journal of Laboratory and Clinical Medicine*, **38**, 1–10.
- Heyns Adu, P., Badenhorst, P.N., Lotter, M.G., Pieters, H., Wessels, P. & Kotze, H.F. (1986) Platelet turnover and kinetics in immune thrombocytopenic purpura: results with autologous ¹¹¹In-labeled platelets and homologous ⁵¹Cr-labeled platelets differ. *Blood*, **67**, 86–92.
- Janssens, A., Tarantino, M., Bird, R.J., Mazzucconi, M.G., Boccia, R.V., Lopez Fernandez, M.F., Kozak, T., Steurer, M., Te Boekhorst, P., Dillingham, K., Kreuzbauer, G. & Woodard, P. (2015) Romiplostim treatment in adults with immune thrombocytopenia of varying duration and severity. *Acta Haematologica*, **134**, 215–228.
- Janssens, A., Rodeghiero, F., Anderson, D., Chong, B.H., Boda, Z., Pabinger, I., Cervinek, L., Terrell, D.R., Wang, X. & Franklin, J. (2016) Changes in bone marrow morphology in adults receiving romiplostim for the treatment of thrombocytopenia associated with primary immune thrombocytopenia. *Annals of Hematology*, **95**, 1077–1087.
- Katsube, T., Ishibashi, T., Kano, T. & Wajima, T. (2016) Population pharmacokinetic and pharmacodynamic modeling of lusutrombopag, a newly developed oral thrombopoietin receptor agonist, in healthy subjects. *Clinical Pharmacokinetics*, **55**, 1423–1433.
- Kuter, D.J., Bussel, J.B., Lyons, R.M., Pullarkat, V., Gernsheimer, T.B., Senecal, F.M., Aledort, L.M., George, J.N., Kessler, C.M., Sanz, M.A., Liebman, H.A., Slovick, F.T., de Wolf, J.T., Bourgeois, E., Guthrie, T.H. Jr, Newland, A., Wasser, J.S., Hamburg, S.I., Grande, C., Lefrere, F., Lichtin, A.E., Tarantino, M.D., Terebelo, H.R., Viallard, J.F., Cuevas, F.J., Go, R.S., Henry, D.H., Redner, R.L., Rice, L., Schipperus, M.R., Guo, D.M. & Nichol, J.L. (2008) Efficacy of romiplostim in patients with chronic immune

- thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet*, **371**, 395–403.
- Kuter, D.J., Rummel, M., Boccia, R., Macik, B.G., Pabinger, I., Selleslag, D., Rodeghiero, F., Chong, B.H., Wang, X. & Berger, D.P. (2010) Romiplostim or standard of care in patients with immune thrombocytopenia. *New England Journal of Medicine*, **363**, 1889–1899.
- Kuter, D.J., Bussel, J.B., Newland, A., Baker, R.L., Lyons, R.M., Wasser, J., Viillard, J.F., Macik, G., Rummel, M., Nie, K. & Jun, S. (2013) Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. *British Journal of Haematology*, **161**, 411–423.
- McMillan, R. (2007) The pathogenesis of chronic immune thrombocytopenic purpura. *Seminars in Hematology*, **44**, S3–S11.
- McMillan, R., Wang, L., Tomer, A., Nichol, J. & Pistillo, J. (2004) Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. *Blood*, **103**, 1364–1369.
- Meyer, O., Herzog, E. & Salama, A. (2012) Platelet kinetics in idiopathic thrombocytopenic purpura patients treated with thrombopoietin receptor agonists. *Transfusion Medicine and Hemotherapy*, **39**, 5–8.
- Neunert, C., Lim, W., Crowther, M., Cohen, A., Solberg, L. Jr & Crowther, M.A. (2011) The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*, **117**, 4190–4207.
- Newland, A., Caulier, M.T., Kappers-Klunne, M., Schipperus, M.R., Lefrere, F., Zwaginga, J.J., Christal, J., Chen, C.F. & Nichol, J.L. (2006) An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptidobody, in patients with immune thrombocytopenic purpura. *British Journal of Haematology*, **135**, 547–553.
- Newland, A., Godeau, B., Priego, V., Viillard, J.F., Lopez Fernandez, M.F., Orejudos, A. & Eisen, M. (2016) Remission and platelet responses with romiplostim in primary immune thrombocytopenia: final results from a phase 2 study. *British Journal of Haematology*, **172**, 262–273.
- Newland, A., Lee, E.J., McDonald, V. & Bussel, J.B. (2018) Fostamatinib for persistent/chronic adult immune thrombocytopenia. *Immunotherapy*, **10**, 9–25.
- Olsson, B., Andersson, P.O., Jernas, M., Jacobsson, S., Carlsson, B., Carlsson, L.M. & Wadenvik, H. (2003) T-cell-mediated cytotoxicity toward platelets in chronic idiopathic thrombocytopenic purpura. *Nature Medicine*, **9**, 1123–1124.
- Rodeghiero, F. (2016) Is ITP a thrombophilic disorder? *American Journal of Hematology*, **91**, 39–45.
- Rodeghiero, F. (2017) ITP and thrombosis: an intriguing association. *Blood Advances*, **1**, 2280.
- Rodeghiero, F. (2018) A critical appraisal of the evidence for the role of splenectomy in adults and children with ITP. *British Journal of Haematology*, **181**, 183–195.
- Rodeghiero, F., Stasi, R., Gernsheimer, T., Michel, M., Provan, D., Arnold, D.M., Bussel, J.B., Cines, D.B., Chong, B.H., Cooper, N., Godeau, B., Lechner, K., Mazzucconi, M.G., McMillan, R., Sanz, M.A., Imbach, P., Blanchette, V., Kuhne, T., Ruggeri, M. & George, J.N. (2009) Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*, **113**, 2386–2393.
- Ruggeri, M., Tosetto, A., Palandri, F., Polverelli, N., Mazzucconi, M.G., Santoro, C., Gaidano, G., Lunghi, M., Zaja, F., De Stefano, V., Sartori, R., Fazi, P. & Rodeghiero, F. (2014) Thrombotic risk in patients with primary immune thrombocytopenia is only mildly increased and explained by personal and treatment-related risk factors. *Journal of Thrombosis and Haemostasis*, **12**, 1266–1273.
- Sarpatwari, A., Bennett, D., Logie, J.W., Shukla, A., Beach, K.J., Newland, A.C., Sanderson, S. & Provan, D. (2010) Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. *Haematologica*, **95**, 1167–1175.
- Shirasugi, Y., Ando, K., Hashino, S., Nagasawa, T., Kurata, Y., Kishimoto, Y., Iwato, K., Ohtsu, T. & Berger, D.P. (2009) A phase II, open-label, sequential-cohort, dose-escalation study of romiplostim in Japanese patients with chronic immune thrombocytopenic purpura. *International Journal of Hematology*, **90**, 157–165.
- Shirasugi, Y., Ando, K., Miyazaki, K., Tomiyama, Y., Okamoto, S., Kurokawa, M., Kiritto, K., Yonemura, Y., Mori, S., Usuki, K., Iwato, K., Hashino, S., Wei, H. & Lizambri, R. (2011) Romiplostim for the treatment of chronic immune thrombocytopenia in adult Japanese patients: a double-blind, randomized Phase III clinical trial. *International Journal of Hematology*, **94**, 71–80.
- Shirasugi, Y., Ando, K., Miyazaki, K., Tomiyama, Y., Iwato, K., Okamoto, S., Kurokawa, M., Kiritto, K., Hashino, S., Ninomiya, H., Mori, S., Yonemura, Y., Usuki, K., Wei, H. & Lizambri, R. (2012) An open-label extension study evaluating the safety and efficacy of romiplostim for up to 3.5 years in thrombocytopenic Japanese patients with immune thrombocytopenic purpura (ITP). *International Journal of Hematology*, **95**, 652–659.
- Stasi, R., Evangelista, M.L., Stipa, E., Buccisano, F., Venditti, A. & Amadori, S. (2008) Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management. *Thrombosis and Haemostasis*, **99**, 4–13.
- Zaja, F., Baccarani, M., Mazza, P., Bocchia, M., Gugliotta, L., Zaccaria, A., Vianelli, N., Defina, M., Tieghi, A., Amadori, S., Campagna, S., Ferrara, F., Angelucci, E., Usala, E., Cantoni, S., Visani, G., Fornaro, A., Rizzi, R., De Stefano, V., Casulli, F., Battista, M.L., Isola, M., Soldano, F., Gamba, E. & Fanin, R. (2010) Dexamethasone plus rituximab yields higher sustained response rates than dexamethasone monotherapy in adults with primary immune thrombocytopenia. *Blood*, **115**, 2755–2762.