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

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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 ≥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 ≥50 × 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 × 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 ≥50 × 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 × 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     |                 |
|                 | ≤3 months       | 3–12 months     | Total           | ≤3 months       |
|                 | (n = 155)       | (n = 156)       | (n = 311)       | (n = 726)       |
| 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\((\times10^9/l)\), 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.

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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 ≥50 × 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.

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**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.
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).

**Bleeding**

The median average weekly romiplostim dose was similar for both ITP duration subgroups (Table SII), did not vary much over time, and generally was ~3–4 µg/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

**Safety**

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 ≥ 50 × 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.
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. patients with 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 (Harker et al, 1998), 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; Heyns Adu et al, 1988; Ballem et al, 1987; Heyns Adu et al, 1988).

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.
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     | Romiplostim | PBO/SOC     | Romiplostim |
| 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; pt-yr, patient-years; SOC, standard of care.
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 has/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.

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