Health-related quality of life in nonsplenectomized immune thrombocytopenia patients receiving romiplostim or medical standard of care

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Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by platelet destruction and insufficient platelet production. The resulting thrombocytopenia reduces patient health-related quality of life (HRQOL). In a randomized, open-label, 52-week study of nonsplenectomized ITP patients treated with romiplostim or medical standard of care (SOC), patients completed the 10-scale ITP-patient assessment questionnaire (PAQ) at the start of the study and after 12, 24, 36, 48, and 52 weeks of treatment. HRQOL changes were examined for all patients in both treatment groups and by responder status, splenectomy status, and after the use of rituximab. Patients in both groups showed marked increases in all HRQOL scales over 52 weeks of treatment. These change scores exceeded the minimally important difference values (a measure of clinical relevance) for most of these scales, especially in responders to treatment. Compared with baseline, patients receiving romiplostim showed statistically significant improvements compared to SOC over 52 weeks for the ITP-PAQ scales of Symptoms, Bother, Activity, Psychological Health, Fear, Overall QOL, and Social QOL. Overall, treatment of ITP was associated with improvement in HRQOL. Patients receiving romiplostim had greater HRQOL improvements than those receiving SOC, but the magnitude of the difference is of uncertain clinical benefit.

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by persistent thrombocytopenia due to antibody binding to platelet antigen(s) causing their premature destruction by the reticuloendothelial system, particularly in the spleen [1]. In addition, recent evidence suggests that there is also insufficient platelet production, possibly immune-mediated [2]. The resulting thrombocytopenia places patients at risk for bruising and bleeding.

Recent international practice guidelines recommend that initial ITP treatment include glucocorticoids, intravenous immunoglobulin (IVIg), or intravenous anti-D. Second-line treatment includes splenectomy or medical therapies such as azathioprine, danazol, rituximab, or the thrombopoietin (TPO) receptor agonists [3,4]. Many of these second-line treatments are associated with significant toxicities or cost [3,4].

Romiplostim is a novel TPO receptor agonist that binds to and stimulates the TPO receptor. It has been shown to increase platelet counts with few adverse events [5]. In two randomized studies, an overall platelet response (weekly platelet counts $\geq 50 \times 10^9$/L during 4 or more weeks of the 24-week study) was achieved by 83% of patients receiving romiplostim versus 7% of patients receiving placebo ($P < 0.0001$) [6]. In addition, 87% of romiplostim versus 38% of placebo patients were able to reduce or discontinue their concurrent ITP medication, including corticosteroids and IVIg [6]. Continuous long-term (up to 156 weeks) treatment with romiplostim produced a platelet response (platelet counts $\geq 50 \times 10^9$/L) in 87% of 142 ITP patients [7]. Finally, romiplostim treatment led to fewer bleeding events, transfusions, treatment failures, and splenectomies when compared with standard of care [8].

ITP has a negative impact on patients' health-related quality of life (HRQOL) [9–11]. In a recent study [11], lower platelet counts were consistently associated with worse HRQOL, as measured by the ITP patient assessment questionnaire (ITP-PAQ), a disease-specific, validated, patient-reported outcome (PRO) questionnaire [12,13]. When compared with placebo, romiplostim treatment was associated with a significant improvement of HRQOL, primarily in splenectomized patients [14,15].

The objective of this study was to compare HRQOL of nonsplenectomized ITP patients treated with either romiplostim or medical standard of care (SOC) [8]. In addition, changes in HRQOL were examined among subgroups of special interest: patients before and after splenectomy, patients before and after rituximab treatment, and treatment responders versus treatment nonresponders.

There were 234 patients available for analysis, with no difference in baseline characteristics between those treated with romiplostim ($N = 157$) and those treated with SOC ($N = 77$; Table I). Overall completion of the ITP-PAQ was above 70% for 93% of romiplostim patients and 90% of SOC patients, a statistically insignificant difference. Although numerically slightly lower for the romiplostim group at baseline, controlling for geographic region, no statistically significant differences were found between the romiplostim and SOC groups for any baseline ITP-PAQ scale (Table II).

Treatment improved ITP-PAQ scores. Compared with baseline, both the SOC and romiplostim groups showed statistically significant improvement ($P < 0.05$) over the 52-week treatment period in scores for all scales other than Work QOL ($P = 0.09$). When change scores from baseline over the 52-week treatment period were compared between the two treatment groups, the romiplostim group showed statistically significantly greater improvements compared with the SOC group on the following ITP-PAQ scales: Symptoms ($P = 0.013$), Bother ($P = 0.0076$), Activity ($P = 0.0246$), Psychological Health ($P = 0.0490$), Fear ($P = 0.0001$), Overall QOL ($P = 0.0246$), and Social QOL ($P = 0.0020$), (Table II). No difference was found between the SOC and romiplostim groups for Fatigue ($P = 0.34$).

To assess the clinical significance of these changes, change scores were compared to MID estimates for the scales of Symptoms, Fatigue, Bother, Activity, Psychological Health, Overall QOL, and Social QOL (Fig. 1a). MID estimates are not available for the other three ITP-PAQ scales. Change from baseline to end of treatment exceeded the MID for both treatment groups on the scales of Symptoms, Bother, Psychological Health, and Overall QOL. For the Activity and Social QOL scales, the change from baseline was below the MID in the SOC group and equal to or above the MID in the romiplostim group. For the Fatigue scale, neither treatment group had a change score exceeding the MID.

Specifically within the SOC arm, between 40 and 49% of the patients achieved an improvement in at least one of the seven scales for which MID values are available that exceeded the MID range sometime during the course of the study, while 61–70% of the patients receiving romiplostim showed improvement of this magnitude. For instance, as illustrated in Fig. 1a, 70% of patients receiving romiplostim had an improvement of 10 or more points in Symptoms (vs. 40% receiving SOC).

Subgroup analyses were conducted to assess the effect of splenectomy, rituximab use, and responder status on ITP-PAQ scores. Of the 77 patients in the SOC treatment arm, 13 had a splenectomy and 16 received rituximab. No statistically significant differences were found when ITP-PAQ scale scores were compared before and after splenectomy or before and after rituximab use (data not shown).

For the analysis by responder status, 54 out of 77 SOC patients (70%) and 139 out of 157 romiplostim patients (89%) were responders. There was no statistically significant difference for adjusted baseline ITP-PAQ scores between these two groups. Change scores from baseline for all but two (Women's Reproductive Health, Work QOL) of the 10 ITP-PAQ scales increased statistically significantly comparing responders vs. nonresponders regardless of treatment group (Table II) and the changes within subgroups by responder status and treatment groups were greater than the MID values for most scales, as shown in Fig. 1b. Romiplostim responders showed a statistically significant increase compared with SOC responders in the following ITP-PAQ scales: Bother ($P = 0.0046$); Fear ($P = 0.0113$); Overall QOL ($P = 0.0232$); Social QOL ($P = 0.0149$); and Work QOL ($P = 0.0268$; Fig. 1b).

These results demonstrate significant improvements in HRQOL over 52 weeks for nonsplenectomized patients for both treatment groups for all scales, except Work QOL and Women's Reproductive Health (neither of which could be analyzed due to small numbers of patients). These improve-

ments in HRQOL exceeded the MID values for Symptoms, Bother, Activity (romiplostim only), Psychological Health, Overall QOL and Social QOL (romiplostim only). But neither treatment increased the 52-week improvement score above the MID for Fatigue. When compared with the SOC group, there were larger change scores from baseline for the romiplostim group on the ITP-PAQ scales of Symptoms, Bother, Activity, Psychological Health, Fear, Overall QOL, and Social QOL. The fact that improvements in the Activity scores exceeded the MID only for those receiving romiplostim is of importance. This suggests that patients perceived more of an improvement in both their ability to exercise and their ability to partake in sporting activities after receiving romiplostim.

The findings in this study suggest a benefit on more dimensions of HRQOL for nonsplenectomized patients than previously identified [8]. Results from prior randomized studies of adult ITP patients [6] showed that splenectomized patients receiving romiplostim reported statistically significant improvements over placebo on four of 10 scales of the ITP-PAQ (Symptoms, $P = 0.0337$, Bother, $P = 0.0126$, Social Activity, $P = 0.0145$, and Women's Reproductive Health, $P = 0.0458$). However, nonsplenectomized patients reported statistically significant improvement over placebo only on the Activity scale ($P = 0.0458$).

Although the results of the current study demonstrate a statistically significant HRQOL benefit on some scales with romiplostim compared with SOC, the magnitude of the clinical benefit is uncertain. For no scales did the extent of improvement in score over SOC patients approach the MID value (10–12.5 points), suggesting that the relative improvement in HRQOL for romiplostim over SOC may not be discernable for the patient.

During the 12-month study, more romiplostim-treated patients (61–70%) exceeded the MID value on any ITP-PAQ scale than did SOC-treated patients (40–49%).

As expected, the subgroup analyses suggest that the beneficial effects of romiplostim on HRQOL found in the full sample are driven by the beneficial effects among responders. Responders to both romiplostim and SOC showed increases above the MID, including the scale of Fatigue, but the perceived benefit in HRQOL exceeded the MID more often for those treated with romiplostim. Romiplostim showed a statistically significant greater increase over SOC for a number of scales (Bother, Fear, Overall QOL, Social QOL, and Work QOL), but the magnitude of the difference was usually less than the MID and therefore of uncertain clinical benefit. However, making comparisons for MID differences in responders is challenging because complete responders to either treatment would maximize the perceived benefit score and minimize any differences between treatment groups.

The subgroup analyses were unable to show a significant HRQOL benefit as measured by the ITP-PAQ for patients who underwent splenectomy or rituximab treatment, most likely due to small patient numbers. It would be helpful to confirm these findings in a larger sample size and with a control group.

Fatigue is a known complaint of patients with ITP and is poorly understood. It has been reported that fatigue in ITP patients was associated with bleeding problems [16]. Although markedly improved from baseline, it is surprising that neither romiplostim nor SOC increased the mean Fatigue score above the MID value in this study, comparable to the results in all prior romiplostim studies [6,8]. This may reflect a weakness of the ITP-PAQ, since patients anecdotally reported much less fatigue with treatment. More likely it simply reflects dilution of the treatment effect by the nonresponding group; responders in both treatment groups clearly had improvements in their Fatigue scale that exceeded the MID.

Several limitations of this study should be noted: first, the MID has not been estimated for a number of ITP-PAQ scales, so clinical significance of the findings cannot be determined for a number of scales. The MID is intended to evaluate change for a particular group and not to compare differences between groups. Further, the sample size for some of the subgroup analyses was small, limiting the power for the analyses. Finally, the MID values themselves represent a range of values; midpoint values

TABLE I. Patient Characteristics

	SOC ($N = 77$)	Romiplostim ($N = 157$)	Total ($N = 234$)
Age Group in Years, *n* (%)			
18–29	9 (12)	20 (13)	29 (12)
30–39	8 (10)	18 (12)	26 (11)
40–49	14 (18)	21 (13)	35 (15)
50–59	10 (13)	28 (18)	38 (16)
60–69	15 (20)	30 (19)	45 (19)
70–79	14 (18)	30 (19)	44 (19)
≥ 80	7 (9)	10 (6)	17 (7)
Age (yrs)			
Mean	55	55	55
SD	19	19	19
Sex, *n* (%)			
Female	46 (60)	85 (54)	131 (56)
Male	31 (40)	72 (46)	103 (44)
Race, *n* (%)			
White or Caucasian	69 (90)	137 (87)	206 (88)
Black or African American	0 (0)	6 (4)	6 (3)
Hispanic or Latino	5 (7)	9 (6)	14 (6)
Asian	1 (1)	5 (3)	6 (3)
American Indian or Alaska Native	1 (1)	0 (0)	1 (0.4)
Other	1 (1)	0 (0)	1 (0.4)
Weight (kg)			
Mean (SD)	82 (23)	82 (20)	82 (21)
Years since ITP Diagnosis[a]			
Mean (SD)	5 (6)	4 (6)	4 (6)
Prior ITP therapies[b]			
≤2	45 (58)	100 (64)	145 (61)
>2	32 (42)	57 (36)	89 (38)

Full analysis set includes all randomized subjects.

[a]Years are calculated as (randomization date − ITP diagnosis date)/365.25. Partial dates of ITP diagnosis with missing day only are imputed as day 15. Partial dates with missing month and day are imputed as July 1.

[b]ITP treatments include: corticosteroid, anti-D, IVIg, danazol, vincristine/vinblastine, cyclophosphamide, azathioprine, rituximab, and others.

TABLE II. Overall Change Scores for ITP-PAQ

	Baseline total score[a]		Overall change in score from baseline to week 52[b]		Overall change in score from baseline to week 52[c]	
ITP-PAQ scale	SOC ($N = 77$)	Romiplostim ($N = 157$)	SOC ($N = 77$)	Romiplostim ($N = 157$)	Responders ($N = 193$)	Non-responders ($N = 41$)
Symptoms	71 (3)	68 (2)	13 (2)	16 (2)†	13 (1)‡	-1 (3)
Fatigue	68 (4)	62 (3)	10 (3)	11 (3)	14 (2)‡	-7 (5)
Bother	71 (4)	64 (3)	13 (3)	17 (3)§	19 (2)‡	4 (4)
Activity	73 (5)	63 (3)	8 (4)	17 (4)†	18 (2)‡	-12 (5)
Psychological Health	69 (4)	64 (3)	16 (3)	19 (3)†	20 (1)‡	3 (4)
Fear	81 (3)	79 (2)	9 (2)	14 (2)‡	13 (1)§	6 (3)
Overall QOL	65 (4)	59 (3)	15 (4)	16 (4)†	18 (2)§	5 (5)
Social QOL	81 (4)	76 (3)	6 (3)	10 (2)§	11 (1)§	8 (4)
Women's Reproductive Health	89 (6)	77 (4)	16 (4)	13 (4)	8 (2)	7 (5)
Work QOL	87 (10)	80 (5)	13 (6)	6 (5)	-1 (3)	-7 (8)

All data presented as Mean (±SE). SOC = Standard of Care.

[a]Analysis of covariance (ANCOVA) adjusted for geographic location was used to compare ITP-PAQ scores at baseline between treatment groups.

[b]The model included a random intercept, and fixed effects for baseline assessment, geographic location, treatment group, assessment week, splenectomy status, and treatment-group-by-assessment week interaction.

[c]The model included a random intercept, and fixed effects for baseline assessment, responder status, assessment week, and interaction between responder status and assessment week. Statistically significant difference between groups: †P=0.05, §P=0.01, ‡P=0.0001.

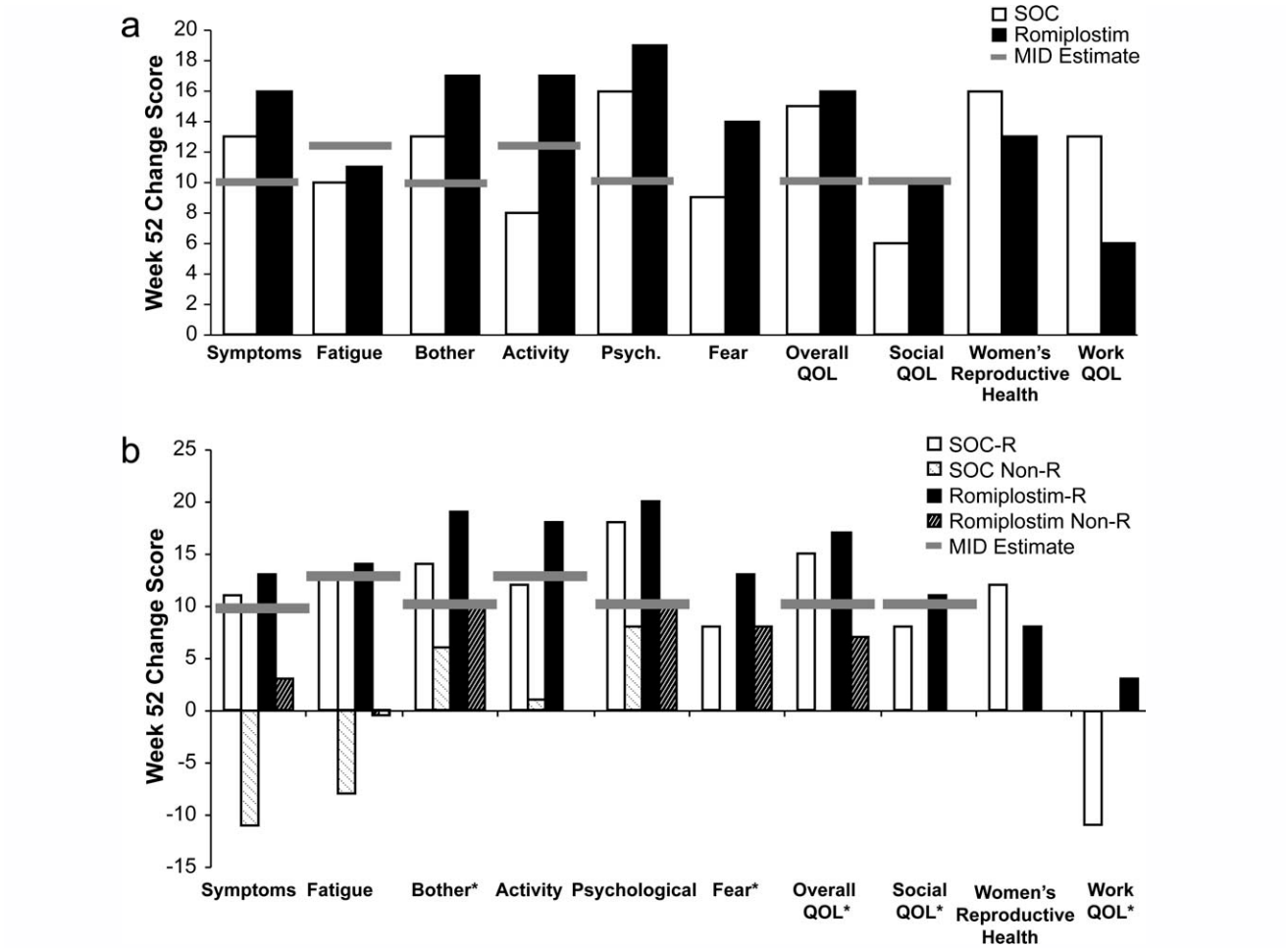

Figure 1. (a) Change in ITP-PAQ scores from baseline to week 52 for romiplostim and SOC. (b) Change in ITP-PAQ scores from baseline to week 52 in responders (R) versus nonresponders (Non-R) to romiplostim and SOC. MID values are indicated by the horizontal bars. MID values are not available for Fear, Women's Reproductive Health, and Work QOL. *$P < 0.05$ comparing romiplostim responders to SOC responders.

within these ranges were chosen for this analysis. The use of the highest or lowest values of the range rather than the midpoint could slightly alter our results.

In conclusion, this study found that second-line ITP treatments significantly increased the HRQOL of nonsplenectomized adult ITP patients and this effect was particularly pronounced in responders, who also demonstrated a reduction in Fatigue. These HRQOL improvements were more evident in those treated with romiplostim than SOC, but the magnitude of this benefit might not be perceived by patients. Future research is needed to further investigate the clinical significance of these findings.

Methods

Study design. A multicenter, randomized, open-label study with a 52-week treatment period was conducted to compare romiplostim with SOC for the treatment of ITP (Supporting Information Fig. 1) [8]. The primary endpoints were the incidence of treatment failure and splenectomy. Patients were eligible for participation if they were nonsplenectomized adults diagnosed with ITP according to the American Society of Hematology (ASH) guidelines [17] and if they had received at least one prior therapy for ITP. In addition, patients were required to have a platelet count of $<50 \times 10^9$/L or have their platelet count fall to $<50 \times 10^9$/L during or after a clinically induced taper or discontinuation of current ITP therapy. Patients were enrolled from 85 investigational sites located in Germany, Belgium, Austria, Italy, France, Spain, Netherlands, United Kingdom, Czech Republic, Poland, Switzerland, United States, Canada, and Australia.

Eligible, consenting patients were randomized in a 2:1 ratio within geographic regions to once-weekly subcutaneous romiplostim or SOC for 52 weeks. Patients randomized to romiplostim were required to complete the taper or discontinuation of medical SOC for ITP as soon as medically feasible after the initiation of romiplostim. The starting dose for romiplostim was 3 mcg kg^{-1}, with dose adjustments allowed based on platelet count, up to a maximum dose of 10 mcg kg^{-1}. Medical SOC treatments (i.e., corticosteroids, IVIg, rituximab, etc.) were selected and prescribed by the local investigator, with dosage adjustments permitted throughout the study.

Health-related quality of life. Health-related quality of life (HRQOL) was included as a secondary endpoint in the study. The ITP-Patient Assessment Questionnaire (ITP-PAQ) was self-administered by patients at baseline, week 12, 24, 36, 48, and at the end of the study (1 week after the last dose of romiplostim). For patients who completed the full study, end of treatment was week 53.

The ITP-PAQ consists of 44 items that comprise 10 scales. Each of the 10 scales is scored 0 to 100, with higher scores indicating better quality of life. Four of the scales measure physical health: Symptoms, Bother, Fatigue, and Activity. Two of the scales measure emotional health: Fear and Psychological Health. The remaining four scales measure other aspects of QOL: Work QOL, Social QOL, Women's Reproductive QOL, and Overall QOL. Work QOL and Women's Reproductive QOL were only completed by those employed for pay and women, respectively.

For a patient-reported outcome (PRO) evaluation, such as an assessment with the ITP-PAQ, patients are the primary stakeholders [18]. Therefore, a relevant change in a PRO measure is that which the patient would consider beneficial or detrimental. The smallest difference in a PRO measure that a patient would consider beneficial or detrimental, regardless of whether it results in a change in the patient's clinical treatment or care, is known as the minimum important difference (MID). For the ITP-PAQ, the MID has been esti-

mated at 8–12 points for Symptoms, Bother, Psychological Health, Overall QOL, and Social QOL, and 10–15 points for Fatigue and Activity. The MID is not available for Fear, Women's Reproductive Health, or Work QOL [9].

Statistical analysis. Demographic and baseline characteristics were summarized using descriptive statistics. Analysis of covariance (ANCOVA) was used to compare ITP-PAQ scores at baseline for patients receiving romiplostim and patients receiving medical SOC. The analysis was adjusted for geographic location of investigational sites (North America, Europe, and Australia). A mixed-effects linear model was used to compare changes from baseline on ITP-PAQ scale scores between treatment groups. The model included a random intercept, and fixed effects for baseline assessment, geographic location, treatment group, assessment week, splenectomy status, and treatment-group-by-assessment week interaction. Treatment group and splenectomy status were represented as time-varying covariates. Missing data were not imputed.

Changes from baseline were compared to the midpoint of the MID estimates for Symptoms (10 points), Bother (10 points), Psychological Health (10 points), Overall QOL (10 points), Social QOL (10 points), Fatigue (12.5 points), and Activity (12.5 points) to determine clinical significance [9].

Subgroup analyses were conducted in the SOC arm using paired *t* tests to evaluate changes in ITP-PAQ scale scores before and after a successful splenectomy (as determined by the investigator) and to evaluate changes in ITP-PAQ scale scores before and after treatment with rituximab.

Additional subgroup analyses were also conducted by responder status, with a responder defined as a patient who did not drop out early and did not have a treatment failure [i.e., (1) did not have a platelet count $\leq 20 \times 10^9$/L for four consecutive weeks at the highest recommended dose and schedule; (2) did not have a major bleeding event; and (3) did not have a change in therapy due to an intolerable side effect or bleeding symptoms] [8]. Adjusted baseline ITP-PAQ scores were calculated controlling for geographical region. A mixed-effects linear model was used to compare changes from baseline on ITP-PAQ scale scores between responder and nonresponder groups. The model included a random intercept, and fixed effects for baseline assessment, responder status, assessment week, and interaction between responder status and assessment week. Only visits prior to change in therapy or splenectomy were included in the analysis. Within each subgroup (either responders or nonresponders), a mixed effects linear model was applied for each ITP-PAQ scale across all assessment points to compare changes from baseline in ITP-PAQ scores between treatment groups. The model included a random intercept and fixed effects of baseline assessment, treatment group and assessment week and interaction between treatment group and assessment week.

Acknowledgments

The authors thank Elizabeth Tschosik, Ph.D. of Health Outcomes Solutions for providing assistance with writing and preparation of this article, and Michelle Zakson, an employee of Amgen Inc, for providing editorial and formatting assistance with the manuscript. DJK performed and designed the research, analyzed the data and wrote the article, SDM analyzed the data and wrote the article, MR, RM, AAG performed the research, analyzed the data and wrote the article, XW analyzed the data and wrote the article, and RRD analyzed the data and wrote the article.

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Contract grant sponsor: Amgen Inc
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Additional Supporting Information may be found in the online version of this article.
Conflict of interest: David J. Kuter is a consultant and has received research funding from Amgen Inc., GlaxoSmithKline, Pfizer, Shionogi, ONO and Eisai Inc. Susan D. Mathias is an employee of Health Outcomes Solutions which has been paid by Amgen Inc. for consulting services. Mathias J. Rummel has no relevant financial relationship(s) to disclose. Romeo Mandanas has received honoraria from Celgene, Genentech/Roche and Amgen Inc., and has also been on the Speakers Bureau for GlaxoSmithKline, Pfizer and Genomic Health. Aristoteles Giagounidis is a consultant and has received honoraria from Celgene, Amgen, Novartis, and GSK. Xuena Wang is employed by and has equity ownership of stock from Amgen Inc. Robert Deuson is employed by and has equity ownership of stock from Amgen Inc.
Published online 15 February 2012 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.23163

References

1. Provan D, Newland A. Idiopathic thrombocytopenic purpura in adults. J Pediatr Hematol Oncol 2003;25 (Suppl 1):S34–S38.
2. Barsam SJ, Psaila B, Forestier M, et al. Platelet production and platelet destruction: Assessing mechanisms of treatment effect in immune thrombocytopenia. Blood 2011;117:5723–5732.
3. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168–186.
4. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190–4207.
5. Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. N Engl J Med 2006;355:1672–1681.
6. 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;371:395–403.
7. Bussel JB, Kuter DJ, Pullarkat V, et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009;113:2161–2171.
8. Kuter DJ, Rummel M, Boccia R, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. N Engl J Med 2010;363:1889–1899.
9. Mathias SD, Gao SK, Rutstein M, et al. Evaluating clinically meaningful change on the ITP-PAQ: Preliminary estimates of minimal important differences. Curr Med Res Opin 2009;25:375–383.
10. McMillan R, Bussel JB, George JN, et al. Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. Am J Hematol 2008;83:150–154.
11. Snyder CF, Mathias SD, Cella D, et al. Health-related quality of life of immune thrombocytopenic purpura patients: Results from a web-based survey. Curr Med Res Opin 2008;24:2767–2776.
12. Mathias SD, Bussel JB, George JN, et al. A disease-specific measure of health-related quality of life in adults with chronic immune thrombocytopenic purpura: Psychometric testing in an open-label clinical trial. Clin Ther 2007; 29:950–962.
13. Mathias SD, Bussel JB, George JN, et al. A disease-specific measure of health-related quality of life for use in adults with immune thrombocytopenic purpura: Its development and validation. Health Qual Life Outcomes 2007;5:11.
14. 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: 409–415.
15. Sanz MA, Aledort L, Mathias SD, et al. Analysis of EQ-5D scores from two phase 3 clinical trials of romiplostim in the treatment of immune thrombocytopenia (ITP). Value Health 2011;14:90–96.
16. Newton JL, Reese JA, Watson SI, et al. Fatigue in adult patients with primary immune thrombocytopenia. Eur J Haematol 2011;86:420–429.
17. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3–40.
18. Wyrwich KW, Bullinger M, Aaronson N, et al. Estimating clinically significant differences in quality of life outcomes. Qual Life Res 2005;14:285–295.