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Improved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: results from two randomized, placebo-controlled trials

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Summary

Health-related quality of life (HRQoL) is a major concern for adults with chronic immune thrombocytopenic purpura (ITP) due to the symptoms associated with the disease and its treatment. This study utilized the ITP-patient assessment questionnaire (ITP-PAQ), a specialized HRQoL questionnaire for ITP, to investigate the humanistic burden of ITP and the impact of romiplostim therapy on HRQoL in two, placebo-controlled, phase 3 clinical trials of splenectomized and non-splenectomized patients. ITP-PAQ was self-administered to ITP patients at baseline, and weeks 4, 12 and 24 of treatment. Splenectomized patients had lower baseline HRQoL scores than non-splenectomized patients in seven of 10 scales ($P < 0{\cdot}05$). After 24 weeks of romiplostim therapy, splenectomized patients showed significant improvements over placebo in four of 10 ITP-PAQ Scales (Symptoms, $P = 0{\cdot}0337$; Bother, $P = 0{\cdot}0126$; Social Activity, $P = 0{\cdot}0145$; and Women's Reproductive Health, $P = 0{\cdot}0184$). Non-splenectomized patients demonstrated significant improvement over placebo in the Activity Scale ($P = 0{\cdot}0458$). Data pooled from the two trials, adjusted for splenectomy status, showed significant improvement for romiplostim-treated patients in six scales; Symptoms, Bother, Activity, Fear, Social Activity and Women's Reproductive Health. These results suggest that adult patients with chronic ITP have improved HRQoL following romiplostim therapy.

Keywords: immune thrombocytopenic purpura, romiplostim, quality of life, health-related quality of life.

Adult immune thrombocytopenic purpura (ITP) is a chronic autoimmune disorder characterized by antibody-mediated platelet destruction and suboptimal platelet production (Cines & Blanchette, 2002). Unlike the disease course in children, ITP in adults typically has an insidious onset and a chronic course (George *et al*, 1996; Cines & Blanchette, 2002; Stasi & Provan, 2004). The signs and symptoms are generally considered to be restricted to bleeding that occurs when the platelet count is $<30 \times 10^9$/l (George *et al*, 1996; Cines & Blanchette, 2002; Stasi & Provan, 2004). Bleeding symptoms may range from mild bruising and mucosal bleeding to severe haemorrhage (Cines & Blanchette, 2002). The treatment goal for adults with ITP is to increase the platelet count to a safe level and to prevent clinically important bleeding. Treatment is often successful in the short-term, however, most current therapies do not provide a durable response and many are associated with substantial side effects that limit their long-term usefulness (Stasi & Provan, 2004; Cines & McMillan, 2005; Matzdorff & Arnold, 2007).

In addition to bleeding symptoms, patients may complain of fatigue that seems to be caused by the ITP (Cines & Bussel, 2005). It is hypothesized that treatment of ITP to increase the platelet count may improve the symptoms of fatigue as well as diminish bleeding symptoms. Side effects of treatments for ITP also may have a significant impact on health-related quality of life (HRQoL). Patients with ITP report HRQoL levels that are lower than the general population and comparable to other chronic conditions such as arthritis and diabetes (Zhou *et al*,

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2007; McMillan *et al*, 2008). These include physical symptoms associated with the disease and its treatments (e.g. visible bleeding and drug side effects), social limitations (e.g. lifestyle adjustments for intravenous therapies, physician visits and/or hospitalizations) and psychological effects (e.g. fear of bleeding, fear of infection after splenectomy, negative body image due to bruising and corticosteroid therapy-associated weight gain) (McMillan *et al*, 2008).

Health-related quality of life is an important consideration when making treatment recommendations to patients with ITP. HRQoL is also used in the approval process for new drugs by several countries and many managed care organizations. Management decisions for adult patients with chronic ITP should be based on judgements that incorporate bleeding symptoms, tolerance to treatment, lifestyle and patient preference; treatment should not be based solely on the severity of thrombocytopenia (Cines & Bussel, 2005; Bussel, 2006; George, 2006). A HRQoL measure that can assess the patient's emotional state and the ability to function both physically and socially may be a useful tool for guiding decisions about when to start treatment, which type of therapy to recommend and also for judging the benefit and risks of treatments (U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health, 2006).

The ITP-patient assessment questionnaire (ITP-PAQ) is the first disease-specific HRQoL questionnaire developed for use in adults with chronic ITP (Mathias *et al*, 2007a). It assesses multiple facets of disease-specific HRQoL, including Symptoms, Fatigue, Bother, Fear, Social Activity and Overall QoL. Taken together with other clinical assessments, the ITP-PAQ can be used to describe the burden of illness as well as an outcome measure to assess the efficacy or effectiveness of ITP treatments. As a disease-specific measure, the ITP-PAQ was designed to be more sensitive in patients with ITP than generic measures such as the Short Form 36 questionnaire (SF-36; McMillan *et al*, 2008) because it contains items specific to the HRQoL issues that were identified as being concerns to patients with chronic ITP (Mathias *et al*, 2008). The objective of this research was to assess the function and well-being of splenectomized and non-splenectomized adult patients with chronic ITP using the ITP-PAQ and to investigate the effect of romiplostim therapy on HRQoL levels over a 24-week period.

Methods

Trial design

Patients were enroled in one of two multicentre, randomized (2:1 ratio for romiplostim vs. placebo), placebo-controlled, double-blind trials conducted at 35 centres in the United States, the United Kingdom, France, the Netherlands and Spain. Both trials were designed to evaluate the efficacy and safety of romiplostim in adult patients with chronic ITP. The trials were conducted in accordance with the principles of the US Food and Drug Administration and International Conference on Harmonization and Good Clinical Practice regulations. The study received local Institutional Review Board approval at each site and each patient provided written informed consent before enroling. Trial designs were identical except that one trial enroled patients who had undergone splenectomy ≥4 weeks prior to screening while the other trial enroled patients who had not had splenectomy (Kuter *et al*, 2008).

Eligible patients were men or women at least 18 years of age or older with a diagnosis of ITP according to American Society of Haematology guidelines (George *et al*, 1996) with a platelet count of $<30 \times 10^9$/l (mean of three counts taken during the screening and pretreatment period). Patients >60 years had to have a bone marrow biopsy confirmation of their diagnosis of ITP. Patients were required to have adequate liver and renal function (serum bilirubin ≤1·5 times the laboratory normal range, serum creatinine ≤176·8 μmol/l) and a haemoglobin level >90 g/l. Patients with a history of a bone marrow stem cell disorder were excluded. Further details on the study protocols have been published elsewhere (Kuter *et al*, 2008).

Patients received subcutaneous injections of romiplostim (or placebo) once per week starting at a dose of 1 μg/kg. Dose adjustment was permitted throughout the 24-week treatment period to maintain platelet counts in the target range of 50 to 200×10^9/l. The maximum permitted dose was 15 μg/kg (subsequent to the phase 3 studies, the maximum dose was 10 μg/kg). For patients who completed the 24-week treatment period, study completion was the first day after the platelet count dropped to $\leq 50 \times 10^9$/l or when the patient reached week 36 with a platelet count $>50 \times 10^9$/l, whichever came first.

HRQoL assessment

The ITP-PAQ consists of 44 questions organized into 10 scales measuring Physical Health (Symptoms, Bother, Fatigue and Activity Scales), Emotional Health (Fear and Psychological Health Scales), Work, Social Activity, Women's Reproductive Health (which includes menstrual symptoms and fertility) and Overall QoL (Mathias *et al*, 2007a). Forty-four questions were designed to quantify feelings, such as fear of bleeding or hospitalization, bother due to ITP symptoms and limitations on physical, social or work function due to ITP symptoms or treatment side effects. Items were scored on Likert-type Scales of various sizes. Scale scores were standardized from 0 to 100, with higher scores indicating better HRQoL. Change in ITP-PAQ scores from baseline to week 24 was a secondary endpoint. The responsiveness, reliability and validity of the ITP-PAQ have been confirmed and were presented elsewhere (Mathias *et al*, 2007a,b). Patients self-administered the ITP-PAQ at baseline (before administration of romiplostim or placebo) and at weeks 4, 12 and 24. Patients were blinded to

their current platelet count results before completing the ITP-PAQ.

Statistical methods

Descriptive statistics were used to evaluate demographic and baseline characteristics for all randomized patients. A *P*-value of 0·05 was used to determine significance. For categorical variables, the number and percentage are reported. Continuous variables are summarized by *n*, mean and SD.

ITP-Patient Assessment Questionnaire Scale scores were computed using data from each assessment. The mean change in ITP-PAQ Scale scores from baseline to week 24 of treatment was calculated for each treatment group. Two-sided *t*-tests were used to compare scale scores for splenectomized and non-splenectomized patients and to determine whether the change from baseline to week 24 in the romiplostim-treated group was significantly different from the change from baseline in the placebo group. This assessment of change in ITP-PAQ scores was used only for patients who completed the trials.

Statistical analyses utilizing ITP-PAQ data from both studies using all four assessments rather than just those from baseline and week 24 were also performed. These *post hoc* analyses included repeated measures analysis using general linear models (GLM) and area under the curve (AUC) analyses. These analyses used all available follow-up data including ITP-PAQ data collected at weeks 4 and 12 in addition to week 24. This is in contrast to the change score analysis that relied on follow-up data from week 24 only. We controlled for age, gender, splenectomy status and the use of baseline ITP medications in these analyses. The repeated measures model included main effects of time and treatment group (romiplostim vs. placebo); treatment interactions were also tested and included when significant. The null hypothesis for the *F*-test stated that the population mean change scores from which these samples were drawn were equivalent. The *F*-value expressed the magnitude of difference between romiplostim and placebo in response to treatment, while the associated *P*-value provided information on whether the difference was significant.

Results

Patient demographics and baseline characteristics

A total of 125 patients were enroled in the two trials (63 splenectomized and 62 non-splenectomized patients; Table I). Baseline platelet counts were low for all patients at baseline (16×10^9/l). Although the mean baseline platelet counts were statistically different between splenectomized and non-splenectomized patients (14×10^9/l vs. 18×10^9/l respectively $P = 0{\cdot}015$), the difference was not clinically important. Patients in the placebo and romiplostim treatment arms were similar with regard to demographic and baseline clinical characteristics. There were 84 patients (55 females, 65·5%) in the romiplostim groups and 41 patients (26 females, 63·4%) in the placebo groups. The mean age was 51·9 years *versus* 55·2 years in the romiplostim- and placebo-treated groups, respectively.

Baseline ITP-PAQ scores

Baseline ITP-PAQ scores were comparable for the romiplostim and the placebo groups, indicating a similar HRQoL level prior to receipt of the investigational treatment (data not shown). Of the 44 individual items contained within the 10 ITP-PAQ Scales, the items with the lowest scores at baseline were: 'lifestyle changes' and 'prevents me from doing things' (Overall QoL Scale), 'bruising' (Symptoms Scale), 'lack of control over health' (Psychological Scale) and 'physical fatigue' (Fatigue Scale) (data not shown). In general, baseline ITP-PAQ scores were lower, representing worse HRQoL in splenectomized *versus* non-splenectomized ITP patients. Splenectomized patients had significantly lower baseline scores for 7 of 10 ITP-PAQ Scales including Symptoms, Bother, Fear, Psychological Health, Work, Social Activity and Overall QoL (Table II, $P < 0{\cdot}05$).

Changes in ITP-PAQ scores during romiplostim treatment

Splenectomized patients treated with romiplostim had significantly greater improvement in HRQoL than those treated with placebo in the Symptoms, Bother, Social Activity and Women's Reproductive Health Scales (Fig 1; $P = 0{\cdot}0337$, 0·0126, 0·0145, 0·0184, respectively). Non-splenectomized patients treated with romiplostim showed significantly greater improvement in HRQoL than those treated with placebo in the Activity Scale (Fig 1; $P = 0{\cdot}0458$). No significant improvement in any mean scale scores were found for placebo patients from baseline to week 24. When the changes in ITP-PAQ scores from baseline to week 24 were compared between patients in the combined romiplostim-treated groups who achieved a durable platelet count response ($n = 42$) (durable response was defined by Kuter *et al*, 2008) and non-responders ($n = 83$), there were significant differences in the Scales of Bother and Psychological Health ($P < 0{\cdot}05$), with responders achieving greater improvements (data not shown). In addition, a correlation analysis was performed relating the ITP-PAQ change scores from baseline to week 24 in patients considered to be overall responders (durable and transient; $n = 72$). Notably, this was a much less stringent definition of response; however, this analysis yielded significant differences in the Bother, Social QoL and Women's Reproductive Health Scales ($P = 0{\cdot}03$, 0·05. 0·01, respectively; data not shown).

The change in ITP-PAQ scores for ITP patients who continued on corticosteroids and other concomitant ITP medications during the entire study period was compared with those who stopped (data not shown). While no statistically significant differences emerged in this analysis, several ITP-PAQ Scale scores including Symptoms, Bother and Work QoL

Table I. Patient characteristics and baseline demographics.

	Splenectomized (n = 63)	Non-splenectomized (n = 62)	P	Romiplostim (n = 84)	Placebo (n = 41)	P
Sex, n (%)						
Female	38 (60·3)	43 (69·4)	0·29	55 (65·5)	26 (63·4)	0·82
Male	25 (39·7)	19 (30·7)		29 (34·5)	15 (36·6)	
Mean age ± SD (years)	52 ± 15	54 ± 18	0·53	52 ± 16	55 ± 17	0·30
Years since ITP diagnosis ± SD	12 ± 11	4 ± 6	<0·0001	8 ± 11	8 ± 8	0·72
Baseline platelet count, mean $\times 10^9$/l ± SD	14 ± 9	18 ± 10	0·015	17 ± 9	15 ± 10	0·46

ITP, immune thrombocytopenic purpura.

Table II. Comparison of mean baseline scores by splenectomy status.

ITP-PAQ Scale	Splenectomized (n = 58*)	Non-splenectomized (n = 61*)	P
Symptoms	59 ± 21	68 ± 19	0·02
Bother	51 ± 32	67 ± 26	0·004
Fatigue	59 ± 27	63 ± 26	0·39
Activity	50 ± 35	55 ± 37	0·46
Fear	69 ± 31	81 ± 23	0·02
Psychological Health	54 ± 33	65 ± 26	0·04
Work†	62 ± 35	84 ± 23	0·004
Social Activity	65 ± 30	78 ± 23	0·01
Women's Reproductive Health†	67 ± 29	73 ± 30	0·47
Menstrual Symptoms	55 ± 36	66 ± 33	0·23
Fertility	80 ± 33	79 ± 37	0·93
Overall Quality of Life	40 ± 30	56 ± 33	0·005

ITP-PAQ, Immune Thrombocytopenic Purpura-Patient Assessment Questionnaire.

*Baseline records for ITP-PAQ were missing in four patients.

†Work: splenectomized n = 33, non-splenectomized, n = 32; Reproductive Health: splenectomized n = 24; non-splenectomized, n = 31. Sample sizes were reduced for Work and Reproductive Health as these scales included subsets of patients. Work included those who worked for pay and Reproductive Health included women only.

were lower (representing worse functioning) for those who continued ITP medication at week 24.

Post hoc repeated measures analysis employing GLM models using data pooled from the two trials confirmed that HRQoL benefits (differences in between-group change scores) of romiplostim occurred regardless of splenectomy status. The reported F- and P-values and associated least square means were generated upon comparing data from romiplostim- and placebo-treated patients (Table III). The results indicated that compared with placebo, romiplostim patients' experienced statistically significant improvements on seven of 10 ITP-PAQ Scales. Compared with placebo, the romiplostim-treated patients showed significantly greater improvement ($P < 0·05$) in HRQoL on three of four Physical Health Scales (Symptoms, Bother and Activity), on two of two Emotional Health Scales (Fear and Psychological) and on Social Activity and Women's Reproductive Health Scales (Menstrual Symptoms Subscale). No differences in improvement between romiplostim and placebo groups were found for Fatigue, Overall QoL, Work and Fertility. The addition of the parameter 'duration of ITP' into the GLM model did not affect these results. In general, AUC analyses confirmed the findings from the GLM with one exception (data not shown). That is, the romiplostim-treated patients showed significantly greater improvement than placebo in the Psychological Scale in the GLM analysis but not in the AUC analysis.

Discussion

Adult ITP is typically a chronic, persistent disorder. The goal of treatment is to minimize risks for bleeding, not cure (George *et al*, 1996). Current treatments are focused on decreasing the rate of platelet destruction by immunosuppression and splenectomy, and the risks of these treatments are substantial, often perceived by patients as being worse than the symptoms of ITP (George, 2006). Both the bleeding symptoms and side effects of the available treatments can have a negative impact on a patient's HRQoL.

It was hypothesized that treatment designed to increase platelet production may be effective and cause fewer side effects than therapies that decrease platelet production by suppressing the immune system or by blocking destruction of platelets by the spleen (e.g. corticosteroids, rituximab, immunoglobulin, anti-D and splenectomy) (Kuter, 2007). Romiplostim (previously AMG531) is a second generation, thrombopoietic growth and differentiation factor for megakaryocytes and platelets; treatment with romiplostim has resulted in sustained, increased platelet counts in both splenectomized and non-splenectomized adult patients with chronic ITP (Bussel *et al*, 2006; Kuter *et al*, 2008).

The current analysis utilized the ITP-PAQ, a disease-specific patient-reported outcome measure, to determine the HRQoL of adult patients with chronic ITP. Using data from two phase 3 clinical trials, we were able to both compare the HRQoL of splenectomized and non-splenectomized patients and to describe HRQoL improvements in ITP patients treated with romiplostim for a 24-week period.

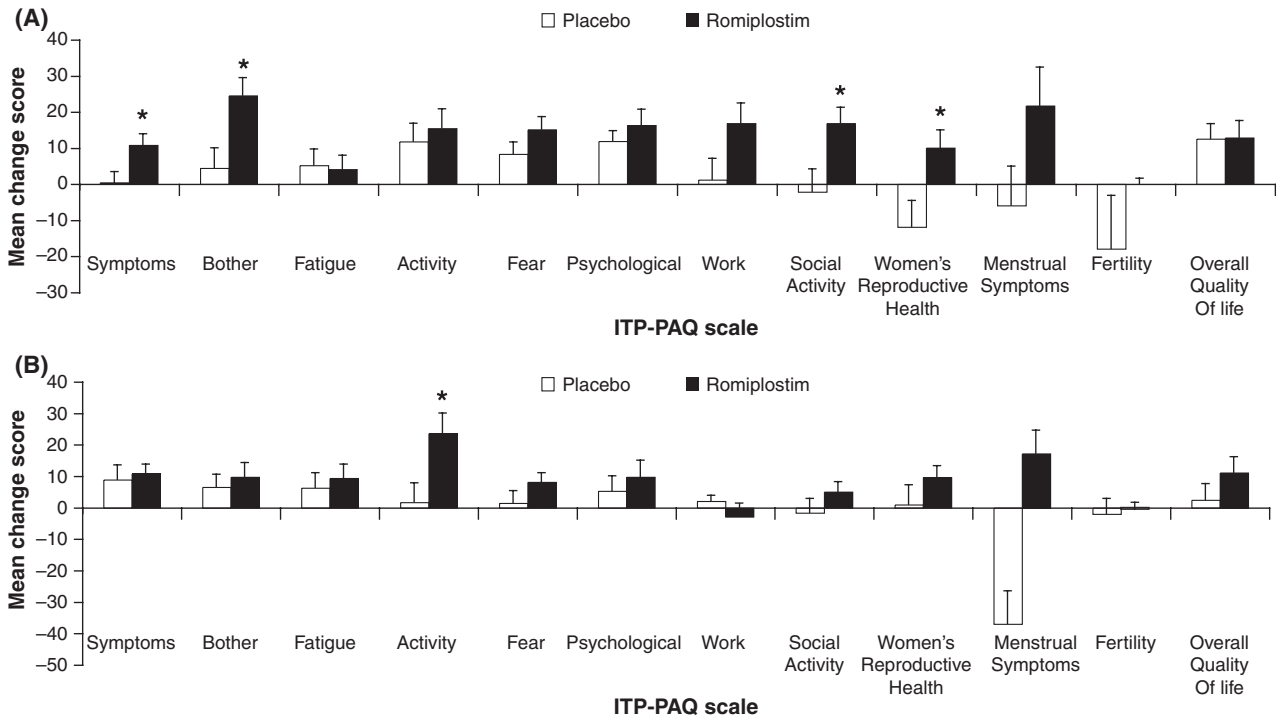

Fig 1. Mean immune thrombocytopenic purpura-patient assessment questionnaire (ITP-PAQ) change scores from baseline to week 24 for splenectomized (A) and non-splenectomized (B) patients. Error bars represent SE; Menstrual Symptoms and Fertility are subscales of the Women's Reproductive Health Scale; $^*P < 0{\cdot}05$.

Table III. Mean ITP-PAQ change scores from baseline to week 24 using GLM repeated measure mixed models and pooled data to compare romiplostim- ($n = 84$) and placebo-treated patients ($n = 41$).

ITP-PAQ Scale	*F*	*P*	Least square means estimate	Standard error
Symptoms	12·96	0·0005	7·48	2·08
Bother	10·52	0·002	8·94	2·76
Fatigue	0·40	0·53	1·78	2·83
Activity	6·04	0·016	8·52	3·47
Fear	12·90	0·0005	7·13	1·99
Psychological	4·25	0·042	5·71	2·77
Work	0·05	0·82	1·11	4·79
Social Activity	9·57	0·0025	9·66	3·12
Women's Reproductive Health	10·98	0·002	12·88	3·89
Menstrual Symptoms	17·07	0·0001	24·23	5·86
Fertility	0·01	0·90	0·39	3·40
Overall Quality of Life	1·82	0·18	4·14	3·07

ITP-PAQ, immune thrombocytopenic purpura-patient assessment questionnaire.

General linear models (GLM) analysis utilized ITP-PAQ data collected at baseline and weeks 4, 12 and 24.

Age, gender, splenectomy status and the use of baseline ITP medications were controlled for these analyses. *P* values <0·05 indicate that romiplostim-treated patients had significantly higher mean change scores (*F*-value) than the placebo-treated patients.

This study demonstrates that splenectomized patients have lower baseline HRQoL levels in many of the ITP-PAQ Scales when compared with non-splenectomized patients. Splenectomy for ITP results in durable complete remissions with normal platelet counts in two-thirds of patients (Kojouri *et al*, 2004). Patients who fail to respond to splenectomy such as the patients enroled in this study may have lower HRQoL levels because they have more severe and refractory disease compared with patients who have not required splenectomy. Also the splenectomized patients enroled in this study had ITP for a significantly longer duration than non-splenectomized patients, which may also contribute to their significantly worse HRQoL.

This is the first double-blind, placebo-controlled study to quantify HRQoL improvements resulting from therapy in ITP patients. Romiplostim therapy for 24 weeks resulted in HRQoL improvements in seven of the 10 ITP-PAQ Scales. It is important to note that HRQoL improvements could be the result of the reduction in concomitant therapy (e.g. corticosteroids, azathioprine or danazol) that have the potential for negative side effects. A reduction in these concomitant ITP therapies after 24 weeks of romiplostim has been reported previously (Kuter *et al*, 2008).

Although fatigue is commonly described by patients with ITP, and it was prominent among the issues raised by the focus groups of ITP patients in the development of the ITP-PAQ (Mathias *et al*, 2008), our data did not document

improvement of fatigue among patients responding to romiplostim. This may be because the duration of the study was relatively short, the number of patients was small and fatigue is a difficult symptom to isolate and quantify. The issue of fatigue in ITP and improvement of fatigue in response to ITP therapy requires further investigation with larger and more focused studies.

Romiplostim therapy improved HRQoL in a greater number of ITP-PAQ Scales for splenectomized patients than non-splenectomized patients. This may be related to the lower baseline scale scores (Symptoms, Bother, Fear, Psychological Health, Work, Social Activity, Overall QoL) of splenectomized patients, providing the opportunity for more improvement of HRQoL scores.

The significant improvement of HRQoL scores was assumed to be related to the previously reported increase in patients' platelet count following romiplostim therapy (Kuter *et al*, 2008). Our analysis of HRQoL could not examine a correlation between level of platelet response and benefit because platelet counts within the target range were often not steady over the course of treatment. In addition, the greater improvement of HRQoL scores in splenectomized patients is not due to a greater platelet count response because both splenectomized and non-splenectomized patients had similar responses to romiplostim (Kuter *et al*, 2008). Therefore, our analysis focused on overall responders. A significant correlation between HRQoL improvement and durable platelet response could only be documented for two individual ITP-PAQ Scales (Bother and Psychological Health). Upon examining the correlation of ITP-PAQ change scores to overall responders (durable and transient), we observed a significant correlation in three ITP-PAQ Scales (Bother, Social Activity and Women's Reproductive Health). Larger studies may help to determine whether improvement of HRQoL correlates with the achievement of a platelet count response.

There were several inherent limitations in this research. The sample size in each group was relatively small, limiting the statistical power to detect changes over time. The duration of the trial was relatively short, especially considering that ITP is a chronic condition that requires long-term therapy to maintain platelet counts in a safe range. In addition, due to a lack of long-term safety data, the extent of HRQoL increases may be less than expected in certain scales because patients may worry about the long-term consequences of receiving an investigational agent. Ongoing larger and longer term studies should address these limitations.

In conclusion, adult patients with chronic ITP have important problems of health and daily life in addition to bleeding symptoms caused by their thrombocytopenia. Effective treatment demonstrated in this study by romiplostim therapy can improve the function and well-being for adult patients with chronic ITP. Further, the utility of the ITP-PAQ has been exhibited in this controlled study as a tool that can be implemented to measure HRQoL in future ITP therapy trials.

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Disclosure

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