A pilot randomized trial of adjuvant rituximab or placebo for non-splenectomized patients with immune thrombocytopenia

Running Title: Randomized trial of Rituximab in ITP

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Abstract

The benefit of adding rituximab to standard treatment in non-splenectomized patients with primary immune thrombocytopenia (ITP) is uncertain. We performed a pilot randomized trial to determine the feasibility of recruitment, protocol adherence and blinding of a larger trial of rituximab versus placebo; and to evaluate the potential efficacy of adjuvant rituximab in ITP. Non-splenectomized adults with newly-diagnosed or relapsed ITP who were receiving standard ITP therapy for a platelet count below 30 x10^9/L were randomly allocated to receive four weekly infusions of 375 mg/m^2 rituximab or saline placebo. Sixty patients were recruited over 46 months, which was slower than anticipated. Protocol adherence and follow-up targets were achieved and blinding was successful for research staff but not for patients. After 6 months, there was no difference between rituximab and placebo groups for the composite outcome of any platelet count below 50 x10^9/L, significant bleeding or rescue treatment once standard treatment was stopped [21/32 (65.6%) vs. 21/26 (80.8%); relative risk=0.81, 95% confidence intervals 0.59, 1.11]. Timely accrual poses a challenge to the conduct of a large randomized trial of rituximab for pre-splenectomy ITP. No difference in the frequency of the composite outcome was observed in this pilot trial (registered at www.clinicaltrials.gov NCT00372892).
Introduction

Primary immune thrombocytopenia (ITP) is a common autoimmune disease characterized by low platelet counts and an increased risk of bleeding. Most adults with acute ITP will achieve an initial platelet count response to corticosteroid-based treatments; however, relapses are common within the first year and additional treatments including splenectomy are frequently required1,2. Aggressive treatment early in the course of the disease may prevent the development of chronic thrombocytopenia and its associated morbidities3 and can reduce or avoid toxicities from prolonged corticosteroid exposure.

Rituximab has been associated with any platelet count response in approximately 60% of ITP patients4 and may avert the need for splenectomy5. Sustained responses are rare, but have been reported to occur in one-quarter6 to one-third7 of patients after 12 and 57 months, respectively. In observational studies, patients with a longer duration of ITP were less likely to respond to rituximab8 suggesting that early treatment may be more effective. One randomized trial reported improved platelet count responses with early rituximab plus dexamethasone compared with dexamethasone alone9. Additional randomized trials are needed to evaluate clinical endpoints and accommodate the variability in standard treatments.

This pilot randomized trial was designed to test the feasibility of recruitment, protocol adherence and blinding while evaluating the effect of rituximab on the
frequency of treatment failure once standard therapy was discontinued. In particular, clinical endpoints were: 1) the frequency of any platelet count below 50 x10^9/L; 2) significant bleeding; or 3) need for rescue treatment. The criteria for deeming this pilot trial a success were: 1) recruitment of 60 patients in 12 months; 2) administration of all study drug infusions to at least 54 of 60 (90%) patients; 3) achievement of complete follow-up for at least 50 of 60 (83%) patients and 4) successful blinding of patients and research staff. Blinding was considered successful if the proportion of correct guesses at treatment allocation was no different than what could be attributed to chance.

**Materials and Methods**

*Study Design*

We conducted a randomized, concealed, blinded, placebo-controlled trial in 7 centers in Canada.

*Patients*

Eligible patients were non-splenectomized adults 18 to 80 years of age with newly-diagnosed or relapsed primary ITP who had a platelet count below 30 x10^9/L and had begun standard treatment at the discretion of their physician. Relapsed ITP was defined as the recurrence of thrombocytopenia (platelet count below 30 x10^9/L) after a previous response to therapy lasting at least 1 month. Exclusion criteria were: any treatment for ITP within 30 days before starting standard treatment; previous treatment with rituximab; significant cardiac,
pulmonary or liver disease; uncontrolled hypertension; venous or arterial thrombosis in the preceding year; acute infection; serological evidence of human immune deficiency virus, hepatitis C, or active or remote hepatitis B infection; use of anticoagulants or anti-platelet medications; and pregnancy or lactation. All patients provided written informed consent.

Study procedures
Using a centralized electronic system, local research pharmacists randomly assigned patients to receive intravenous rituximab 375 mg/m² or saline placebo once per week for 4 consecutive weeks. Randomization was stratified by center and ITP stage (newly-diagnosed or relapsed) in a 1:1 ratio using undisclosed blocks of 2 to 6. Patients were randomized within 30 days of starting standard treatment and followed for 6 months from randomization. Standard treatment was permitted for up to 8 weeks to accommodate the use of oral prednisone taper and allow sufficient time for the onset of rituximab; thereafter, the occurrence of any of a platelet count below 50 x10⁹/L, significant bleeding or rescue treatment was considered a treatment failure. Each study drug infusion was administered using a standard volume-based rate escalation protocol preceded by the administration of hydrocortisone 100mg intravenously, diphenhydramine 50mg orally or intravenously and acetaminophen 650mg orally to minimize infusion-related reactions and avoid unblinding.

Outcomes
The primary efficacy outcome was treatment failure, defined as the composite of:
1) any platelet count below \(50 \times 10^9/L\); 2) significant bleeding, defined as grade 2 severity from any anatomical site as per the ITP Bleeding Scale\(^{11}\), which defines bleed grades (0, none; 1, mild; or 2, marked) by objective criteria at each of 9 anatomical sites based on events that occurred since the last study visit; or 3) rescue treatment administered because of severe thrombocytopenia, bleeding or a planned invasive procedure. Secondary efficacy outcomes were quality of life measured using the Medical Outcomes Study Short Form 36 (SF-36)\(^{12}\); proportion of patients with a complete platelet count response (platelet count of \(100 \times 10^9/L\) or greater) and overall platelet count response (platelet count of \(30 \times 10^9/L\) or greater with doubling from baseline) without rescue treatment at 6 months (these definitions were amended from the original protocol to comply with 2009 consensus recommendations\(^{10}\)). Additional laboratory outcomes were: change in CD19-positive lymphocytes by flow cytometry and levels of immunoglobulin (Ig)G, IgA and IgM by nephelometry at baseline, 1 month, 3 months and 6 months after the first study drug infusion. Research staff were blinded to CD19 results. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (Version 3)\(^{13}\).

**Study oversight**

The protocol was approved by the research ethics board at each participating center and by Health Canada. The methods centre was the McMaster Transfusion Research Program in Hamilton Ontario.
Statistical Analysis

Data from patients were analyzed by study-group assignment using the intention-to-treat principal. Relative risks with 95% confidence limits were calculated for the composite endpoint and each of its components. Kaplan Meier curves were used to estimate the distribution of the time to treatment failure and Cox regression analysis was used to calculate hazard ratios with 95% confidence intervals. The difference in mean platelet counts between groups was calculated in a post-hoc analysis using a mixed model taking into account repeated platelet count measures and adjusted for baseline platelet counts at the time of randomization. Change scores for quality of life measures were analyzed using ANCOVA adjusting for baseline scores. All analyses were carried out using SAS 9.2 (SAS institute, Cary, NC). A convenient sample size of 60 patients was felt to be adequate to address the feasibility objectives.

Role of the funding source

This was an investigator-initiated trial funded by Hoffmann-LaRoche. The investigators were responsible for design and oversight of the trial, analysis and interpretation of the data and writing the protocol and manuscript. Study drug was provided by the funder who had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation or approval of the manuscript or decision to publish the data.
Results

Between October 2006 and July 2010, 126 patients were approached for participation in the trial and 60 patients were randomized (Figure 1). Reasons for slow accrual were a high number of refusals (N=53) and exclusions for hepatitis B core antibody seropositivity (N=8). Two patients (1 in each group) withdrew consent before receiving a single study drug infusion and were not evaluable for responses. Four additional patients (3 were in the placebo group) either withdrew consent or could not be located; their data were included up to the point of last follow-up.

Thirty-three patients were allocated to receive rituximab and 27 were allocated to placebo. Baseline characteristics were balanced between groups (Table 1). Median age for the cohort was 40 years [interquartile range (IQR), 30.5 – 59.0] and 58% were female. Median baseline platelet count was 15 x10^9/L (IQR, 9 – 23) and patients had ITP for a median of 1 year (IQR, 0 – 3.5) prior to randomization. Median duration of ITP among newly-diagnosed patients (N=28) and relapsed patients (N=32) was 1.0 month (1.0 – 1.5) and 36.0 months (7.5 – 90.0), respectively. All patients received standard treatment which consisted of corticosteroids, intravenous immune globulin (IVIg), rhesus immune globulin, romiplostim and/or platelet transfusions.

Protocol adherence targets were achieved since 57 (95%) of 60 patients received all study drug infusions and follow-up was complete for 52 (86.7%) of 60
patients, although one or more scheduled visits was missed by 6 (11.5%) of the 52 patients. Blinding success, measured after the administration of four study drug infusions, was achieved for study investigators, research coordinators and infusion nurses; however patients guessed correctly at treatment allocation more often than could be attributed to chance [proportion of correct guesses = 35/50 (70%); 95% CI 57% – 83%].

Twenty-one (65.6%) of 32 patients assigned to rituximab and 21 (80.8%) of 26 patients assigned to placebo met the composite endpoint of treatment failure [relative risk (RR) = 0.81, 95% CI 0.59-1.11] (Table 2). Proportions of patients meeting each of the components of the composite outcome were also similar between groups. No difference was detected in the event-free distribution of patients who received rituximab compared to placebo (p=0.12; Figure 2); hazard ratio in the rituximab group = 0.65; 95% CI 0.35-1.19. Rescue treatments consisted of prednisone, dexamethasone, IVIg and rhesus immune globulin for the majority of patients who received them; others received azathioprine, danazol, romiplostim and platelet transfusion. Two patients in the placebo group underwent splenectomy.

Bleeding events were common in both groups, especially skin petechiae, oral purpura and epistaxis. Patients with grade 1 (minor) and grade 2 (significant) bleeding from each anatomical site are shown in Table 3. Using the SF-36, no treatment effect was found for change in quality of life summary scores for
physical (p=0.45) or mental (p= 0.32) domains when controlling for baseline scores.

Mean platelet counts were higher in patients receiving rituximab than patients receiving placebo without the use of rescue treatment (p<0.0001) (Figure 3). At 6 months, complete platelet count response (CR) was achieved by 17 (53.1%) patients in the rituximab group and 12 (46.2%) patients on placebo (RR= 1.15, 95% CI 0.68, 1.95). Overall platelet count response was achieved by 20 (62.5%) and 19 (73.1%) patients in the rituximab and placebo groups respectively (RR= 0.86, 95% CI 0.60, 1.22).

The percentage of CD19-positive lymphocytes decreased to undetectable levels by one month after rituximab infusions (from 11.2% to <0.1%) and began to repopulate at 6 months. No change in CD19-positive lymphocytes was observed in patients receiving placebo except for a slight decrease at 3 months relative to baseline values (from 12% to 8.5%). In the rituximab group, mean IgG and IgM levels at 6 months were significantly lower than baseline although values remained within the normal reference range (IgG 9.17 g/L; IgM 1.34 g/L). Those receiving placebo had a transient decrease in IgG levels at 1 month compared to baseline although mean values remained within the normal reference range (mean IgG, 9.61 g/L).
Two serious adverse events were reported in patients receiving rituximab and 1 serious adverse event was reported in patients receiving placebo (Table 4). Twenty infusion-related events were reported in the rituximab group including sore throat, nasal congestion, cough, pruritus, skin rash, chest pain and dyspnea. Ten such events were reported in patients receiving placebo including dyspnea and rigors.

Discussion

This pilot randomized trial of rituximab or placebo for non-splenectomized adults with newly-diagnosed or relapsed primary ITP demonstrated that a larger trial is feasible, although accrual and patient blinding pose logistical challenges. Statistically significant differences were not observed between groups for the proportion of patients meeting criteria for treatment failure, although the direction of the treatment effect favored rituximab. Mild adverse events were common with rituximab and one patient discontinued treatment due to serum sickness.

The rate of accrual in this trial was slower than expected for several reasons. First, the rate of refusals was high [53/126 (42.1%)], often because patients were unwilling to be randomized to placebo. Second, we noticed an unexpected number of patients with hepatitis B core antibodies, which we later learned were often passively transferred from IVIg infusions used as standard treatment\textsuperscript{14}. Finally, during the course of the trial, the use of rituximab off-label to treat ITP increased significantly\textsuperscript{15} further compromising enrolment. These barriers to
accrual pose challenges for the successful conduct of future trials of rituximab in ITP.

In an attempt to mask interventions, we used a saline placebo and universal premedication before each infusion. We observed that blinding was successful for research staff but not for patients, possibly as a result of minor infusional reactions. Despite previous recommendations to evaluate the success of blinding in clinical trials\textsuperscript{16}, the value of such assessments has recently been challenged because of unavoidable confounding due to pre-conceived beliefs about efficacy and harms of treatment\textsuperscript{17}. Nevertheless, difficulties in maintaining patient blinding in an ITP trial of rituximab may impact future trials that incorporate subjective outcomes such as patient-reported bleeding severity\textsuperscript{18}. We anticipate that any effect of hydrocortisone predmedication on platelet count and/or bleeding would have been equal in both groups.

We enrolled both newly-diagnosed and relapsed patients prior to splenectomy. This avoided over-treating some patients who may have undergone spontaneous remission but captured others at a more advanced stage of illness\textsuperscript{19}, potentially diluting the effect of rituximab. On balance, this study population reflected a realistic application of rituximab in the sequence of ITP treatments recognizing existing variability in practices.
This is one of the first ITP trials to capture global impairments in hemostasis using a composite outcome that incorporates both laboratory endpoints (platelet counts) and clinical endpoints that are meaningful to patients (bleeding and rescue treatment)\textsuperscript{20}. Most trial-related events were due to platelet count criteria, followed by rescue treatment and bleeding. Differences in the frequencies of each of these components challenge the interpretation of a composite outcome in future ITP trials\textsuperscript{21}; however, the suitability of the singular use of any of the individual components as a primary outcome is also problematic. For example, the platelet count is a surrogate endpoint that reflects disease activity but lacks a stable correlation with clinical events; thresholds for initiating rescue treatment may be subjective and dependent on other determinants; and a trial powered to detect differences in serious bleeding would be very large and possibly unfeasible\textsuperscript{22}.

The endpoints in this trial were meant to reflect a conservative assessment of treatment failure. In the groups of patients with first-events attributable to thrombocytopenia (n=23), rescue treatment (n=16) and bleeding (n=3), the median lowest platelet counts were 15 x10\textsuperscript{9}/L, 32 x10\textsuperscript{9}/L and 224 x10\textsuperscript{9}/L respectively. Six of those events – 3 in the placebo group and 3 in the rituximab group – occurred despite normal platelet counts: 3 rescue treatments were prednisone tapers beyond the first 8 weeks; and 3 bleeding events were grade 2 menstrual bleeding (n=2) or epistaxis (n=1). Besides assessing feasibility, this pilot trial helped to uncover challenges with current outcome measures.
commonly used in ITP trials. Appropriate outcomes, taking into account clinical and platelet count criteria, require careful consideration.

In this study, CR (platelets >100 x10^9/L) at 6 months was observed in 12 (46.2%) of 26 patients after standard treatment alone: 10 patients received prednisone, one patient received 2 cycles of dexamethasone and IVIg and one patient received dexamethasone, prednisone, IVIg and romiplostim. Three large ITP cohort studies that used similar outcomes reported rates of CR following corticosteroid-based therapy of 31/124 (25%) at 2 months, 61/115 (53.0%) at 3 months and 209/689 (30.3%) after a median follow-up of 36 months. The control rate of CR we observed was somewhat higher than expected, possibly because standard treatments were intensified during the initial 8 week period, or because previous cohort studies may have included a greater case mix of patients. In a previous randomized trial of rituximab, the rate of CR among controls (who received one course of dexamethasone) was 17/52 (32.7%); however, the total dose of corticosteroid was less than most standard therapies.

Previous studies in ITP have shown that rituximab can modify disease activity. Evidence–based guidelines offer a Grade 2C recommendation for its use for patients who have failed corticosteroids, IVIg or splenectomy and expert consensus suggests that rituximab may be a reasonable second-line option. In a systematic review of 19 observational studies enrolling 313 patients of whom 46.2% were not splenectomized, rates of complete (platelet count >150 x10^9/L)
and overall (platelet count >50 x10⁹/L) responses with rituximab were 43.6% (95% CI, 29.5% to 57.7%) and 62.5% (CI, 52.6% to 72.5%), respectively, after a median follow up of 9.5 months⁴. In those reports, 9 patients (2.9%) died. Median time to response was 5.5 weeks and responses lasted a median of 10.5 months. In a prospective observational study of 60 adults with ITP, 24 (40%) achieved a platelet count above 50 x10⁹/L and at least twice their inclusion value at 1 year and 20 (33%) maintained their platelet count response at 2 years⁵. In one previous randomized trial of rituximab plus dexamethasone or dexamethasone alone for treatment-naïve ITP patients, a platelet count of 50 x10⁹/L or higher after 6 months without rescue treatment was achieved by 31/49 (63%) patients in the rituximab group compared with 19/52 (36%) controls (absolute risk reduction 27%; 95% CI 8% - 46%)⁹. The trial was stopped prematurely because of the large treatment effect; however, bleeding was not assessed and over half of the patients did not complete follow-up. Our trial did not protocolize standard treatment, reflecting current practice variability and we recorded bleeding as part of the primary composite efficacy outcome. Our results suggest that the treatment effect with rituximab in the setting of new and relapsed disease may not be as large as previously suggested.

Strengths of this trial were the randomized allocation, attempts to blind all persons involved, the use of clinical and laboratory endpoints and the incorporation of a validated ITP bleeding tool. We accommodated variability in choice and duration of standard treatments to enhance generalizability of the
results and had high rates of follow-up. Limitations were the sample size which was insufficient to detect a difference in efficacy and the relatively short evaluation period.

Further research is needed to establish the efficacy and safety of rituximab for non-splenectomized patients with ITP. A large randomized trial would require many centers and commitment from investigators and patients to ensure timely recruitment. For uncommon conditions and rare side effects, alternative methods of comparative effectiveness research may be useful including retrospective analyses of existing clinical or administrative databases and longitudinal registries. Given barriers to a large future trial, including the challenges we identified and the increasing use of rituximab for this condition, our findings, while limited by wide confidence limits, represent the best available estimates of the effects of rituximab on clinical and platelet-count endpoints in this population.
Acknowledgements

Principal Investigator: Donald Arnold; Steering Committee: Mark Crowther, Nancy Heddle, John Kelton, Richard Cook, Ralph Meyer, Anne McLeod; Data Safety Monitoring Board: Tom Kouroukis, James George, Lehana Thabane, Dean Fergusson; Methods Center (McMaster Transfusion Research Program): Julie Carruthers, Yang Liu, Aicha Traore, Laura Molnar, Luqi Wang. D. Arnold had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

We thank the Research Coordinators Lianna Butler, Ruth Cameron (Hamilton); Martha Lenis, Deborah Sanfelice (Toronto); Elizabeth Chatelain (Ottawa); Susan Janke, Carla Girolametto, Kelly Walker (Grand River); Laura Meraw, Darlene TenHaaf (London); Evani Goll, Boris Feldman, Luke Tse (Vancouver); Lisa Gray, Blaine Gallant, Susan Pleasance (Halifax); the study pharmacists: Gita Sobhi and the McMaster University Medical Centre pharmacy team (Hamilton); Mara Pavan (Vancouver); Jeff Doi (Toronto); Theresa Rooney (London); Anne Marie Dugal (Ottawa); Anna Granic (Grand River); and the patients for their commitment.

Financial support: This was an investigator-initiated study funded by Hoffmann-LaRoche. D. Arnold holds a New Investigator Award from Canadian Institutes for Health Research in partnership with Hoffmann-LaRoche. M. Crowther holds the Leo Pharma Chair in Thromboembolism Research at McMaster University. D Cook is a Canada Research Chair in Critical Care. R. Cook is a Canada Research Chair in Statistical Methods for Health Research. Dr Crowther is a Career Investigator of the Heart and Stroke Foundation of Canada, and holds the Leo Pharma Chair in Thromboembolism Research at McMaster University.

Author contributions

D. Arnold designed and performed the research, contributed data, analyzed data and wrote the paper. N. Heddle designed and performed the research, analyzed the data and critically edited the paper. J. Carruthers performed the research, analyzed the data and critically edited the paper. D. Cook designed the research, analyzed the data and critically edited the paper. M. Crowther designed the research, analyzed the data and critically edited the paper. R. Meyer designed the research, analyzed the data and critically edited the paper. Y. Liu analyzed the data and critically edited the paper. R. Cook designed the research, analyzed the data and critically edited the paper. A. McLeod designed and performed the research, contributed data, analyzed the data and critically edited the paper. J. MacEachern performed the research, contributed data, analyzed the data and critically edited the paper. J. Mangel performed the research, contributed data, analyzed the data and critically edited the paper. D. Anderson performed the research, contributed data, analyzed the data and critically edited the paper. L.
Vickars performed the research, contributed data, analyzed the data and critically edited the paper. A. Tinmouth performed the research, contributed data, analyzed the data and critically edited the paper. A. Schuh performed the research, contributed data, analyzed the data and critically edited the paper. J. Kelton designed and performed the research, contributed data, analyzed data and wrote the paper. All authors provided final approval for the paper to be published.

Conflict of interest statement

D. Arnold: Research funding (Roche, Amgen, GlaxoSmithKline); advisory board member (Amgen, GlaxoSmithKline); consultancy (Amgen); speaking honoraria (Roche, Amgen, GlaxoSmithKline, Talecris); travel to meeting (Amgen).

J. Kelton: Research funding (Roche, Amgen); advisory board member and chair (Amgen, GlaxoSmithKline).

A. McLeod: Research funding (Sanofi Aventis, Bayer Healthcare, Boehringer-Ingelheim) advisory board member (Amgen, Sanofi Aventis)

R. Meyer: Research Funding: Dr. Meyer is Director of the NCIC CTG Clinical Trials Group which has received research funding from Amgen Canada, Ariad Pharmaceuticals, Astex Therapeutics, Astra Zeneca, Bristol-Myers Squibb, Celgene, Lilly, GlaxoSmithKline, Janssen-Ortho, Merck Fosst Canada, Novartis, Oncothyreon, Orthobiotech, Pfizer, Roche, S*Bio Ptd Ltd, Sanofi-Aventis, Schering Canada, Zymogenetics; Honoraria (Celgene, Lilly).

A. Tinmouth: advisory board member (Amgen, GlaxoSmithKline, Novartis, Bayer).

M. Crowther: Advisory board member (Bayer, BI, Pfizer, Leo Pharma, Alexion, Artisan, CSL Behring); Research funding (Bayer, Pfizer, Leo Pharma, Octapharma); Expert testimony (Bayer, CSL Behring); Educational materials (Pfizer, Octapharma, CSL Behring)

Reference List


(21) Heddle NM, Cook RJ. Composite outcomes in clinical trials: what are they and when should they be used? *Transfusion* 2011;51(1):11-3.


Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Rituximab (N=33)</th>
<th>Placebo (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females (N, %)</strong></td>
<td>19 (57.6)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td><strong>Age (median, IQR)</strong></td>
<td>40 (30 – 59)</td>
<td>40 (31 – 59)</td>
</tr>
<tr>
<td><strong>ITP stage (N, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly-diagnosed</td>
<td>17 (51.5)</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>Relapsed</td>
<td>16 (48.5)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td><strong>Duration of ITP (months)</strong></td>
<td>3 (1 – 47)</td>
<td>8 (1 – 40)</td>
</tr>
<tr>
<td>(median, IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline platelet count (x10^9/L)</strong></td>
<td>15 (4 – 23)</td>
<td>14 (10 – 23)</td>
</tr>
<tr>
<td>(median, IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard treatments (N, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>18 (54.5)</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>13 (39.4)</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>IVIg</td>
<td>13 (39.4)</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>RhIg</td>
<td>2 (6.1)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Solumedrol</td>
<td>2 (6.1)</td>
<td>0</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>2 (6.1)</td>
<td>0</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>0</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Platelet transfusions</td>
<td>1 (3.0)</td>
<td>0</td>
</tr>
<tr>
<td>Combination</td>
<td>11 (33.3)</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td><strong>Evaluation period (days)</strong></td>
<td>138 (130-144)</td>
<td>137 (114-142)</td>
</tr>
<tr>
<td>(median, IQR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IQR = interquartile range; IVIg = intravenous immune globulin; RhIg = rhesus immune globulin. * Evaluation period was from the completion of standard treatment (8 weeks from the start of standard treatment) until the end of follow-up (6 months from randomization).
### Table 2. Clinical and laboratory endpoints.

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Rituximab (n=32)</th>
<th>Placebo (n=26)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy endpoints (at any time)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure (composite)*</td>
<td>21 (65.6)</td>
<td>21 (80.8)</td>
<td>0.81 (0.59, 1.11)</td>
</tr>
<tr>
<td>Any platelet count below 50 x10^9/L</td>
<td>17 (53.1)</td>
<td>16 (61.5)</td>
<td>0.86 (0.55, 1.35)</td>
</tr>
<tr>
<td>Rescue treatment</td>
<td>14 (43.8)</td>
<td>17 (65.4)</td>
<td>0.67 (0.41, 1.08)</td>
</tr>
<tr>
<td>Significant bleeding†</td>
<td>7 (21.9)</td>
<td>6 (23.1)</td>
<td>0.95 (0.36, 2.48)</td>
</tr>
<tr>
<td><strong>Platelet count endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete platelet count response‡</td>
<td>17 (53.1)</td>
<td>12 (46.2)</td>
<td>1.15 (0.68, 1.95)</td>
</tr>
<tr>
<td>Overall platelet count response¶</td>
<td>20 (62.5)</td>
<td>19 (73.1)</td>
<td>0.86 (0.60, 1.22)</td>
</tr>
<tr>
<td>Mean platelet count without rescue treatment (mean)</td>
<td>131 x10^9/L</td>
<td>96 x10^9/L</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

RR= relative risk; OR= odds ratio. *Proportion of patients with any platelet count below 50 x10^9/L, rescue treatment or significant bleeding (primary efficacy endpoint). †Significant bleeding was defined as bleeding grade 2 from any anatomical site as defined by the ITP Bleeding Score. ‡Complete response = platelet count above 100 x10^9/L at 6 months without rescue treatment. ¶Overall response = platelet count above 30 x10^9/L and doubling from baseline at 6 months without rescue treatment.
Table 3. Patients with grade 1 (minor) and grade 2 (significant) bleeding during the trial, as measured by research coordinators using the ITP Bleeding Score11.

<table>
<thead>
<tr>
<th></th>
<th>Grade 1 bleeding</th>
<th>Grade 2 bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rituximab (n=32)</td>
<td>Placebo (n=26)</td>
</tr>
<tr>
<td></td>
<td>Rituximab (n=32)</td>
<td>Placebo (n=26)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 (53.1%)</td>
<td>12 (46.2%)</td>
<td>3 (9.4%)</td>
</tr>
<tr>
<td>Oral</td>
<td>4 (12.5%)</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5 (15.6%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1 (3.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>0</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Gynecological</td>
<td>2 (6.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Ocular</td>
<td>1 (3.1%)</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 4. Adverse events reported in the rituximab and placebo groups.

<table>
<thead>
<tr>
<th>Event</th>
<th>Rituximab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events*</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infusion reactions†</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Other‡</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total adverse events reported</strong></td>
<td><strong>76</strong></td>
<td><strong>53</strong></td>
</tr>
</tbody>
</table>

*Two serious adverse events in the rituximab group were serum sickness and accidental fall; and one serious adverse event in the placebo group was adrenal hemorrhage. †Infusion reactions were adverse events that were temporally related to study drug infusions. ‡Occurred in fewer than 5% of patients.
Figure legends

**Figure 1.** Patient flow

**Figure 2.** Time to composite outcome (platelet count less than 50 x10⁹/L, significant bleeding or rescue treatment) among patients receiving rituximab (solid line) or placebo (dashed line) plus standard treatment. X-axis is time in observation period once standard treatment was discontinued.

**Figure 3.** Mean (+/- standard error) platelet counts for rituximab (solid line) and placebo (dashed line) plus standard treatment without rescue treatment.
Figure 1. Study Flow.

Non-splenectomized patients with newly diagnosed or relapsed ITP (N = 126)

Patient refusals prior to screening (N = 53)
- Unwilling to accept rituximab (N = 15)
- Unwilling to accept placebo (N = 10)
- Geographic inaccessibility (N = 5)
- Chose other treatments (N = 5)
- Too ill to participate (N = 2)
- Time requirement too great (N = 3)
- No reason identified (N = 13)

Consenting patients (N = 73)

Screen failures (N = 13)*
- HBcAb seropositivity (N = 8)
- Platelets not less than 30x10^9/L (N = 2)
- Active infection (N = 1)
- Elevated creatinine (N = 1)
- Angina (N = 1)
- Elevated liver enzymes (N = 1)
- HIV infection (N = 1)

Randomized (N = 60)

Allocated to rituximab (N = 33)
- Consent withdrawn before any study drug infusion (N = 1)

Consent withdrawn (N = 1), but data used up until time of last follow-up.

Allocated to placebo (N = 27)
- Consent withdrawn before any study drug infusion (N = 1)

Incomplete follow-up:
- Unable to contact (N = 2)
- Consent withdrawn (N = 1)
- Censored at time of splenectomy (N = 2)
- Data used up until last follow-up.

Analyzed (N = 32)

Analyzed (N = 26)

*Some patients had more than one reason for exclusion.
A pilot randomized trial of adjuvant rituximab or placebo for non-splenectomized patients with immune thrombocytopenia

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