Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura – results of a prospective multicenter phase 2 study

Running Title: Rituximab for Chronic ITP in Nonsplenectomized Adults

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The Établissement Français du Sang was the trial promoter and Roche France, provided an open grant.

Preliminary results of this study were presented, in part, during an oral communication delivered at the December 2006 meeting of the American Society of Hematology, Orlando, FL.

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Abstract

Whether rituximab could effectively and safely avoid splenectomy for adults with chronic immune thrombocytic purpura (ITP) remains unresolved. A multicenter, prospective, open-label, single-arm, phase 2 trial was conducted to assess rituximab safety and efficacy in adult splenectomy candidates with chronic ITP. Sixty patients with chronic (≥6 months) ITP and platelet counts <30x10⁹/L received a weekly intravenous infusion of rituximab (375 mg/m²) for 4 weeks. All other ITP treatments were stopped. A good response was defined as a platelet count ≥50x10⁹/L, with at least a doubling of the initial value at 1 and 2 years after the first rituximab infusion. Patients who required another treatment during follow-up were considered nonresponders. Sixteen patients experienced transient side effects that necessitated treatment discontinuation for only 1. Good 1-year responses were obtained in 40% of the patients (24/60 [95% confidence interval: 28–52%]). At 2 years, 33.3% (20/60 patients) had good responses and 6.7% (4/60) has sustained platelet counts ≥30x10⁹/L without treatment. Thirty-six (60%) patients failed to respond; 25 of them underwent splenectomy. Based on these results, rituximab was an apparently safe and effective splenectomy-avoiding option in some adults with chronic ITP. This trial is registered at http://clinicaltrials.gov as NCT00225875.
Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by low platelet counts and may be responsible for mucocutaneous bleeding of variable severity.\textsuperscript{1} ITP is usually chronic (>6 months) in adults and, after this time, the probability of spontaneous remission is low. Standard management is to initiate steroids, anti-Rh\textsubscript{0}(D) immune globulins and/or intravenous immunoglobulins (IVIg) for the more severe forms.\textsuperscript{2-5} The response rate is high but most often transient. That the spleen plays a major role in the removal of damaged platelets has long been known and, to date, splenectomy is still considered the ‘gold standard’ treatment in many countries for the management of chronic ITP with platelet counts <30x10\textsuperscript{9}/L, especially when hemorrhagic complications are present. About two-thirds of chronic ITP patients who undergo splenectomy achieve lasting responses.\textsuperscript{6} As suggested in the guidelines of the American Society of Hematology (ASH)\textsuperscript{7} and the British Committee for Standards in Haematology (BCSH),\textsuperscript{8} splenectomy should be considered the main second-line therapy for patients who fail to respond durably to first-line therapy, with persistent platelet counts <30x10\textsuperscript{9}/L. However, increasing numbers of patients are reluctant to undergo splenectomy and physicians are hesitant to recommend it.\textsuperscript{9,10} In addition, the risk of overwhelming post-splenectomy infections, although rare, is not predictable and represents a major concern.\textsuperscript{11-13} Moreover, some authors reported that, despite initial good responses to splenectomy, the risk of late relapse persists during long-term follow-up\textsuperscript{14,15} and severe morbidity resulting from surgery is associated with 11–30\% postoperative complications requiring prolonged hospitalization or re-admission.\textsuperscript{11,16} For these reasons, an effective and safe alternative to splenectomy would improve management of chronic ITP.

Rituximab is a chimeric, humanized monoclonal antibody directed against the CD20 determinant on B cells. It was initially developed for the treatment of malignant lymphoma but has also been used in autoantibody-mediated disorders, such as rheumatoid arthritis,\textsuperscript{17} systemic lupus erythematosus,\textsuperscript{18} autoimmune hemolytic anemia,\textsuperscript{19} or thrombotic
thrombocytopenic purpura. Case reports and several uncontrolled studies described its promising results in ITP patients. Arnold et al. conducted a systematic review of published reports on rituximab use in adults with chronic ITP. A complete response, usually observed 3–8 weeks after the first infusion, was obtained in 46% of patients. The median response duration was 10.5 months (interquartile range (IQR): 6.3–17.8 months) but long-term responses were not mentioned in all published studies. Arnold et al. pointed out the heterogeneity of patients’ prior rituximab use and particularly their splenectomy status. Moreover, the short follow-up in some reports and the possible bias due to the retrospective design of most of the studies make it difficult to draw definitive conclusions regarding efficacy. Despite the lack of evidence-based data, rituximab is now commonly used to manage chronic refractory ITP in Europe and North America, and is increasingly proposed before splenectomy. Thus, the BCSH guidelines suggested that rituximab might be of value for patients who failed to respond to first- and second-line therapies. Whether it could be an effective and safe splenectomy-avoiding strategy in adults with chronic ITP remains unresolved. To assess rituximab efficacy and safety in nonsplenectomized adults with chronic ITP (duration ≥6 months), we conducted a prospective, multicenter, open-label, single-arm phase 2 trial using Fleming’s single-stage design.

**PATIENTS AND METHODS**

**Patients**

Eight French Hematology and Internal Medicine Departments enrolled patients. The protocol was approved by the Henri-Mondor Hospital Institutional Review Board and all patients gave their written informed consent according to the Declaration of Helsinki before undergoing eligibility screening. Inclusion criteria were the following: age ≥18 years; ITP diagnosis satisfying ASH guidelines; and ITP lasting ≥6 months prior to inclusion; at least 1 previous
treatment for ITP; and platelet count <30x10^9/L at inclusion. Patients were included if their treating physicians considered them candidates for splenectomy. Exclusion criteria were: previous splenectomy or prior rituximab use, other disease(s) known to be associated with immune thrombocytopenia, such as, human immunodeficiency or hepatitis C virus infection, lymphoproliferative disorders, thyroid or liver disease, and definite systemic lupus erythematosus (≥4 American Rheumatism Association criteria^23). Patients wishing to become pregnant during the 12 months following rituximab infusion, or with previous or current cardiovascular disease, bone-marrow disorder or active cancer were also excluded.

**Study design**

Rituximab (375 mg/m^2; Roche France®) was infused intravenously once weekly for 4 weeks. Patients were vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* at least 2 weeks before the first rituximab administration. Before each infusion, patients were premedicated with paracetamol (1 g) and intravenous methylprednisolone (60 mg). All treatments active against ITP had to be stopped at least 2 weeks before the first rituximab infusion, except steroids, which could be maintained in patients with bleeding and/or platelet counts <20x10^9/L. In the latter situation, steroids had to be stopped within 21 days following the first rituximab infusion. No other treatments potentially active against ITP were given to patients during the 2 years of follow-up.

Every patient’s bleeding severity was assessed in at inclusion and during follow-up using a previously described standardized bleeding score.^24

**Response and toxicity criteria**

The primary endpoint of the study was to assess the response rate to treatment 1 year after the first rituximab infusion. A good response was defined as a platelet count ≥50x10^9/L with a
≥2-fold increase of the inclusion value; an intermediate response was defined as a platelet count ≥30x10⁹/L but <50x10⁹/L and at least twice the inclusion value. Patients with platelet counts <30x10⁹/L or with increases less than twice their inclusion value were considered nonresponders. Patients requiring another treatment to manage ITP during follow-up, including a new rituximab cycle, were also considered to be nonresponders, regardless of their platelet counts.

Secondary endpoints were: the response rate 2 years after the first rituximab infusion, according to the same criteria, and the number of splenectomies performed 1 and 2 years after the first rituximab infusion.

Toxicity and side effects were recorded on standardized case-report forms.

**Funding**

The study was initiated by the investigators and partially financed with an open grant from Roche France®, which played no role in designing the study, collecting and analyzing the data or writing the manuscript.

**Statistical methods**

Fleming’s single-stage design was used. Briefly, Fleming’s one-stage design tests the hypothesis that, if π, the true response rate to the test drug, is ≤ π₀, the lowest acceptable response rate indicating potential drug efficacy, it would imply that the experimental agent warrants no further investigation. Should this hypothesis be rejected (i.e., the test therapy has significant efficacy), it can be concluded that the true response is >π₀ and that the test-drug’s efficacy makes it worthy of further investigation. In the present study, we set the value of π₀ at 25%, meaning that, should rituximab obtain a 1-year good response rate <25%, it would be considered ineffective. With a 2.5% one-sided test level, 56 patients had to be recruited to
detect a 1-year good-response rate ≥45% with 90% power. To account for losses-to-follow-up and consent withdrawal, we decided to recruit 65 patients.

Patient characteristics are reported as numbers (%) or medians (IQR, expressed as: 1st; 3rd quartiles). Median follow-up was 18 (range: 2–36) months. The 1-year good-response-rate estimates [95% confidence interval (CI)] are reported. The primary analysis was based on a binomial test comparing the observed response rate to 25%. Analyses of secondary endpoints used point estimates and 95% CI but not statistical tests.

An ancillary objective was to determine whether baseline characteristics were associated with good response at 1-year, using Wilcoxon’s rank-sum test or Fisher’s exact test. A multiple logistic-regression model with backward stepwise model selection was used to remove potential confounders. All variables achieving $P < .20$ in the previous analysis were considered in the multivariate model, and retained in the model at a threshold of $P = .05$. Model results are expressed as odds ratios (OR) [95% CI].

The probability of a patient achieving and sustaining a good response during follow-up was estimated with its point-wise 95% CI using multi-state models.26

Analysis was performed on an intent-to-treat basis: the data obtained from all patients included in the trial were analyzed, except those who withdrew their consent. Patients receiving other treatment with known effect on ITP were considered treatment failures, regardless of the reason why it was administered. Except for the primary analysis, in which a one-sided test at the 0.025 level was used, all other tests used were two-sided at a 0.05 level.

**RESULTS**

**Patient characteristics**

Among 65 patients assessed for eligibility, 3 were excluded: 1 who had already participated in another trial and 2 others because they did not fulfill the inclusion criteria. Two additional
patients withdrew their consent and did not receive rituximab. Thus, 60 patients were included and all but the 1 who developed transient serum sickness received all 4 rituximab infusions. No patient was lost-to-follow-up.

Table 1 summarizes the main patient characteristics. All the patients had previously received steroids and/or IVIg and >80% had responded transiently to those first-line therapies. Twenty-one patients with a median platelet count of $15 \times 10^9$/L were taking steroids because of bleeding at the time of the first rituximab infusion and in accordance with the protocol, they were discontinued for all of them within the following 3 weeks.

**Efficacy**

At 1 year, 24 patients had good responses (40% [95% CI: 28–52%]), with normal platelet counts ($\geq 150 \times 10^9$/L) for 18 and platelet counts $> 50 \times 10^9$/L and at least twice their inclusion values for 6. Whisker plots of the platelet counts of the 24 responders are shown in Fig. 1. The median time to response was 4 (IQR: 3; 7) weeks. That 40% good responses differed significantly from 25% ($P = .007$). Two (3%) patients had intermediate responses and 34 (57%) did not respond to rituximab.

Relationships between baseline characteristics and the response pattern at 1 year are detailed in Table 2. A multivariate logistic-regression model for treatment failure showed that younger age was the only independent factor significantly predictive of a good response at 1 year (OR: 1.82 [1.26–2.63] per 10 years; $P = .001$).

The response at 1 year was also associated with the magnitude of the initial response to rituximab. Among the 21 patients who had platelet counts $\geq 150 \times 10^9$/L within the first 2 weeks following rituximab infusions, 18 (86%) had good responses at 1 year, while only 6 (40%) of the 15 patients with platelet counts $\geq 50 \times 10^9$/L but $< 150 \times 10^9$/L shortly after starting rituximab had good responses at 1 year ($P < .01$). Lastly, none of the 24 patients whose
platelet counts did not rapidly reach ≥50x10⁹/L achieved a good response at 1 year.

After 2 years of follow-up, 20 of the 24 1-year responders were still good responders, 1 initial responder had an intermediate response and 3 others had relapsed (Fig. 2). The 2 patients with intermediate responses at 1 year had persistent intermediate responses at 2 years. One patient, who had been a nonresponder at 1 year and did not receive any treatment potentially active against ITP after the rituximab infusions, spontaneously achieved an intermediate response at 2 years.

Overall, at 2 years, 24 (40%) patients had platelet counts ≥30x10⁹/L off treatment. Among the 36 nonresponders, 25 underwent splenectomy, with 23 undergoing surgery during the year following rituximab infusions. Splenectomy led to good responses for 15 (60%) after a median follow-up of 18 (range: 2–36) months. Eleven nonresponders at 2 years were not splenectomized: 1 developed systemic lupus erythematosus treated with steroids, 2 had persistently low platelet counts without bleeding off treatment and 8 received other medications after rituximab failure. Among the latter, 5 achieved good responses, 3 did not respond to those medications and 2 of them are scheduled to undergo splenectomy.

Safety

All but 1 patient, who developed reversible serum sickness after 2 infusions, received 4 rituximab infusions. Fifteen (25%) patients experienced transient minor side effects that did not necessitate treatment withdrawal (Table 3). One patient, who developed sigmoiditis after the second rituximab infusion, recovered rapidly on antibiotics and went on to receive the last 2 infusions of rituximab without any problem; no new infection occurred during follow-up.

Eight severe events judged unrelated to rituximab infusions were recorded: an 85-year-old woman died of myocardial infarction 16 months after rituximab infusions; 58- and 61-year-old women and a 62-year-old man developed atrial fibrillation 4, 6 and 23 months after
rituximab infusions, respectively; colon cancer was diagnosed in a 63-year-old man 3 months after rituximab infusions; a 75-year-old woman developed pancreatic cancer 6 months post-rituximab infusions; another patient developed Guillain–Barré syndrome at month 18; and, the last developed renal colic after the second rituximab infusion, but the full regimen could be administered without renal disease recurrence.

**DISCUSSION**

This report describes, for the first time, the results of a phase 2 prospective trial designed to assess rituximab efficacy at 1 and 2 years, and safety with long-term follow-up obtained from a homogeneous nonsplenectomized adult population with chronic ITP. We chose to evaluate rituximab efficacy in a single-arm, phase 2 trial because its short-term efficacy had been reported to be 25–50%\(^{21}\) but the long-term response in a homogeneous nonsplenectomized adult population had never been prospectively studied. Our objective was not to compare rituximab to splenectomy, because the expected response rate after splenectomy (~65%)\(^{6}\) would surely be higher than that of rituximab. However, splenectomy may be associated with immediate morbidity, a long-term and unpredictable risk of fatal overwhelming sepsis,\(^{11-13}\) and it has also been emphasized that the risk of long-term relapse post-splenectomy has been underestimated.\(^{14,15}\) Therefore, finding a safe alternative therapeutic option to splenectomy which could induced a long-term remission is still an unmet need for patients with severe chronic ITP.

We considered that >25% response rate 1 year after the first rituximab infusion would imply that the biologic may be used as a splenectomy-avoiding agent and that the observed responses reflected the impact of rituximab rather than the natural course of ITP. Indeed, only patients with chronic ITP (i.e., lasting ≥ 6 months) were included in our study and it had been shown that, for adult ITP, the likelihood of spontaneous remission after 6 months of follow-up
was very low.\textsuperscript{28}

The phase 2 design that we used cannot provide definitive answers and does not demonstrate that rituximab is the best splenectomy-avoiding option. However, its results certainly showed that rituximab was apparently safe and effective pre-splenectomy option that warrants consideration in routine practice for adults with chronic ITP. Indeed, after 2 years of follow-up, good responses persisted in 33\% of the patients and 40\% of the patients had treatment-free platelet counts $\geq 30 \times 10^9$/L. Based on their large meta-analysis, Arnold et al.\textsuperscript{21} found an overall response defined as a platelet count $> 50 \times 10^9$/L in 62\% of the patients and thrombocytopenia recurred in only 10\% of them. However, the median follow-up had been only 9.5 months (IQR: 6; 21 months). Other recent studies that included splenectomized and nonsplenectomized ITP patients reported sustained responses in 35–67\% with median follow-up 9–54 months long.\textsuperscript{29-31} But Schweizer et al.\textsuperscript{32} reported conflicting results, with only 2 long-lasting remissions among 14 patients.

According to our multivariate analysis, only younger age was associated with a long-term good response. Patients with long-term good responses were more frequently females and had received fewer previous treatments but these differences did not reach statistical significance. To date, although it has been suggested that women and younger patients might respond better,\textsuperscript{21,33} factors predictive of ITP response to rituximab have not yet been clearly established. The optimal timing of rituximab administration in ITP also remains a matter of debate, even though early administration might have a better disease-modifying effect.\textsuperscript{29,30,34}

Notably, an early response to rituximab (i.e., occurring within 2 weeks after the first infusion) had been found to be associated with a better long-term response.\textsuperscript{35} We confirmed that finding, because 18 of our 21 patients who had recovered normal platelet counts within the 2 weeks following their first rituximab infusion, still had normal platelet counts at 1 year. However, as reported by Stasi et al.,\textsuperscript{36} some patients had slow platelet-count rises, indicating
that a late response to rituximab is possible, albeit infrequent (~10%).

We did not observe any life-threatening side effect and only 1 patient in our cohort developed a severe infection. All patients, except the 1 who was diagnosed with transient serum sickness after the first 2 infusions, received 4 infusions, in accordance with the study protocol. Severe infections have been reported after rituximab was given to treat autoimmune diseases but most of those patients were severely immunocompromised.\textsuperscript{37,38} The good safety profile and the rarity of infections observed in our study could be explained by the small number of therapies preceding rituximab. This observation suggests that rituximab is a safe treatment in nonsplenectomized ITP patients and argues for its early administration during the course of ITP before considering the use of cytotoxic agents. We also observed 8 severe events, particularly 4 cardiovascular complications and 2 cancers judged unrelated to rituximab, but because of the single-arm design of our study, we cannot be absolutely sure that one of those complications was not causally related. However, as in the general population, these events occurred mainly in patients >60 years. Moreover, no cancer or cardiovascular complications were reported in the meta-analysis by Arnold et al.\textsuperscript{21} that included >300 patients or in concurrently published studies\textsuperscript{29,31,32,39} not included in that meta-analysis.

Our results demonstrated that, when administered before splenectomy, rituximab achieved 33% good responses after 2 years of follow-up. Moreover, compared to historical data, rituximab does not seem to lower the response rate to splenectomy should it be required later due to rituximab failure. Rituximab should therefore be considered a pre-splenectomy therapeutic approach, particularly for patients with chronic ITP who are at high risk of undergoing the surgery and/or who are reluctant to do so.
Acknowledgments

The Établissement Français du Sang was the trial promoter and Roche France, provided an open grant. The authors thank Janet Jacobson for editorial assistance, Doctor Isabelle Martin-Toutain and Professor Jean-Paul Vernant’s group for patient recruitment, and Laetitia Grégoire and Samia Baloul for their help in patient monitoring.

Authorship


Conflict-of-interest disclosure: B. Godeau is a consultant for Roche France and for LFB. The other authors have no competing financial interests to declare.
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safety profile of low-dose rituximab for the treatment of autoimmune cytopenias in adults.

Haematologica. 2007;92:1695-1698.
Table 1. Baseline characteristics of the 60 immune thrombocytopenic purpura patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>48</td>
</tr>
<tr>
<td>Range</td>
<td>18–84</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>40 (67)</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.9</td>
</tr>
<tr>
<td>IQR</td>
<td>0.9; 5.2</td>
</tr>
<tr>
<td>Platelet-count nadir within 15 days of inclusion, ×10⁹/l</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14.0</td>
</tr>
<tr>
<td>IQR</td>
<td>7.0; 19.5</td>
</tr>
<tr>
<td>Bleeding score at inclusion</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.5</td>
</tr>
<tr>
<td>IQR</td>
<td>0; 4</td>
</tr>
<tr>
<td>Previous therapy</td>
<td></td>
</tr>
<tr>
<td>Median number of therapies</td>
<td>2</td>
</tr>
<tr>
<td>IQR</td>
<td>2; 3.5</td>
</tr>
<tr>
<td>Previously took corticosteroids, no. (%)</td>
<td>57 (95)</td>
</tr>
<tr>
<td>Response to corticosteroids, no./total no. (%)</td>
<td>49/57 (86)</td>
</tr>
<tr>
<td>Previously received IVIg, no. (%)</td>
<td>35 (58)</td>
</tr>
<tr>
<td>Response to IVIg, no./total no. (%)</td>
<td>30/35 (86)</td>
</tr>
<tr>
<td>Corticosteroids at inclusion, no. (%)</td>
<td>21 (35)</td>
</tr>
</tbody>
</table>

IQR: interquartile range, expressed as the 1st; 3rd quartiles; IVIg: intravenous immunoglobulins.
Table 2. Relationships of baseline characteristics with the response pattern at 1 year retained by multivariate logistic-regression analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Good response</th>
<th>Intermediate response/failure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Age, yr, mean ± SD</td>
<td>39 ± 18</td>
<td>55 ± 15</td>
<td>.002</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>19 (79)</td>
<td>21 (58)</td>
<td>.16</td>
</tr>
<tr>
<td>Years since ITP diagnosis, median (IQR)</td>
<td>1.5 (0.9; 3.5)</td>
<td>2.0 (0.8; 6.1)</td>
<td>.64</td>
</tr>
<tr>
<td>Platelet-count nadir within 15 days of inclusion, ×10⁹/L, median (IQR)</td>
<td>16.0 (7.5; 20.5)</td>
<td>14.0 (7.0; 19.0)</td>
<td>.58</td>
</tr>
<tr>
<td>Bleeding score at inclusion, median (IQR)</td>
<td>1 (0; 3)</td>
<td>2 (0; 4.5)</td>
<td>.64</td>
</tr>
<tr>
<td>Number of previous therapies, median (IQR)</td>
<td>2 (1.5; 3)</td>
<td>3 (2; 4)</td>
<td>.09</td>
</tr>
<tr>
<td>Initial response to corticosteroids, no./total no. (%)</td>
<td>20/23 (87)</td>
<td>29/34 (85)</td>
<td>1</td>
</tr>
<tr>
<td>Initial response to IVIg, no./total no. (%)</td>
<td>10/12 (83)</td>
<td>20/23 (87)</td>
<td>1</td>
</tr>
</tbody>
</table>

IQR: interquartile range, expressed as the 1<sup>st</sup>; 3<sup>rd</sup> quartiles.
Table 3. Adverse events recorded for the 60 immune thrombocytopenic purpura patients treated with rituximab

<table>
<thead>
<tr>
<th>Side effect</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, urticaria*</td>
<td>5</td>
</tr>
<tr>
<td>Fever, myalgia*</td>
<td>4</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
</tr>
<tr>
<td>Minor upper respiratory tract infection</td>
<td>2</td>
</tr>
<tr>
<td>Headache*</td>
<td>2</td>
</tr>
<tr>
<td>Transient hypertension*</td>
<td>1</td>
</tr>
<tr>
<td>Mild and transient neutropenia</td>
<td>1</td>
</tr>
<tr>
<td>Hypogammaglobulinemia complicated by minor upper respiratory tract infection</td>
<td>1</td>
</tr>
<tr>
<td>Transient serum sickness</td>
<td>1</td>
</tr>
<tr>
<td>Sigmoiditis</td>
<td>1</td>
</tr>
</tbody>
</table>

*Infusional adverse events; all the others occurred later.
Figure 1. Whisker plots of successive platelet counts of the 24 patients with immune thrombocytopenic purpura whose response to rituximab persisted at week 48. The central horizontal bold line is the median; the lower and upper box limits are the 1st and 3rd quartiles, respectively; and the whiskers extend to the most extreme data points, which do not exceed 1.5× the interquartile range of the box.
**Figure 2. One- and 2-year outcomes.** The figures in grey boxes are the numbers of patients in each group in the interim between 1 and 2 years.
Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura - results of a prospective multicenter phase 2 study

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