Long-term outcomes of patients treated with rituximab as second-line treatment for adult immune thrombocytopenia – Follow-up of the RITP study

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Summary

RITP was a double-blind randomized, 78-week follow-up trial in which 109 adults with immune thrombocytopenias (ITP) who failed to achieve adequate response to steroids, were randomized to receive rituximab or placebo. Here, we provide the duration of response, splenectomy and mortality rates based on extended follow-up after completion of the RITP study. Extended follow-up data were retrospectively collected for 72 (83%) patients out of the 84 patients who were not splenectomized during the initial RITP study. For the present analysis, median [interquartile range] duration of follow-up after randomization was 72 [62–82] months. Median duration of response among patients who achieved an initial response was significantly longer in patients who received rituximab (8 [5–16] months) as compared to placebo (1 [1–3] months), P = 0.036. Overall, 35 patients underwent splenectomy (13 in the rituximab, and 22 in the placebo arm, P = 0.12). Eleven patients (10%) died during the study: five in the rituximab and six in the placebo arms, including four deaths from severe bleeding. Although most rituximab-treated patients eventually relapsed, a longer duration of response and a trend towards lower splenectomy rate were observed in rituximab-treated patients.

Keywords: bleeding, corticosteroids, immune thrombocytopenia, rituximab, splenectomy.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by immune-mediated platelet destruction associated with impaired production, causing thrombocytopenia and an increased risk of bleeding.1

Treatment is indicated in patients with low platelet count (i.e. <30 × 10^9/L) who present with bleeding or who are at high risk of bleeding.2,3 The main goals of treatment are as follows: (i) to achieve sustained, haemostatic platelet counts and thereby to prevent serious bleedings and deaths; and (ii) to cure the patient if possible with the fewest possible toxic effects.1

Corticosteroids remain the main first-line treatment in adults. However, not all patients respond to steroids and most relapse after an initial response. Thus, approximately 70% of the patients require a second-line therapy. Although it has never been licensed for ITP, rituximab is among the most widely used second-line therapies, especially in Europe. Rituximab is often administered following steroid failure to avoid splenectomy or to avoid the use of therapies that require continuous administration or that are more

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expensive. The advantage of rituximab includes its ability to induce relatively long remissions following a single treatment course with a treatment-free period thereafter. The main disadvantages of rituximab are the lack of a robust predictive factor of response and the high relapse rate, as around half of the responding patients relapse after 1-5 years. Furthermore, data on sustained response rates beyond two years are limited.

The Rituximab as Second-Line Treatment in ITP (RITP) study was a randomized placebo-controlled trial in which ITP patients who failed to achieve adequate response to or relapsed after steroids were randomized to receive rituximab or placebo. The study endpoints were treatment failure (splenectomy or meeting criteria for splenectomy), response rates and duration of response during a 78-week follow-up. Apart from a longer duration of response in the rituximab arm, the study showed no significant differences in the other outcomes.

The aims of this study were to determine the long-term relapse rate and duration of response, as well as splenectomy and mortality rates during an extended open follow-up after completion of the RITP study.

Methods

Study design

The design of the RITP study has been reported in detail previously. The extension of the follow-up was approved by Ethics Committees in Norway and Tunisia. Informed consent was acquired from participating patients in Norway. Platelet counts, splenectomy status, ITP medication and death were retrospectively extracted from medical records and from the time of completion of the RITP study up to the time of last available encounter. Data on survival were intended to be collected for all patients whereas other endpoints were planned to be extracted for patients with no splenectomy (whether in relapse or not) at the end of the RITP study.

In order to be able to compare splenectomy rates, data were extracted for patients with no splenectomy (whether in relapse or not) at the end of the RITP study.

The primary outcome of the present analysis was relapse after achieving a response. Response was defined in the RITP study as a platelet count of at least \(30 \times 10^9/l\) with at least a doubling of the baseline count in the absence of any other new ITP therapy, or by a platelet count of at least \(100 \times 10^9/l\) four weeks after first study drug administration [complete response (CR)]. Prednisone (or prednisolone) was allowed during the RITP study, but a stable or a decreasing dose was required to qualify a response. Relapse was defined as the occurrence after an initial response of a platelet count \(<30 \times 10^9/l\) or splenectomy related to ITP or administration of ITP medication, depending on which event occurs first. Secondary outcomes were splenectomy, use of other ITP medications and death.

Statistical analysis

Standard descriptive statistics are displayed. A competitive risk model, with death as the competitive risk, and Gray’s test were used for the analysis of splenectomy. The Kaplan–Meier method and log-rank test were used for the analysis of death and relapse. Median time and two-sided 95% confidence interval (CI) are displayed for Kaplan–Meier method estimates.

Time to splenectomy and time to death were measured from the date of the first RITP study drug administration; patients were censored at date of last available data or 70 months after first RITP study drug administration. Time to relapse was measured from the date of response; patients with no relapse were censored at date of last available data or 70 months after first RITP study drug administration.

Patients with no information available after the end of RITP were censored at the end of that study.

Cox proportional hazard regression was used to assess the hazard ratio (HR) and 95% CIs of relapse in the subgroup of patients with overall response (OR). The model was adjusted for RITP study drug, age, sex and duration of ITP at inclusion in the RITP study (>1 year vs. ≤1 year). Results are cumulated over the double-blind (RITP study) and extended open follow-up. Statistical analysis was performed using SAS/STAT 15.1 software under Windows.

Results

Characteristics of the 109 patients from the original cohort have been reported previously (median age 46 years; 73% females). As previously reported, during the RITP study, 76/109 patients achieved response (40 in the rituximab, 36 in the placebo arms) including 28 and 21 CR, in the rituximab and placebo arms respectively.

Data on open extended follow-up were collected for 72 (83%) patients out of the 87 patients with no splenectomy during the double-blind RITP study. For the present analysis, median duration of follow-up after randomization was 72 months (interquartile range: 62–82).

Figure 1 shows probability of first relapse in all responding patients. Six responding patients relapsed during the extended follow-up, of whom four after achieving CR. Median duration of response was significantly longer in patients who received rituximab (8.2 [5.5–16.7] months) as compared to placebo (1.8 [1.3–3.6] months), \(P = 0.036\). The rate of first relapse two years after response was 69.1% in the rituximab arm and 80.6% in the placebo arm. The crude and adjusted HRs for relapse were 0.58 and 0.55 respectively (95% CI: 0.34–0.97 and 0.32–0.93 respectively). None of the factors we adjusted for was associated with relapse (sex and age, \(P > 0.20\); duration of ITP > 1 year, \(P = 0.13\)).

Median time to relapse in the 49 patients who achieved CR during the RITP study was 17 [8.0–34.3] months in the
rituximab group vs. 11 [3-6-not estimable] months in the placebo group, \( P = 0.55 \).

A total of 35 patients underwent splenectomy: 13 in the rituximab and 22 in the placebo arm, including five patients in the rituximab and eight patients in the placebo arm who were splenectomized during the extended follow-up. Two years after the first RITP study drug administration, the cumulative incidence of splenectomy was 17.2% (95% CI: 8.4%–28.7%) in the rituximab arm and 26.4% (95% CI:15.4%–38.8%) in the placebo arm. There was a non-significant trend towards longer time to splenectomy in the rituximab arm compared to the placebo arm (\( P = 0.12 \); Fig. 2).

Several patients in both arms received second-line medications including rituximab and/or thrombopoietin receptor agonists after relapse. Nine patients received rituximab: four in the rituximab arm and five in the placebo arm; with a median time to (re)-treatment with rituximab of 32 [22–40] and 22 [8–38] months respectively. Seven patients received thrombopoietin receptor agonists; five in the rituximab and two in the placebo arms with a median time to treatment of 32 and 4.5 months respectively. We did not register any patient treated with immunosuppressant.

Eleven patients (10%) died: five in the rituximab and six in the placebo arms (\( P = 0.56 \); Fig. 3). Ten of them died during the extended follow-up. Median age at death was 70 years. The cause of death is shown in Table I. Four patients died of severe haemorrhage. Last platelet count before death was \(< 10 \times 10^9/l\) in three and \(16 \times 10^9/l\) in the fourth patient. Five patients had a cancer diagnosis. No case of progressive multifocal leukoencephalopathy or hepatitis B reactivation was reported.

Discussion

The results reported in the initial publication were based on a 78-week (18-month) follow-up. To our knowledge, the data provided here are the longest single study follow-up reported on the effect of rituximab in ITP. The extended follow-up study shows a non-significant trend towards a lower rate of splenectomy in the rituximab arm. Although the probability of maintaining a response was similar in the two study arms after three years, the duration of response was significantly longer in patients treated with rituximab as compared to placebo. Interestingly, some patients in both arms were still in remission at six years.

Godeau et al. showed in a single arm study that splenectomy was avoided in a third of the patients treated with rituximab.\(^5\) Two subsequent randomized controlled trials, including ours, failed to show a significant difference in splenectomy rate between the rituximab and placebo arms.\(^7,9\) Allowing corticosteroids during the study may have contributed in reducing the difference between the two study arms and hence masking some of rituximab’s effect. The non-significant lower splenectomy rate in the rituximab arm might reflect that despite the equal number of patients relapsed in both arms, relapses may have been less severe in the rituximab arm.

It is well-known that the response to rituximab is transient in the majority of patients, with five-year sustained response rates ranging between 20 to 30%.\(^8,10\) In the recent prospective registry-based study that included 248 adult ITP patients, the five-year sustained response rate was 30%, which is slightly higher than the sustained response rate
observed in our study.8 Of note, very few patients were still in response beyond three years, which affects the precision of estimates beyond that time. Interestingly, some patients in both study arms had a sustained response after six years; however, it is not possible to conclude whether that is attributed to the medications received (rituximab and or steroids) or because of a spontaneous remission. Despite the transient response and comparable long-term rates of sustained response, the duration of response in rituximab-treated patients was 4.5 times longer than in the patients who initially received placebo (8.2 months vs. 1.8 months). It has been reported that younger females with a shorter duration of disease achieve a longer response to rituximab.6 In our study, we fail to show an association between gender, age, or duration of ITP prior to rituximab and the duration of response.
Four patients out of 11 died of haemorrhage. All four patients had thrombocytopenia with platelet count <10–20 × 10⁹/l before death. These data illustrate that ITP is a serious and occasionally a fatal disease. A recent study showed that in chronic ITP, a platelet count <25 × 10⁹/l was associated with a 7- and 4.5-fold increase in the risk of haemorrhage requiring hospitalization at respectively one and five years, as compared to ITP patients with normal platelet counts.11 It also showed that the risk of death was markedly higher among patients with a bleeding event requiring a hospital contact. Therefore, every effort should be made to increase the platelet count to a haemostatically safe level.11

The longer duration of response and trend towards fewer patients receiving a retreatment including splenectomy, rituximab or thrombopoietin receptor agonists, and the longer time to retreatment with these therapies in the rituximab-treated patients indicate that rituximab is an effective therapy. In addition, rituximab implies a limited number of administrations, leading to a treatment-free response lasting for many months, a major advantage over thrombopoietin receptor agonists or other maintenance therapies. During that period of time, patients do not have to take any ITP medication, especially corticosteroids, and can avoid frequent hospitalizations.6

Altogether, in our opinion, rituximab remains an attractive medication in ITP. Whether earlier use of rituximab and/or its use in a subgroup of patients (e.g. young females) can improve its efficacy remains to be confirmed through new prospective studies.12,13,14

The retrospective collection of data and some missing data in the long-term follow-up represent a limitation of the study. Another limitation is the lack of follow-up data on safety. Strengths of the study are the initial randomized design and the prolonged follow-up.

In the future, efforts should be made to enhance the initial response to rituximab and to prolong the duration of response. Our ongoing PROLONG study (NCT03010202) will determine if the response can be prolonged by administration of maintenance therapy with rituximab. Other ongoing studies are exploring various combinations with rituximab which could prolong the duration of remission and possibly cure the patients.

## Conflicts of interest

WG declares research grants from Bayer and BMS and lecture honoraria and fees for participation in advisory board meetings for Amgen and Novartis; MM declares lecture honoraria and consulting fees from Amgen and Novartis, and research support from Roche; BD works for a Contract Research Organisation with contracts with pharmaceutical companies. The other authors declare no relevant conflict of interest.

## Author contributions

WG, ET, PAH, BD planned the study and analyzed the results; WG, ET, PAH, AW, AK, MM, NBR collected data; ET and WG drafted the manuscript; All authors critically reviewed the manuscript.

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