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ABR, annualised bleed rate; CBDR, Canadian Bleeding Disorders Registry; FIX, factor IX; rFIX, recombinant factor IX; rFIXFc, recombinant factor IX-Fc fusion protein; SHL, standard half-life; WFH, World Federation of Hemophilia

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RESEARCH ARTICLE

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Long-term safety and efficacy of rituximab in 248 adults with immune thrombocytopenia: Results at 5 years from the French prospective registry ITP-ritux

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Abstract

Rituximab is a second-line option in adults with immune thrombocytopenia (ITP), but the estimated 5-year response rate, only based on pooled retrospective data, is about 20%, and no studies have focused on long-term safety. We conducted a prospective multicenter registry of 248 adults with ITP treated with rituximab with 5 years of

follow-up to assess its long-term safety and efficacy. The median follow-up was 68.4 [53.7-78.5] months. The incidence of severe infections was only 2/100 patient-years. Profound hypogammaglobulinemia (<5 g/L) developed in five patients at 15 to 31 months after the last rituximab infusion. In total, 25 patients died at a median age of 80 [69.5-83.9] years, corresponding to a mortality rate of 2.3/100 patient-years. Only three deaths related to infection that occurred 12 to 14 months after rituximab infusions could be due in part to rituximab. At 60 months of follow-up, 73 (29.4%) patients had a sustained response. On univariate and multivariate analysis, the only factor significantly associated with sustained response was a previous transient response to corticosteroids (P = .022). Overall, 24 patients with an initial response and then relapse received retreatment with rituximab, which gave a response in 92%, with a higher duration of response in 54%. As a result of its safety profile and its sustained response rate, rituximab remains an important option in the current therapeutic armamentarium for adult ITP. Retreatment could be an effective and safe option.

1 | INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder defined by low platelet count, mainly secondary to platelet destruction, but also to impaired megakaryopoiesis mediated by autoantibodies and $CD8^+$ T cells.[1,2] Steroids are considered first-line treatment. However, among adults, less than 40% of newly diagnosed ITP patients will recover within 12 months.[3,4] Therefore, second-line treatments are frequently needed in these patients, depending on their platelet count and comorbidities. Over the past 20 years, rituximab has been considered a valid off-label second-line option in most guidelines,[5,6] with a 60% initial response in adult ITP.[7-13] Nevertheless, the estimated five-year response rate, based on pooled retrospective data, is only about 20% among adults, and no robust predictor of long-term response has been demonstrated.[14]

Assessing the tolerance and particularly the potential risk of severe infection with rituximab is also crucial. Because of rituximab's mechanism of action, the risk of infection was initially a concern,[10,15] and rituximab has been associated with several severe and sometimes fatal opportunistic infections, including progressive multifocal leukoencephalopathy.[16] No studies have focused on long-term safety in ITP, and the data observed in other autoimmune diseases such as rheumatoid arthritis (RA) or antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis cannot be extrapolated to ITP patients. This is because rituximab is frequently associated with long-term steroids, or another immunosuppressive therapy and/or is given repeatedly in these diseases.[17,18]

The last important issue is the efficacy of retreatment for patients who initially respond to a first course of rituximab. Other autoimmune diseases exhibit high risk of relapse, for which maintenance treatment is used by most groups.[19,20] However, only few retrospective data are available regarding the efficacy and safety of retreatment with rituximab in patients with ITP.[21]

In July 2010, a French prospective registry (the ITP-ritux registry) was set up with a planned follow-up of 5 years, and adult patients with a diagnosis of primary persistent or chronic ITP have been included for 2 years. The objective was to prospectively assess the safety and efficacy of rituximab in adults with primary ITP. The results after a median follow-up of 2 years were previously published.[9]

Here, we report on the final data after 5 years of follow-up that allow for the first prospective study assessing the long-term safety and efficacy of rituximab in ITP and including a large group of patients. Moreover, because several patients with relapse after initial treatment with rituximab have undergone retreatment, our study also gives data regarding the safety and efficacy of rituximab retreatment.

2 | METHODS

2.1 | The ITP-ritux registry

The ITP-ritux registry was set up by the French referral center for adult immune cytopenias, and the extensive description of the protocol has been previously published.[9] Briefly, inclusion in the registry was started in July 2010 and closed in July 2012 after the inclusion of 248 consecutive adults with a diagnosis of primary ITP. They had received rituximab during the study period, with a planned follow-up duration of 5 years regardless of platelet response to rituximab.[9] Patients with secondary ITP were excluded. The choice of rituximab regimen — "lymphoma" regimen with four weekly intravenous infusion at 375 mg/m^2 or "RA" regimen with two fixed 1-g rituximab infusions 2 weeks apart — was based on the physician's preference.

2.2 | ITP definitions

In accordance with international guidelines, complete response (CR) was defined as platelet count >100 × 10^9/L, and response (R) as

platelet count 30 to 100 × 10^9/L, with at least a 2-fold increase from baseline.[22] The patients who required another treatment effective in ITP, including a new rituximab course, were considered to have treatment failure regardless of platelet count. A sustained response was defined as platelet count >30 × 10^9/L, without any additional ITP treatment and without any bleeding.

The phases of ITP (ie, "persistent" and "chronic") were defined according to international guidelines.[22]

2.3 | Collection of data

Data were collected by using an electronic case report form at the time of first rituximab infusion and at one, three, and six-month follow-up visits, then every 6 months or at disease relapse. Research study nurses regularly visited each center to update the clinical and biologic data for the enrolled patients. Missing data were minimized during the visits by study nurses, and the request to complete missing data by the physician in charge of the patient at the final follow-up (July 2017). Data were censored at 60 months of follow-up, except for retreatment with rituximab, for which data were censored at July 2017 or last news date.

All episodes of adverse events (AEs) mentioned (ie, in responders and nonresponders) were systematically retrospectively reviewed by two of the authors (SD and BG). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

2.4 | Ethics

This study was approved by the French authorities and the institutional review board of Henri Mondor, Créteil and was registered at www.ClinicalTrials.gov (NCT01101295). Research was conducted in accordance with the Declaration of Helsinki.

2.5 | Statistical analysis

Continuous variables are described with mean ± SD or median (quartiles 1-3 [Q1-3]), and categorical variables are reported as number (%). The incidence of events is presented with 95% confidence intervals (CIs). The recurrence rate after an initial response was examined by the Kaplan-Meier method. The incidence rate of malignancies and the mortality rate in our cohort were compared with those of the French general population, based on Institut de Veille Sanitaire data[23,24] and INSEE data, respectively, by standardized incidence/mortality ratios. Comparison of the two rituximab regimens involved the log-rank test, and multinomial logistic regression was used to compare nonresponders and sustained responders at 60 ± 6 months. Predictors of 60-month response were analyzed by multivariate analysis with a logistic regression model testing all variables with $P < .20$ on univariate analysis. $P < .05$ was considered statistically significant. Missing data were not imputed. Analysis was performed with Stata SE v14.0 (College Station, TX, USA).

3 | RESULTS

As indicated in our first report, 248 patients were included.[9] The mean age at ITP diagnosis was 51 ± 20 years; 159 were females; 102 (41%) had persistent and 146 (59%) chronic ITP; and 25 (10%) previously underwent splenectomy. In total, 173 (70%) received four infusions of 375 mg/m^2 and 72 received two fixed 1 g infusions 2 weeks apart. Our first report showed that 61% of the patients had an overall initial response, and the probability of sustained response at 1 year was significantly associated with ITP duration <1 year and previous transient CR to corticosteroids. In all, 38 patients showed minor infusion-related reactions, seven had 11 infectious events and 13 died, including three from infections. In the present report, we grouped all the AEs (ie, those already reported and observed during the 2 years after the first rituximab course and those observed afterward). For efficacy and predictors of response, we focused our results on the long-term response only.

3.1 | Follow-up

At the end of the study (July 2017), the median follow-up was 68.4 [53.7-78.5] months, with a follow-up of at least 60 months for 175 (70.6%) patients. Two patients were lost to follow-up just after the rituximab infusions, until they needed ITP treatment 70 and 75 months after the infusion, and were considered as missing data. Only six patients had a follow-up <1 year, 12 had a follow-up from 12 to 24 months, 16 had a follow-up from 24 to 36 months, and 19 had a follow-up from 36 to 48 months.

3.2 | Safety

According to the CTCAE classification, 299 AEs were noted in 135 (54.4%) patients: 59 (19.7%) grade I, 137 (45.8%) grade II, 74 (24.8%) grade III, 2 (0.7%) grade IV and 27 (9%) grade V.

3.2.1 | Infusion-related AEs

We have already reported that only 38 patients showed a minor intolerance after the first rituximab infusion. Among the 30 patients with retreatment by rituximab, six new minor and reversible infusion-related AEs were observed in four patients. This included skin rashes (n = 2), cytolytic hepatitis without relapse at the second infusion (n = 1) and a serum sickness after each of the 3 rituximab infusions (n = 1).

3.2.2 | Infections

Between the date of the first infusion of rituximab and the end of follow-up, a total of 103 infections occurred in 59 (23.8%) patients after a median of 33.9 [18.4-47] months. Thirty-two were severe (grade III to V) and occurred in 21 (8.5%) patients (median age: 72 years [49-78]) with at least another contributing factor in 14/21 (66.7%) patients. The severe infections are detailed in Table 1.

TABLE 1 Grade 3 to 5 infections encountered after rituximab therapy for adults with immune thrombocytopenia

Number, Sex, age (y)	Site of infection	Infectious agent(s)	Delay after last RTX infusion (mo)	Course (s) of RTX	Last γ-globulin level (g/L)	Outcome	Contributing factors
1, F, 84	Septic shock	ND	50	1	NA	Death	
2, F, 38[a]	Pneumopathy	ND	2	1	NA	Recovery	Down syndrome
3, M, 76	Acute cholangitis	ND	23	1	NA	Recovery	
	Surgical site (total hip prosthesis)	*Staphylococcus, Streptococcus, Corynebacterium, Enterobacter cloacae*	35	1	NA	Recovery	
4, M, 72	Ureteral endoprosthesis infection	*Escherichia coli*	31	1	6.5	Recovery	Diabetes
5, M, 84	Bronchitis	ND	42	1	14.6	Recovery	Diabetes, vinblastine, spln
	Bronchitis	ND	45	1	14.6	Recovery	Diabetes, spln
	Pneumopathy	*Pneumocystis jirovecii*	56	1	14.6	Recovery	Diabetes, MMF, spln
	Surgical site (inguinal hernia)	ND	59	1	14.6	Recovery	Diabetes, spln
6, F, 49	Pneumopathy	*Pneumocystis jirovecii*	1	2	4	Recovery	Hypoγ, diabetes, steroids
7, F, 53	Pneumopathy	ND	56	1	10.9	Recovery	
8, M, 74	Pneumopathy	ND	11	1	NA	Recovery	COPD
9, M, 70[a]	Pneumopathy	*Enterococcus faecium*	12	1	5.4	Death	Diabetes, vincristine, steroids, spln
10, M, 67[a]	Skin and soft tissue	ND	2	1	12.4	Recovery	
	Pneumopathy	ND	2	1	NA	Recovery	COPD
11, F, 38[a]	Pneumopathy	*Streptococcus pneumoniae*	18	1	10.2	Recovery	
12, M, 84	Pneumopathy	ND	29	1	NA	Recovery	
13, M, 74[a]	Bone	*Staphylococcus aureus*	13	1	NA	Death	Diabetes, steroids, vincristine
14, M, 48	Surgical site (total hip prosthesis)	*Staphylococcus aureus*	18	1	NA	Recovery	
15, F, 74[a]	Pyelonephritis	*Escherichia coli*	1	1	6.2	Recovery	Cirrhosis, diabetes, steroids
[a]	Pneumopathy	ND	2	1	6.2	Recovery	Cirrhosis, diabetes, steroids
	Digestive tract	ND	1	1	6.2	Recovery	Cirrhosis, diabetes, steroids
[a]	Sinus	*Aspergillus fumigatus*	2	1	6.2	Recovery	Cirrhosis, diabetes, steroids
[a]	Pyelonephritis	*Streptococcus*, group D	4	1	6.4	Recovery	Cirrhosis, diabetes, steroids
[a]	Septic shock	*Enterobacter cloacae*	14	1	9.3	Death	Cirrhosis, diabetes, steroids, gynecological cancer
16, M, 21	Skin and soft tissue	ND	3	3	14.4	Recovery	
17, M, 72	Skin and soft tissue	ND	27	1	NA	Recovery	Diabetes, spln
18, F, 87	Pyelonephritis	*Escherichia coli*	46	1	6.4	Recovery	
	Pyelonephritis	*Escherichia coli*	48	1	6.4	Recovery	Steroids
19, F, 80	Pneumopathy	ND	24	1	NA	Death	Diabetes
20, F, 36	Fever without a focus	ND	54	2	NA	Recovery	Steroids, spln
21, M, 78	Pneumopathy	ND	58	1	14.1	Recovery	Diabetes, azathioprine

Abbreviations: COPD, chronic obstructive pulmonary disease; F, female; M, male; mo, months; MMF, mycophenolate mofetil; NA, not available; ND, not determined; spln, splenectomy; RTX, rituximab; y, year.

[a]Infections previously described.

The incidence of severe infections was 2/100 patient-years (95% CI, 1.3-3), and the median time to onset was 27.4 [13.1-45.9] months after the first rituximab infusion and 20.5 [2.75-45.25] months after the last rituximab infusion. Among the 21 patients with grade III-IV infection, 18 (85.7%) were nonresponders to rituximab. Among the 220 patients with an available pattern of response at 60 ± 6 months after the first rituximab infusion, two (3.9%) grade III-IV infections occurred among 51 patients with a sustained response vs 18 (10.7%) among nonsustained responders (P = .17). Nearly one third of these infections occurred within 1 year after rituximab infusion (10/32, 31.25%), then were evenly divided over the four following years.

Regarding opportunistic infections, we observed one case of previously reported aspergillosis sinusitis, and two cases of *Pneumocystis jirovecii* pneumonia in patients who had several infection risk factors and who were on prolonged treatment with steroids or other immunosuppressants (Table 1). No case of progressive multifocal leukoencephalopathy occurred.

3.2.3 | Malignancy

Thirteen patients (5.2%) had 14 malignancies after a median of 39.9 [30-48.2] months. Malignancies occurred at a median age of 75.5 [65.75-79.75] years. There were two malignant lymphoproliferative disorders (T-cell large granular lymphocytic leukemia and large B-cell lymphoma). Among the 12 solid tumors, no over-representation of one type of malignancy was found, with three pulmonary adenocarcinomas, two basal cell carcinomas, two prostatic adenocarcinomas, one bladder adenocarcinoma, one hepatocarcinoma, one cholangiocarcinoma, one gynecological cancer, and one breast cancer. The incidence of malignancy was 1.2/100 patient-years (95% CI, 0.7-2.1). Comparison with the incidence of malignancy in the French general population showed that the standardized incidence ratio (SIR) was not significantly increased, at 1.18 (95% CI: 0.59-2.12, P = 0.66).

3.2.4 | Venous thrombosis and cardiovascular events

Ten venous thrombosis cases occurred in nine patients (median age: 76 years [57.25-79.5]), after a median of 41.1 [28-43.9] months, including three pulmonary embolisms, four deep venous thrombosis, one pulmonary embolism secondary to deep venous thrombosis, one portal vein thrombosis and one retinal vein occlusion. All cases showed at least one other contributing factor, including splenectomy in four patients (Table S1). The incidence of thromboembolic events was 0.8/100 patient-years (95% CI, 0.4-1.6).

Cardiovascular events were observed in 12 patients (three women, median age: 76.5 years [63-83]) after a median of 35 [18.5-45.5] months, including five heart failures, two episodes of high blood pressure, two stenting for ischemic heart disease, one stenting for peripheral artery disease, one pacemaker implantation for bradyarrhythmia and one atrial fibrillation. Without taking into account age and male sex, all but two patients had at least one cardiovascular risk factor.

3.2.5 | Autoimmune diseases

Twelve women (median age: 33.5 years [25.75-49]) had another autoimmune disease after a median of 43.5 [25.5-51.25] months, including autoimmune hemolytic anemia (n = 2 patients), systemic lupus erythematosus (n = 3, including one associated antiphospholipid syndrome), Crohn's disease (n = 2), Hashimoto thyroiditis (n = 2), Sjögren's syndrome, polymyalgia rheumatica and unclassified mild autoimmune disease (n = 1, each).

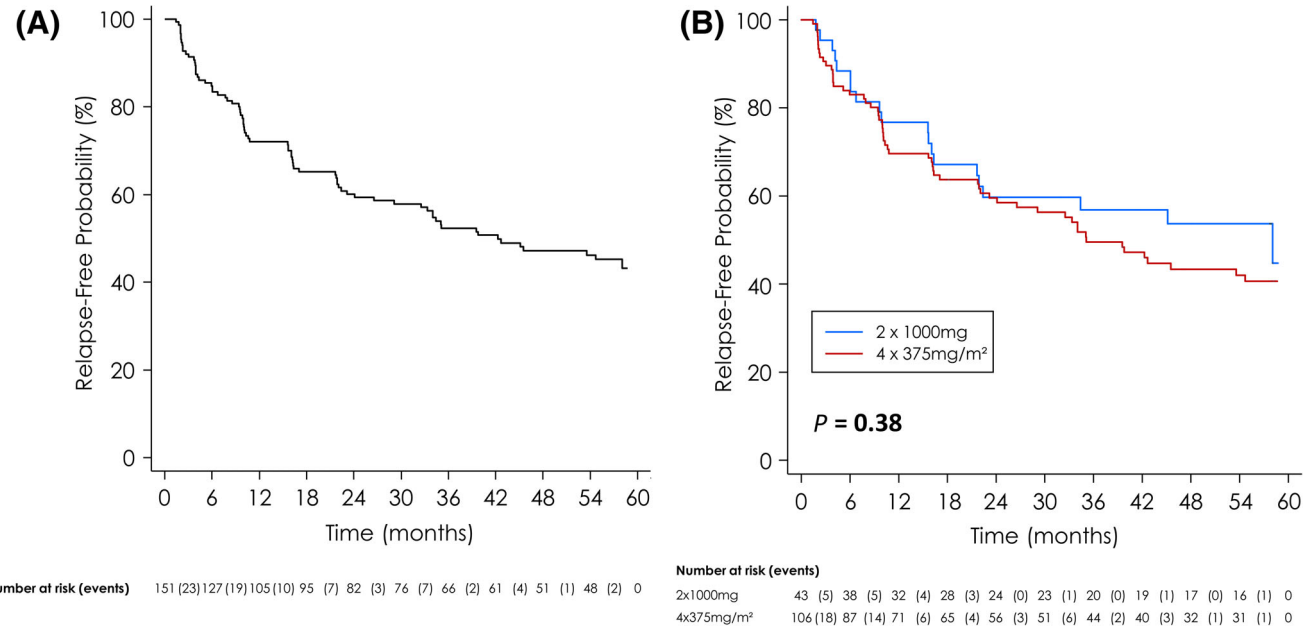

FIGURE 1 Relapse-free survival curve among the 151 adults with immune thrombocytopenia who had an initial response to rituximab (A) and according to the 2 rituximab regimens (B) [Color figure can be viewed at wileyonlinelibrary.com]

3.2.6 | Hypogammaglobulinemia and neutropenia

Gammaglobulin level was not systematically monitored. Among the 142 (52%) patients with available data, five with median age 49 years [40-57] showed profound hypogammaglobulinemia (<5 g/L) after a median of 25 [15-31] months after the last rituximab infusion. The median lowest gammaglobulin level in these five patients was 3.12 [2.5-3.13] g/L. Hypogammaglobulinemia was symptomatic in only one patient (patient six, Table 1). One patient eventually had a diagnosis of common variable immunodeficiency (CVID). Of note, one additional patient had a diagnosis of CVID because of granulomatous lymphadenitis, but gammaglobulin levels and vaccine responses were uninterpretable because of sequential administration of intravenous immunoglobulin for ITP.

Added to the sole episode of profound late-onset neutropenia described in our first report, only another case of transient and asymptomatic neutropenia (nadir at 120 cells/mm^3) occurred 43 months after rituximab infusion.

3.2.7 | Obstetrical events

Overall, four women became pregnant: two had an uneventful pregnancy, one had an early miscarriage and one had a fetal death in utero with concurrent lupus nephritis, occurring after a median of 45 [33.5-52.25] months after the last rituximab infusion.

3.3 | Mortality

Including the 13 deaths reported in our first report, 25 (10.1%) patients died at a median age of 80 [69.5-83.9] years, at a median of 26.2 [12.6-43.9] months after the first rituximab infusion, corresponding to a mortality rate of 2.3/100 patient-years (95% CI, 1.6-3.4). Deaths were mainly related to infections (n = 5), malignancies (n = 5), bleeding (n = 3), "old age" (n = 2), suicide, cachexia, heart failure (n = 1, each) or an unknown cause (n = 7). Among the five deaths from infections, three were already reported and were considered possibly related to rituximab; the two remaining were observed

TABLE 2 Univariate analysis of predictors of sustained response at 60 ± 6 months after rituximab therapy for adults with immune thrombocytopenia

Variables	No response or response with relapse (n = 169)	Sustained response (n = 51)	OR [95% CI]	*P*-value
Age (y), median [Q1-3]	51.9 [35.2-69.5]	46.9 [29.3-62.6]	0.99 [0.98;1.01]	.24
Sex, M/F (%)	61 (36.1) /108 (63.9)	14 (27.5) /37 (72.5)	0.67 [0.34;1.34]	.26
ITP duration <1 y before RTX infusion[a], n (%)	105 (62.1)	25 (50.0)	1.64 [0.87;3.10]	.13
Bleeding at ITP diagnosis[b], n (%)	67 (41.9)	23 (46.0)	1.18 [0.62;2.24]	.61
No. of previous treatment lines, median [Q1-3]	3 [2–4]	3 [2–4]	0.98 [0.78;1.24]	.99
Previous splenectomy before RTX infusion, n (%)	22 (13.0)	2 (3.9)	0.27 [0.06;1.20]	.086
Previous response to steroids (among patients previously receiving steroids)				.047
No response, n (%)	40 (23.7)	15 (29.4)	Ref	
Response, n (%)	87 (51.5)	17 (33.3)	0.52 [0.24;1.15]	
CR, n (%)	36 (21.3)	18 (35.3)	1.33 [0.59;3.03]	
Previous response to IVIg				.93
No IVIG, n (%)	46 (27.2)	16 (31.4)	1.31 [0.52;3.33]	
No response, n (%)	34 (20.1)	9 (17.6)	Ref	
Response, n (%)	64 (37.9)	18 (35.3)	1.06 [0.43;2.62]	
CR, n (%)	25 (14.8)	8 (15.7)	1.21 [0.41;3.57]	
Platelet count at ITP diagnosis (×10^9/L) (n = 192), median [Q1-3]	20 [7-44]	13.5 [5–42]	0.99 [0.98;1.01]	.60
Lower platelet count in the month preceding first RTX infusion, median [Q1-3] (×10^9/L)	16 [7–24]	17 [7-26]	1.01 [0.99;1.02]	.30
RTX infusion regimen (other excluded)				.64
Four infusions, n (%)	49 (29.0)	16 (31.4)	Ref	
Two infusions, n (%)	119 (70.4)	33 (64.7)	0.85 [0.43;1.68]	

Abbreviations: 95% CI, 95% confidence interval; CR, complete response; F, female; M, male; ITP, immune thrombocytopenia; RTX, rituximab; IVIg, intravenous immunoglobulins; y, year; OR, odds ratio.

[a]Missing data for one patient, excluded from analysis.

[b]10 missing data were excluded from analysis.

TABLE 3 Multivariate analysis of predictors of sustained response at 60 ± 6 months after rituximab therapy for adults with immune thrombocytopenia

Variables	OR [95% CI]	*P*-value
ITP duration <1 y before RTX infusion	1.54 [0.75;3.16]	.24
Previous splenectomy before RTX infusion	0.15 [0.02;1.22]	.077
Previous response to steroids (among patients previously receiving steroids)		.022
No response	Ref	
Response	0.48 [0.21;1.09]	
CR	1.44 [0.21;3.54]	

Abbreviations: 95% CI, 95% confidence interval; CR, complete response; F, female; ITP, immune thrombocytopenia; M, male; OR, odds ratio; RTX, rituximab.

24 and 49 months after the last rituximab infusion, with the implication of rituximab doubtful.

The age-, sex- and year-standardized incidence of mortality was 2.3/100 person-years for the studied population, vs 1.4/100 person-years for the general population in France. The standardized mortality ratio (SMR) was therefore 1.69 (95% CI: 1.09-2.49, *P* = .02).

3.4 | Efficacy

As indicated in our first report, 151 (60.9%) patients had an initial response to rituximab, including 80 (32.3%) who achieved CR; 78 (51.6%) showed relapse after a median of 10.2 [4.2-23.2] months after the first rituximab infusion. The relapse-free survival curve seemed to plateau after 36 months of follow-up (Figure 1A). We observed no significant difference between the two rituximab regimens (*P* = .38, Figure 1B). At 60 months of follow-up, 73 (29.4%) patients had a sustained response.

We studied predictors of long-term sustained response at 5 years for the 220 patients with an available pattern of response at 60 ± 6 months after the first rituximab infusion. On univariate analysis, the only factor significantly associated with sustained response at 60 ± 6 months was a previous transient response to corticosteroids (*P* = .047, Table 2), which remained associated on multivariate analysis (*P* = .022, Table 3). Other factors such as age or duration of ITP were not significantly associated with long-term sustained response. Univariate analysis revealed a better, although not significant, sustained response to rituximab in females less than 40 years old than to females greater than 40 years old: 32.2% long-term response in 66 women <40 years old vs 20.9% in 93 women ≥40 years old (*P* = .126, Table S2).

3.5 | Retreatment with rituximab

Overall, 28 patients with relapse received retreatment with rituximab 12 to 68 months after the first course of rituximab: 19 patients received two courses, five patients received three courses, one patient received four courses and three patients received five courses. The response to retreatment was not evaluable in two patients, including one who received rituximab at last follow-up and another who received concurrent treatment with a thrombopoietin receptor agonist. In the two patients with no response to rituximab at the first course, retreatment also resulted in no response. Among the 24 evaluable patients with response to the first course, 22 (92%) showed response to the second course. In 19 patients (79%), the pattern of response (CR or R) was similar to the first course (17 CR, 2 R), it was worse (from CR to R) in one patient and was better in the remaining two (from R to CR, Figure S1A). The median duration of the response to retreatment in the 22 responders was 23 [12.25-27.75] months for the first course and 23.5 [13-36] months for the retreatment. The duration of response to retreatment was similar (±3 months) to the first course in three patients; was increased in 12 patients (54%, with a median increase of 14.5 [10-21.25] months); and was decreased in five patients (with a median decrease of 14 [10-21] months, Figure S1B). Nine patients with CR after retreatment and thereafter showed relapse received 16 other rituximab courses (one to three new retreatments). At the end of follow-up, 14 (50%) patients showed sustained response after one (n = 8) to four additional courses of rituximab, at a median follow-up of 75.5 [64.25-79.75] months after the first infusion, and after a median follow-up of 30 [16.25-39.25] months after the last rituximab infusion. The safety was good, and only three patients had a new infectious event (patients 6, 16 and 20, Table 1). None died.

4 | DISCUSSION

This large multicenter prospective study including 248 adults receiving rituximab for ITP shows that nearly one third had a sustained response at 5 years. Patients with relapse after an initial response may benefit from additional courses of rituximab. The long-term safety of rituximab is reassuring, with no unexpected long-term complications.

Assessing the long-term tolerance of rituximab and particularly the risk of severe infection is crucial. Arnold *et al*.,[10] in a meta-analysis conducted 10 years ago, reported poor tolerance of rituximab in ITP, with several deaths related to infection. However, a recent meta-analysis did not find an increased risk of infection.[12] Our study confirms these reassuring data with an incidence of severe infections of two cases/100 patient-years. This incidence rate is in the lower range of the severe infections rate observed in other autoimmune diseases treated with rituximab and particularly in large cohorts of patients with RA (1.5-7.9/100 patient-years).[17,25-30] Chronic ITP could be associated itself with an increased risk of serious infections, with an SIR of 8.74 (95% CI, 7.47-10.18).[31] So, the relation between the incidence of severe infections we observed and the use of rituximab is questionable, because most of our patients with severe infection had comorbidities or received prolonged treatment with steroids or immunosuppressants. Consistent with the transient duration of B-cell

depletion secondary to the use of rituximab, it is not a surprise that the incidence of severe infections we observed was higher during the first year, when B-cell depression induced by rituximab is substantial, with one third of infections seen. Severe infections observed several years after rituximab were rare and mostly occurred in older patients with contributing factors. However, even if the role of rituximab was questionable, our results suggest that rituximab should be used with caution in older patients with ITP, particularly if the patient has received prolonged treatment with steroids or immunosuppressants. Of note, opportunistic infections appeared exceptional, with no case of progressive multifocal leukoencephalopathy and only two cases of *P. jirovecii* pneumonia.

Regarding venous thrombosis, these events occurred after a median of >3 years after rituximab infusion, and with at least another contributing factor in all cases. Moreover, ITP could be associated with increased risk of thromboembolism[32,33] as well as splenectomy, performed in four of the nine patients exhibiting venous thrombosis, because of lack of sustained response with rituximab.[34,35]

Several studies suggested that ITP could be associated with increased risk of hematologic malignancies.[36-38] In our study, we found no over-representation of late-onset malignancy, and the SIR was similar to the general French population, which gives reassuring data for the use of rituximab.

Less than 5% of our patients developed another autoimmune disease. As expected, we mostly observed autoimmune hemolytic anemias (Evans' syndrome) and systemic lupus erythematosus.[39] Patients with primary ITP may rarely later develop another autoimmune disease.[40] Given the low proportion of onset of another autoimmune disease observed in our series, it is unlikely that rituximab was responsible.

Rituximab has been associated with the occurrence of late-onset neutropenia. This event was mainly reported in patients with treatment for malignant conditions, but also in those with autoimmune diseases such as RA or ANCA-associated vasculitis.[41-43] Our results show that this event is rare, transient and without severity in the field of ITP, with only two episodes in our entire cohort.

A large cohort study conducted in the United States of patients receiving rituximab for various conditions, including autoimmune diseases, showed that gammaglobulin level was not consistently monitored by physicians, which disallows the identification of patients at risk for infection.[44] The authors reported a significantly increased risk of severe infection in the 6 months after rituximab infusion, with the highest risk among patients with hypogammaglobulinemia. We also previously reported that profound symptomatic hypogammaglobulinemia related to CVID can occur several years after rituximab infusions in ITP patients.[45] Unfortunately, in our present study, gammaglobulin levels were not systematically monitored, and we are unable to give a strong evaluation of the risk of hypogammaglobulinemia in the entire cohort of patients. However, among the 142 patients with available data, profound hypogammaglobulinemia developed in five. These data show that severe hypogammaglobulinemia is a rare complication of rituximab in ITP. It may occur several years after rituximab infusion, and that argues for a systematic monitoring of gammaglobulin levels in the years after rituximab infusion, including in patients in CR.[45]

Our study found a higher SMR in ITP patients, as compared with the general French population. We cannot exclude any effect of rituximab, particularly because at least one fifth of deaths were secondary to an infectious cause. Nevertheless, among deceased patients, the median age was 80 years, and contributing factors were frequently associated in deaths from an infectious cause. Moreover, the SMR in our cohort is consistent with the 1.3- to 2.2-fold higher mortality rate described in ITP patients observed in several epidemiological studies, including in rituximab-naive patients, mainly because of infection and bleeding.[46-48]

The main retrospective study regarding long-term response of rituximab in ITP conducted by Patel *et al*., including 72 adults, found a five-year response rate estimated at only 21%.[14] Our prospective study including a much higher number of patients gives more encouraging results, with a sustained response at 60 months in almost one third of adults, without any significant difference whatever the rituximab regimen (ie, the "lymphoma-like" or "RA" regimen). Interestingly, the survival curve (Figure 1) seemed to plateau after 36 months of follow-up, which suggests that some patients could be cured and that this could be not just a transient sustained remission. Identifying robust predictors of long-term sustained response could be useful for physicians to better select patients, who are more prone to take advantage from rituximab avoiding non-useful infusions. Several studies suggested that rituximab could be more effective in young females with a short duration of ITP.[49-53] However, most of these studies were retrospective, and none provided information about the rate of long-term response. On univariate and multivariate analysis, we found the 5-year response to rituximab better in patients with a previous transient response to steroids treatment. In contrast, the long-term response was not associated with duration of ITP, age or sex, even if univariate analysis revealed a better, although not significant, long-term response in females <40 than ≥40 years old. Our population appears older than that of other studies, with a median age of 51 years, which may be why young or female members were not significant prognostic factors.[50] Of note, rituximab was also effective in splenectomized patients. In practice, although our results provide some evidence for considering rituximab, especially for patients with at least transient response to steroids, there is no reason to not treat other groups of patients. That includes older patients, patients with a rather long duration of ITP, or those who did not achieve at least a transient response to corticosteroids.

In view of the relatively modest long-term response of rituximab, several strategies are currently in development, including combining rituximab with other treatments such as dexamethasone.[50,54,55] Another option could be to repeat rituximab infusion as maintenance therapy, as commonly done in other autoimmune diseases such as RA or ANCA-associated vasculitis.[17,18] However, we have only few data in the literature assessing the efficacy and safety of repeated infusions of rituximab in ITP patients, and maintenance treatment has never been prospectively tested. In our study, among the 26 evaluable patients with retreatment, the second course allowed for a response

in more than 80%, with a higher duration of response in more than half. The safety was reassuring. Our results argue for retreatment in patients with previous response to rituximab without associated risk factors for infections and under regular monitoring of gammaglobulin levels before and after retreatment.

This cohort is the first large prospective study that evaluated the long-term safety and efficacy of rituximab for adult ITP. The small number of patients lost to follow-up, because of the methodology used, and the high number of patients, provide a set of relevant data on consecutive patients in "real life". Nevertheless, we acknowledge missing data, particularly regarding gammaglobulin levels, because of the observational design of this study. Our reassuring results regarding safety cannot be extrapolated to new therapeutic combinations with rituximab, such as dexamethasone or ciclosporin, which may exhibit better efficacy, but prospective and comparative studies are lacking.[50,51,54,56] Moreover, no patient in this study received biosimilars, and therefore additional studies are needed. However, biosimilars have shown similar efficacy as the reference rituximab in other diseases, such as RA or immune-mediated thrombotic thrombocytopenic purpura.[57,58]

To conclude, this prospective study shows that, at 5 years after one rituximab course, the safety of rituximab for adult ITP is reassuring, with less than 10% of patients experiencing severe infection, predominantly in older patients with contributing factors, and that the sustained response rate is almost one third. Gammaglobulin levels should be monitored to identify patients at risk for infection. Moreover, results on retreatment with rituximab are encouraging, and this strategy may be proposed in patients with previous response, and without associated risk factors for infections. Therefore, rituximab remains an important option to consider in the current therapeutic armamentarium in adult ITP. It appears as a good way to maintain safe platelet count in ITP with less toxicity than prolonged treatment with corticosteroids, without the need for a splenectomy and may avoid prolonged therapy with thrombopoietin receptor agonists.

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CONFLICT OF INTEREST

B.G. served as an expert for AMGEN, Novartis, LFB and Roche. He received funds for research from AMGEN and Roche.

AUTHOR CONTRIBUTIONS

B.G. and M.K. designed the study and initiated this work; B.G., S.D., M.M., and F.C.P wrote the report; B.G., S.D., R.L., and F.C.P. performed all statistical analyses; and all authors made substantial contributions to acquisition of data, revised the article critically and gave final approval of the manuscript to be submitted.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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