

The Journal of Rheumatology

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DOI: 10.3899/jrheum.150051

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Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years

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ABSTRACT. Objective. Final evaluation of the longterm safety of rituximab (RTX) in rheumatoid arthritis (RA) up to 11 years.

Methods. Pooled observed case analysis of data from patients with moderate to severe, active RA in a global clinical trial program.

Results. As of September 2012, 3595 patients received a mean of 4 courses (range 1–20) of RTX over 11 years [14,816 patient-years (PY)]. Of these, 1246 patients had > 5 years of followup (8970 PY). A pooled placebo population (n = 818) was included in the analysis. The overall serious infection event (SIE) rate was 3.76/100 PY (2.71/100 PY in patients observed for > 5 yrs) and comparable with rates reported previously at 9.5 years (3.94/100 PY and 3.26/100 PY, respectively). SIE rates continued to be similar before and during/after development of low immunoglobulin levels, and serious opportunistic infections remained rare. Rates of cardiac events remained consistent with previous analysis and with rates in the general RA population. No increased risk of malignancy over time was observed.

Conclusion. This final report demonstrates that RTX remains well tolerated over time and multiple courses. No new safety risks were identified and there was no increase in the rate of any types of adverse events with prolonged exposure to RTX during 11 years of observation. (J Rheumatol First Release August 15 2015; doi:10.3899/jrheum.150051)

Key Indexing Terms:

RHEUMATOID ARTHRITIS

RITUXIMAB

SAFETY

Rituximab (RTX), an anti-CD20 monoclonal antibody, has been shown to improve signs and symptoms of disease and reduce radiographic damage in patients with rheumatoid arthritis (RA)^{1,2}. A previously published analysis found that exposure to multiple courses of RTX over 9.5 years of observation was associated with a well-tolerated safety profile³.

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Sponsored and funded by F. Hoffmann-La Roche, Genentech (a member of the Roche group), and Biogen Idec. Support for third-party writing assistance for this manuscript, furnished by Vivian Chen, PharmD of Health Interactions, was funded by F. Hoffmann-La Roche Ltd.

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Accepted for publication June 17, 2015.

While these data are reassuring, continued monitoring of the longterm safety of RTX is necessary to understand the potential risk associated with prolonged and repeated peripheral B cell depletion. In particular, the potential cumulative risks of serious infection events (SIE) and malignancies require further followup. The objective of our analysis was to provide the final report on the longterm safety of RTX over 11 years of observation in the clinical trial program. It represents 2854 additional patient-years (PY) of followup with the inclusion of an additional 401 patients treated with RTX, pooled from an RTX RA open-label prospective study⁴. This update not only increases the probability of detecting uncommon and infrequent safety risks, but also affords rheumatologists a higher level of confidence in the data.

MATERIALS AND METHODS

Safety data were evaluated from patients with moderate to severe, active RA treated with RTX plus methotrexate (MTX) from a global clinical trial program (8 randomized clinical trials, 2 longterm open-label extensions, 1 open-label prospective study)^{1,4,5,6,7,8}. Eligibility criteria and study designs have been previously presented^{1,5,6,7,8}. Each RTX course consisted of either 2 × 1000 mg or 2 × 500 mg intravenous infusions, 2 weeks apart. Repeat treatment was based on the physician's decision of clinical need and included evidence of active disease (either swollen/tender joint counts ≥ 8 or Disease Activity Score in 28 joints ≥ 2.6). Safety assessments were conducted as previously reported³. The analysis consisted of the following populations: the RTX all-exposure population (all patients exposed to at least 1 or part of

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1 RTX infusion, regardless of dose), the RTX longterm population (a subset of the all-exposure population with > 5 yrs followup from first RTX exposure), and the pooled placebo population (all patients receiving placebo during placebo-controlled and study followup periods). Our longterm followup was completed in September 2012; the final results are provided here.

RESULTS

Demographics. As of September 2012, 3595 patients received a mean of 4 courses (range 1–20) of RTX over 11 years, providing 14,816 PY of observation in the RTX all-exposure population. Of these patients, 1246 patients (8970 PY) were followed for > 5 years (RTX longterm population). The placebo population included 818 patients (1107 PY). Patients in the RTX longterm population had a longer mean RA disease duration and a greater number ($n = 2.3$) of previous disease-modifying antirheumatic drugs (excluding MTX) than the all-exposure and placebo populations. Baseline demographics and disease characteristics were otherwise similar across groups. The placebo population included patients with a substantially shorter mean duration of followup compared with the RTX populations (> 50% withdrew from placebo followup by 1 yr and 93% withdrew by 3 yrs).

The greatest number of withdrawals occurred following the first 2 courses (1034 patients, 29%), principally for nonsafety reasons and because 2 studies limited patients to receiving 1 or 2 courses per protocol. Across the trials, there was a normal expected dropout rate (1–14%) for subsequent courses. Overall, withdrawals due to adverse events (AE) were infrequent (241 patients, 7%). Most withdrawals were attributed to “other” reasons that included insufficient therapeutic response, failure to return, violation of selection criteria at entry, other protocol violation, refused treatment/did not cooperate, withdrew consent, administrative/other (including patient entry to extension protocols), lost to followup, physician’s decision to withdraw, and pregnancy. Data from the patients who remained in the study were largely complete with any missing data considered to be missing at random.

AE and serious AE (SAE). Rates of AE and SAE remained similar in the RTX all-exposure, RTX longterm, and placebo populations (Table 1). The rate of all AE over time was highest during the first 6 months after the first RTX exposure, in part because of infusion-related reactions (IRR) that predominantly occurred with the first infusion of the first course. Rates of AE and SAE subsequently decreased and remained stable thereafter, irrespective of the number of RTX courses received (Figure 1A–1B). SAE that occurred in > 1% of patients receiving RTX were RA exacerbations ($n = 83$, 2%), pneumonia ($n = 74$, 2%), osteoarthritis ($n = 55$, 2%), and falls ($n = 62$, 2%).

There were 78 deaths in the all-exposure population (0.53 events/100 PY, 95% CI 0.42–0.66) and 7 in the placebo population (0.63 events/100 PY, 95% CI 0.30–1.33). Death

rates were consistent with the previous analysis and with the rate expected in the general US population, adjusted for age and sex⁹. Frequent causes of death included malignancies ($n = 19$), cardiovascular events ($n = 15$), infections ($n = 15$), respiratory disorders ($n = 8$), and nervous system events ($n = 4$), which are consistent with those expected in this RA population of biologic-treated patients. The incidence of death did not appear to increase over multiple courses and there have been no fatal IRR. There was no evidence of an increased rate of any type of fatal event with prolonged RTX exposure.

In the all-exposure population, 241 patients (7%) withdrew prematurely from their respective study because of AE (including SAE). The incidence of AE leading to withdrawal was highest in the first course and decreased thereafter with each treatment course. The most common types of AE leading to withdrawal were musculoskeletal and connective tissue disorders (mainly RA exacerbation), IRR, neoplasms (benign, malignant, and unspecified), and infections and infestations.

Infections. The overall rates of all infections and SIE changed very little from the previous analysis of this cohort and remained similar across analysis populations (Table 1). The rate of SIE generally remained stable over time (Figure 1C) and over multiple treatment courses (Figure 1D). A numerically higher SIE rate between Year 5 and Year 6 was not observed in subsequent years. Large CI were observed at > 9 years because of low PY exposure. The most frequent SIE in the all-exposure population were lower respiratory tract infections, predominantly pneumonia (2%).

Infections of interest in RA. Serious opportunistic infections remained rare (all-exposure, 0.05 events/100 PY; placebo, 0.09 events/100 PY). No additional serious opportunistic infections occurred since the 7 events previously reported³. A subanalysis of patients who went on to receive approved biologic agents for RA, namely tumor necrosis factor (TNF) inhibitors or abatacept, showed that the use of subsequent biologics after RTX therapy was not associated with an increased SIE rate (Table 2). Although limited by small patient numbers, SIE rates were similar in patients who received their biologic < 6 months ($n = 98$) and ≥ 6 months ($n = 255$) after last RTX dose (3.65 events/100 PY, 95% CI 1.64–8.13 vs 4.28, 95% CI 2.53–7.22).

Screening for latent tuberculosis (TB; by means of purified protein derivative testing) in the RTX clinical development program was not mandated by protocol, although it can be assumed that patients who received a prior TNF inhibitor would have undergone such screening. Two cases of pulmonary TB, treated with anti-TB medication, occurred in the all-exposure population and both were reported previously³. No cases were observed of extrapulmonary TB, atypical mycobacterial infection, or multidrug-resistant TB.

One case of *de novo* hepatitis B was reported previously¹. Within the RTX RA clinical development program, there

Table 1. Summary of AE rates per 100 PY.

Variables	RTX All-exposure, n = 3595	RTX Longterm, > 5 Yrs, n = 1246	Pooled Placebo, n = 818
Exposure, PY	14,816	8970	1107
AE rate (95% CI)	239.11 (236.63–241.61)	219.36 (216.31–222.44)	315.43 (305.14–326.06)
SAE rate (95% CI)	13.82 (13.24–14.43)	11.88 (11.19–12.62)	13.82 (11.79–16.19)
Infection rate (95% CI)	75.70 (74.31–77.11)	70.52 (68.81–72.28)	90.39 (84.96–96.17)
SIE rate (95% CI)	3.76 (3.46–4.09)	2.71 (2.39–3.07)	3.79 (2.80–5.13)

AE: adverse event; PY: patient-years; RTX: rituximab; SAE: serious adverse events; SIE: serious infection events.

were no reported cases of hepatitis B viral reactivation (patients with active hepatitis B infection, defined by the presence of HBsAg, were excluded from the RA clinical trials; however, patients who tested negative for HBsAg and hepatitis B DNA but positive for hepatitis B core antigen were included). As of the data cutoff, 131 (6.5%) of 2096 evaluable patients in the all-exposure population were enrolled with a positive test for hepatitis B core antigen. This group of patients received up to 16 courses of RTX. The overall proportions of these patients who experienced AE, SAE, or liver function test abnormalities were consistent with those in the all-exposure population, and there were no liver-related SAE.

Infection risk in patients with low immunoglobulin (Ig) levels. Depending on study protocols, Ig serum levels were measured every 8–16 weeks throughout treatment periods. Mean Ig concentrations decreased from baseline over time and over courses. The largest decreases were observed in IgM levels. At pre-RTX Day 1 baseline, few patients ($\leq 2.2\%$) from the RTX all-exposure population had total Ig, IgA, IgG, or IgM concentrations below the lower limit of normal (LLN). After RTX treatment (postbaseline), $\leq 3.9\%$ had IgA or total Ig levels below LLN at any time, while 14.8% had IgG levels $< LLN$ and 37.9% had IgM levels $< LLN$ at any time. The proportion of patients with IgM but not IgG or IgA below the LLN continued to increase over the first 5 RTX courses (data not shown). The clinical relevance of low Ig serum levels and potential to predispose individuals to infections was evaluated. An analysis was performed to assess the rates of serious infections in patients before and after a low ($< LLN$) IgG or IgM level for at least a 4-month period (or 2 consecutive study visits). Out of 3595 patients (24%), 863 developed IgM $< LLN$ for at least 4 months while 143/3595 (4%) developed IgG $< LLN$ for at least 4 months. For both of these Ig classes, SIE rates per 100 PY were similar before (IgM 2.80, 95% CI 2.09–3.75; IgG 6.75, 95% CI 4.48–10.15) and during/after development of low Ig (IgM 3.84, 95% CI 3.20–4.62; IgG 8.16, 95% CI 5.86–11.36).

SIE rates in patients who developed low IgG levels were higher than corresponding rates in patients who never developed low IgG and higher than those in the all-exposure population, both before and after development of low IgG

levels, suggesting that these patients may have a higher inherent risk of developing SIE. Limitations of the Ig analysis included low patient numbers in the IgG subgroup (n = 143), lack of a placebo comparator, and lack of correlation between SIE onset and recording of low Ig levels.

Cardiac events. Myocardial infarction (MI) was the most frequent cardiac AE (58 events in 52 patients). Most affected patients had ≥ 1 risk factor for MI. The rate of MI in patients receiving RTX (0.39 events/100 PY, 95% CI 0.30–0.51) was consistent with rates in the general RA population (0.48, 95% CI 0.34–0.94 to 0.59 events/100 PY, 95% CI 0.37–0.61)¹⁰.

Malignancies. There was no evidence of an increased risk of malignancy of any type over time or RTX course (exclusion criteria for study entry included history of prior malignancy). In the all-exposure population, there were 109 confirmed malignancies (0.74 events/100 PY, 95% CI 0.60–0.88), excluding nonmelanoma skin cancers (NMSC) and non-malignant events. These rates were comparable with rates observed in the placebo population (0.81 events/100 PY) and those in the general RA population (1.17/100 PY¹¹ and 1.30/100 PY, 95% CI 1.19–1.41¹²). A total of 68 NMSC (0.46/100 PY) were reported. For solid tumors, the most frequently reported malignancy was breast cancer (16 events, 0.14/100 PY, 95% CI 0.08–0.22 in female patients only), comparable with or lower than RA observational studies (0.13/100 PY¹¹ and 0.21/100 PY, 95% CI 0.17–0.26¹²). Age- and sex-matched standardized incidence ratios (SIR) for all confirmed malignancies did not indicate an increased risk of malignancy for patients receiving RTX with RA (1.07, 95% CI 0.88–1.29) compared with the general US population (SEER database¹³) and compared with published data in adults with RA (1.05, 95% CI 1.01–1.09¹⁴). The SIR of breast cancer for patients with RA receiving RTX (0.63, 95% CI 0.36–1.03) was also comparable with the published data in adults with RA (0.84, 95% CI 0.79–0.90¹⁴). The observed incidences of all malignancies (overall and by type) in RTX clinical trials were (based on reported data in the literature) within the expected ranges for the RA population.

DISCUSSION

We report here the final results of the global RTX clinical trial program in RA. These longterm followup data confirm

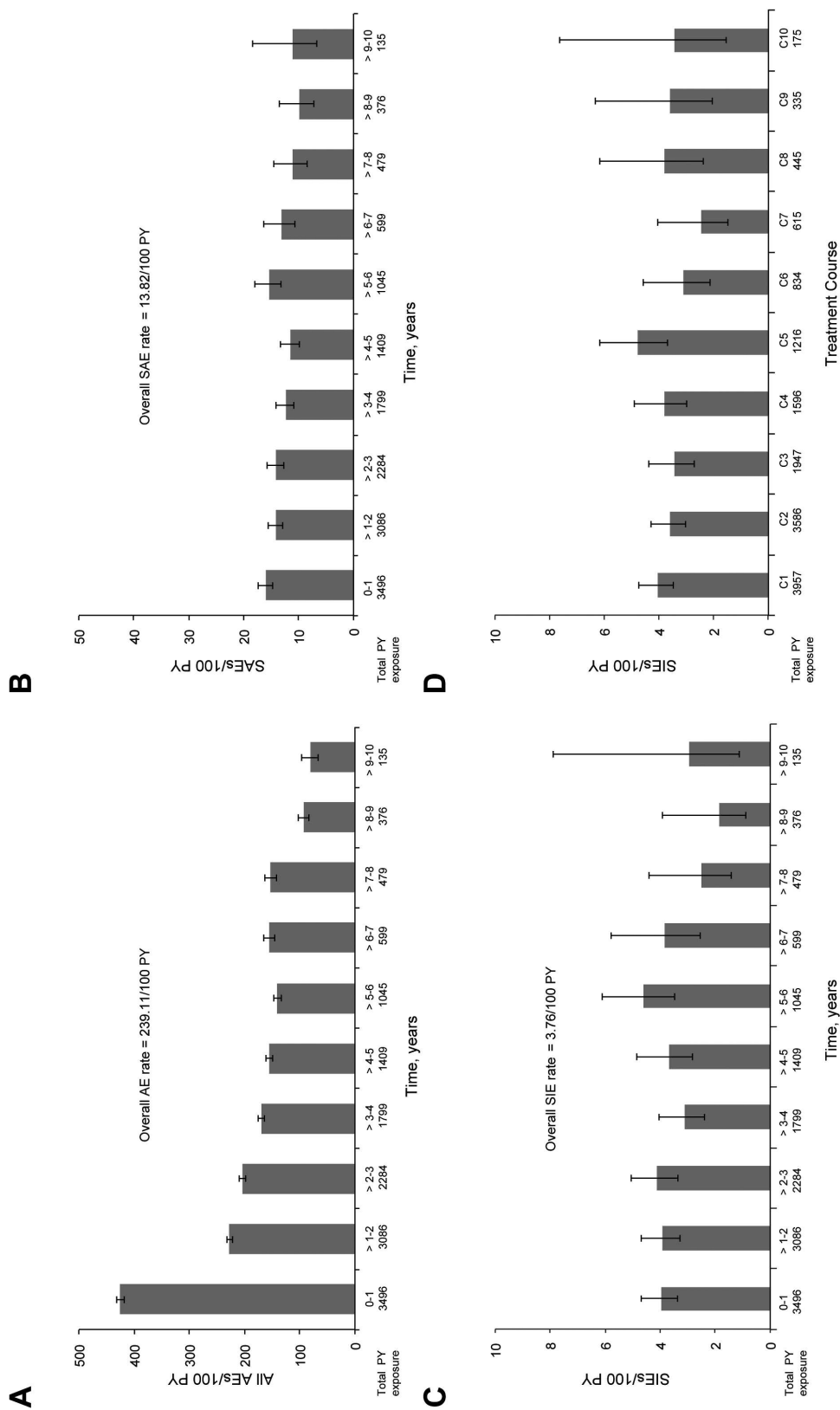


Figure 1. A. Rate of AE over time in 1-year increments (all-exposure population). B. Rate of SAE over time in 1-year increments (all-exposure population). C. Rate of SIE over time in 1-year increments (all-exposure population). D. Rate of SIE by treatment course (all-exposure population). Only data up to 10 years has been presented because data > 10 years represented < 100 PY exposures. Error bars represent 95% CI of the rate per 100 PY. AE: adverse events; SAE: serious adverse events; SIE: serious infection events; PY: patient-years.

Table 2. SIE rates before and after treatment with biologics, including TNF inhibitors. Multiple occurrences of the same event in 1 individual are counted multiple times. DMARD received after the first day of study RTX dose are the DMARD of interest. N is the number of patients receiving treatment with a DMARD post-RTX.

Variables	All Patients Receiving Any Biologic Following RTX Treatment, n = 353		Subset of Patients Receiving a TNF Inhibitor Following RTX Treatment, n = 280	
	Before Other Biologic, During RTX Treatment	After Other Biologic, After RTX Treatment	Before TNF Inhibitor, During RTX Treatment	After Other TNF Inhibitor, After RTX Treatment
Total exposure, PY	727.48	491.61	514.45	387.30
Serious infections, n	32	20	22	14
Serious infections/100 PY	4.40	4.07	4.28	3.61
95% CI	3.11–6.22	2.62–6.31	2.82–6.49	2.14–6.10

SIE: serious infection events; TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drugs; RTX: rituximab; PY: patient-years.

that RTX has a consistent safety profile over time and multiple courses up to 11 years of observation. While the number of patients in this update (n = 3595) did not significantly increase from what was previously reported (n = 3194), the total exposure time increased significantly by 2854 additional PY, representing a total followup time of 14,816 PY. An additional 619 patients more than the previous analysis were observed for > 5 years, with some having received up to 20 RTX courses over 11 years. No new safety signals or increased reporting rates of any types of AE were observed with increasing duration of exposure or courses of treatment. Rates of all AE were highest during the first 6 months, owing in part to IRR. Rates of AE and SAE subsequently decreased and remained stable thereafter, irrespective of the number of RTX courses received. Rates of all infections and serious infections remained similar to the previous analysis despite the increased observation time and additional courses.

Serious opportunistic infections remained rare. No additional cases of confirmed progressive multifocal leukoencephalopathy (PML) in the RA clinical trial program have been reported other than the single case described in 2008¹⁵. The occurrence of confirmed PML from spontaneous reporting and clinical trial sources remains very rare (8 confirmed cases in 271,615 patients treated with RTX, based on patient market exposure estimates as of November 2013). Thus, the reporting rate of confirmed PML in patients with RA is 2.95 (95% CI 1.27–5.8) per 100,000 patients, which has remained stable over time (Roche data on file). Unreported cases of PML are not included in this calculation, which underscores the importance of physician vigilance and reporting of PML cases to most accurately estimate its prevalence. Although there were no reported cases of hepatitis B viral reactivation within the RA clinical development program, hepatitis B virus screening may be considered for high-risk patients before initiation of treatment with RTX. Use of subsequent biologics, including TNF inhibitors, in patients with RA previously treated with RTX was not associated with an increased SIE rate. Rates of MI and malignancies (overall and by type) continued to be consistent with

those observed in the placebo population and in epidemiologic data from other RA cohorts.

These findings indicate that repeated peripheral B cell depletion with RTX did not give rise to any increased safety risk over time or increased reporting rates of any types of AE (including serious infections, cardiovascular events, malignancies, or fatal AE) in the global RA clinical trial program. With the exceptions of IRR and low Ig concentrations, the overall safety profile of RTX remains similar to that of the placebo population and consistent with published data for moderate to severe RA and with previous analyses of this patient cohort.

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