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# Safety of biological therapies following rituximab treatment in rheumatoid arthritis patients

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## ABSTRACT

**Objective:** To assess the safety of biological disease-modifying antirheumatic drugs (DMARD) in rheumatoid arthritis (RA) patients following rituximab.

**Methods:** RA patients who participated in an international rituximab clinical trial programme were included. Patients who had received one or more rituximab courses and entered safety follow-up (SFU) were permitted additional biological DMARD. Serious infection events (SIE) were collected.

**Results:** Of 185 of 2578 patients who entered SFU and received another biological DMARD, 88.6% had peripheral B-cell depletion at the time of initiation of another biological agent. Thirteen SIE (6.99 events/100 patient-years) occurred following rituximab but before another biological DMARD and 10 SIE (5.49 events/100 patient-years) occurred following another biological DMARD. SIE were of typical type and severity for RA patients. 153 had received one or more tumour necrosis factor inhibitor(s). No fatal or opportunistic infections occurred.

**Conclusions:** In this analysis, treatment with biological DMARD after rituximab was not associated with an increased serious infection rate. Sample size with limited follow-up restricts definitive conclusions.

## METHODS

### Patients and follow-up

Patients with active RA who received one or more courses of rituximab (either  $2 \times 500$  mg or  $2 \times 1000$  mg infusions given 2 weeks apart) during participation in one of nine trials in an international clinical trial programme were included in the analysis.<sup>3-7</sup> Patients who withdrew from the treatment phase of their respective trial entered safety follow-up (SFU) during which SIE, peripheral CD19+ cell counts (a surrogate marker for CD20+ B cells) and concomitant medications were collected. Peripheral B-cell counts were monitored at regular intervals for 48 weeks or more. During SFU, patients were permitted to receive standard of care therapy, which may have included additional biological therapies at the discretion of the treating physician. Patients who received an additional biological agent comprised this study population. After the study treatment phase, patients were followed for at least one year for SFU. Patients remained in SFU if their CD19+ cell counts at the end of one year were below the lower limit of normal (LLN) or had returned to baseline values, whichever was less. SFU time was thus variable among patients.

## Safety

SIE were predefined as infections that required intravenous antibiotics or met the regulatory criteria for a serious adverse event, in which at least one of the following applied: required inpatient hospitalisation or prolongation of an existing hospitalisation; were immediately life-threatening; resulted in persistent or significant disability or incapacity; were medically significant, when an intervention was required to prevent one of the previously mentioned outcomes; or were fatal.<sup>4,5</sup> The rates (events per 100 patient-years) of SIE while on rituximab but before the initiation of a biological DMARD were calculated and compared with rates after initiating a biological DMARD.

## RESULTS

### Patients

At data cut-off (November 2007), 2578 patients (5013 patient-years) had been treated with one or more courses of rituximab within the clinical trial programme, with many patients receiving multiple courses. A total of 185 patients received subsequent treatment with biological DMARD. Of the 185 patients, 153 (81%) received TNF inhibitors (etanercept, infliximab and adalimumab) as their

Infection is one of the leading causes of morbidity and mortality in rheumatoid arthritis (RA) patients,<sup>1</sup> and RA patients have approximately twice the rate of infection compared with matched non-RA controls.<sup>2</sup> Given the multiple RA therapies with different mechanisms of action, the safety of switching among different biological agents, particularly with regard to the rate of infection, is an important consideration.

Rituximab, a monoclonal antibody that selectively targets CD20-positive B cells, is effective and well tolerated in the treatment of RA patients who have had an inadequate response to one or more tumour necrosis factor (TNF) inhibitor(s).<sup>3-6</sup> The pharmacodynamic effect of rituximab may be long lasting, and in patients who have discontinued treatment, the safety of treatment with other biological disease-modifying antirheumatic drugs (DMARD), during this period of B-cell depletion, has not been established.

Here, we describe the rate of serious infection events (SIE) in RA patients previously treated with rituximab and who subsequently received a biological DMARD therapy. A majority of these patients were peripherally B-cell (CD20+) depleted when another biological therapy was initiated.

**Table 1** Baseline demographic and disease characteristics of patients treated with biological DMARD following rituximab treatment

Characteristic*	All patients receiving another biological DMARD after rituximab (n = 185)
Age, years (SD)	51.2 (12.3)
Female, n (%)	145 (78.4%)
RA disease duration, years (SD)	11.9 (9.2)
Previous DMARD,† n (SD)	4.0 (2.4)
Previous TNF inhibitors, n (SD)	1.3 (0.9)
Swollen joint count, n (SD)	24.5 (13.0)
Tender joint count, n (SD)	37.8 (15.9)
C-reactive protein, mg/dl (SD)	3.7 (4.1)
DAS28-ESR (SD)	7.0 (0.9)

\*Mean values are reported when applicable. †Excludes methotrexate.

DAS28, disease activity score based on 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

biological DMARD following rituximab (including three patients who had taken other biological agents before the TNF inhibitor), 25 patients received abatacept, nine received anakinra (including two patients who subsequently took a TNF inhibitor) and one received natalizumab in a clinical trial and then was subsequently treated with etanercept. The demographic and disease characteristics of this population are summarised in table 1.

The median time from the last dose of rituximab to the first biological DMARD was 7 months (range 0.5–37 months), with a mean of 9 months (SD 6). The median follow-up time after the receipt of the subsequent biological agent was 11 months (range 0–45 months) and the mean was 12 months (SD 9). The median follow-up time before the receipt of another biological DMARD was 10 months (range 1–40 months), with a mean of 12 months (SD 9). At the time of receiving further RA treatment, the majority (88.6%) had peripheral B-cell depletion, with CD19+ cell levels less than LLN ( $\leq 80$  cells/ $\mu$ l), with a mean CD19+ B-cell count of 27.3 cells/ $\mu$ l (SD 53.4) (range 0–317).

### Serious infections

The overall rate of SIE was 4.31 events/100 patient-years (95% CI 3.77 to 4.92) during the 5013 patient-years of observation for the 2578 patients across the rituximab RA clinical trial programme. Of the 185 patients who withdrew and received another biological DMARD, 13 SIE in 12 patients over 186.05 patient-years of follow-up were reported (6.99 events/100 patient-years; 95% CI 4.06 to 12.03) during treatment with rituximab and before the receipt of another biological DMARD (table 2). The specific SIE that occurred while on rituximab, but

before subsequent exposure to another biological DMARD, included gastroenteritis, pneumonia, diverticulitis, diarrhoea, bronchitis, urinary tract infection (UTI), septic arthritis of the right hip, shigella and cellulitis (table 3). One of the cases of gastroenteritis occurred after the receipt of cyclophosphamide, but before the receipt of etanercept.

Three patients experienced two SIE. One patient had two cases of pneumonia (before and after starting anakinra). A second patient had pneumonia before starting adalimumab and a UTI after starting adalimumab. A third patient experienced bronchitis and one case of UTI before starting etanercept.

Overall, the infections were variable and typical for RA patients. All but three of the patients with SIE were also taking concomitant glucocorticoids. There were no opportunistic or fatal infections.

### All patients receiving a biological DMARD

Following the initiation of the biological DMARD, 10 SIE in 10 patients over 182.31 patient-years were reported (5.49 events/100 patient-years; 95% CI 2.95 to 10.19). The median time to SIE after initiating another biological agent was 4 months (mean 7 months (SD 8), range 0–23 months). Ten patients experienced an SIE after the receipt of a subsequent biological DMARD, which included pneumonia, UTI, cellulitis, erysipelas, viral meningitis, wound infection and bacterial arthritis.

Among the 10 patients who had SIE after biological DMARD, the median peripheral B-cell count at the time of the infection was 17.5 (range 1–312, interquartile range (IQR) 2–59.0; table 3). Eight patients had peripheral B-cell counts less than LLN at the time of receiving the biological DMARD and at the last measurement before the SIE following another biological agent. The median B-cell levels of these eight patients were 4.5 cells/ $\mu$ l (range 1–59, IQR 2–40.5). One of the eight patients had an IgG level less than LLN (5.2 g/l) before the SIE; this patient experienced a UTI while on adalimumab and subsequently had an IgG level greater than LLN 18 days after the onset of infection. The IgM level for this patient was 0.35 g/l, which was less than LLN (0.5 g/l).

### Patients receiving TNF inhibitor

The rate of SIE of the TNF inhibitor subgroup following rituximab treatment, but before the TNF inhibitor, was 6.63 events/100 patient-years (95% CI 3.57 to 12.32). The rate of SIE of the TNF inhibitor subgroup was 4.93 events/100 patient-years (95% CI 2.46 to 9.85) after receiving the TNF inhibitor (table 2).

### DISCUSSION

The study population comprised a select group of patients with advanced RA, many of whom had previously been treated with

**Table 2** Serious infection rate in patients who received treatment with another biological DMARD

	Overall (N = 2578)	Patients receiving any biological agent after rituximab treatment (n = 185)		Patients receiving TNF inhibitor after rituximab treatment (n = 153)	
		Before other biological agent	After other biological agent	Before other TNF inhibitor	After other TNF inhibitor
Total exposure, patient-years	5013	186.05	182.31	150.87	162.41
Serious infections, n	216	13	10	10	8
Serious infections/100 patient-years	4.31	6.99	5.49	6.63	4.93
95% CI	3.77 to 4.92	4.06 to 12.03	2.95 to 10.19	3.57 to 12.32	2.46 to 9.85

DMARD, disease-modifying antirheumatic drug; TNF, tumour necrosis factor.

**Table 3** SIE reported before and after another biological DMARD therapy following rituximab treatment

SIE*	Subsequent RA biological DMARD post-rituximab	Time from last rituximab dose to subsequent biological DMARD (days)	Day of onset after biological DMARD†	Last CD19+ cell count before biological DMARD	Last CD19+ cell count before SIE‡ (days from CD19+ cell count to SIE)
Before other biological agent					
Diarrhoea	ABA	392	NA	5	7 (59)
Gastroenteritis	ADA	459	NA	36	1 (38)
Diverticulitis	ADA	211	NA	4	34 (65)
Pneumonia**	ADA	181	NA	3	0 (15)
Pneumonia§	ANK	171	NA	1	1 (21)
Diverticulitis	ANK	515	NA	10	0 (11)
Bronchitis¶‡‡	ETN	521	NA	166	116 (44)
Infection of right hip	INF	262	NA	0	1 (12)
UTI¶‡‡	ETN	521	NA	166	359 (51)
Gastroenteritis	Post-CYC, pre-ETN	239	NA	11	0 (21)
Shigella infection	INF	358	NA	8	4 (52)
Cellulitis‡‡	INF	114	NA	0	0 (42)
UTI‡‡	INF	366	NA	40	6 (12)
After other biological agent					
Erysipelas	ETN	148	18	2	2 (39)
Cellulitis	ETN	43	51	3	59 (8)
Arthritis, bacterial**	ETN and INF	156	417 days after starting INF, 77 days after starting ETN	1 (INF), 53 (ETN)	53(83)
Pneumonia	ABA	148	201	4	122 (6)
Pneumonia§	ANK	171	5	1	1 (28)
Meningitis (viral)	ADA	382	41	16	7 (37)
UTI**	ADA	181	173	3	2 (73)
UTI††	ETN	230	713	0	28 (62)
Cellulitis	ETN	166	512	2	2 (82)
Wound infection	ETN	389	94	85	312 (45)

\*Patients with multiple serious adverse events are indicated. †In the case of serious infection before receipt of another biological disease-modifying antirheumatic drug (DMARD), this is not available (NA). In the case of a serious infection after another biological DMARD, this refers to the duration following receipt of the biological DMARD to serious infection events (SIE). ‡The lower limit of normal of peripheral CD19+ B-cell counts is  $\leq 80$  cells/ $\mu$ L. Note that CD19+ cell counts were often taken at various time intervals before the SIE (range 6–83 days; median 39 days). §The same patient experienced SIE before and after the receipt of anakinra (ANK). ¶Patient experienced bronchitis followed by urinary tract infection (UTI) 4 months later. \*\*Patient experienced pneumonia before receipt of adalimumab (ADA) and experienced UTI after receipt of ADA. ††Patient took blinded natalizumab before etanercept (ETN). ‡‡Four events were not categorised as serious adverse events per protocol, but required intravenous antibiotics. ABA, abatacept; CYC, cyclophosphamide; INF, infliximab; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

multiple RA therapies, including biological agents before receiving rituximab, and then withdrew from clinical trials and subsequently received further biological therapy. In this analysis, the rate of SIE in patients who withdrew from rituximab and received a subsequent biological DMARD was 6.99 events per 100 patient-years (95% CI 4.06 to 12.03) before exposure to another biological DMARD and 5.49 events/100 patient-years (95% CI 2.95 to 10.19) after exposure to another biological agent. The majority of patients were B-cell depleted at the time of receiving another biological agent. The nature of the infections reported and their clinical course were consistent with SIE typical of patients with RA treated with DMARD or other biological therapies.<sup>8,9</sup> Importantly, there were no fatal or opportunistic infections pre or post another biological DMARD following rituximab treatment.

Although the current study is not a controlled trial of combination therapy, this analysis provides a unique opportunity to examine indirectly the potential effects of biological therapy combined with low/depleted B-cell levels. Of note is the fact that in studies in which TNF inhibitors have been used in combination with other biological agents (eg, anakinra and abatacept),

increased rates of infections have been reported, even with low patient numbers and short durations of follow-up.<sup>10,11</sup>

However, given the small sample size, the short follow-up, and wide confidence intervals of the point estimates, these data should be considered preliminary. In earlier data analysis, with a report of 107 patients, the rates of serious infections were numerically different but continued to remain within the range of the confidence intervals.<sup>12</sup> One additional consideration is that these patients represent patients previously enrolled in clinical trials and may differ from patients who did not meet inclusion/exclusion criteria.

In conclusion, these data appear to suggest that despite patients being B-cell depleted in the peripheral blood when further RA biological DMARD were initiated, the rate and nature of SIE remain consistent with those observed during rituximab treatment and within expectations for patients treated with biological therapies. Further data are warranted before definitive conclusions can be drawn regarding the risk of SIE in patients who receive another biological DMARD while B-cell depleted. Controlled studies to assess the safety of biological DMARD in combination with rituximab are ongoing.

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**Role of the study sponsors:** Data collection was co-sponsored by F Hoffmann-La Roche Ltd, Biogen Idec, Inc and Genentech, Inc. Statistical analyses were conducted by qualified statisticians who were employees of the sponsors. All the authors had access to and involvement in the interpretation of the data and input into the content of this manuscript (supervised by MCG).

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# Corrections

The department of one of the authors who co-authored all of the below papers has found that the affiliations were not correct. The correct affiliations for Professor P Emery, for all of the below articles, are: <sup>1</sup>Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds; <sup>2</sup>NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, UK.

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