Journal of
Clinical & Cellular Immunology

de la Torre et al., J Clin Cell Immunol 2013, S6
DOI: 10.4172/2155-9899.S6-005

Research Article Open Access

Impact of Non-Fixed Versus 6 Month Fixed Retreatment Schedules on Serum Immunoglobulins Following Rituximab in Patients with Rheumatoid Arthritis

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Abstract

Objectives: To assess the incidence of secondary hypogammaglobulinemia in patients with rheumatoid arthritis (RA) following multiple cycles of rituximab (RTX) related to two different therapy regimens.

Methods: 73 patients with RA were retreated using 6 months-fixed strategy and 63 patients using a non-fixed regimen. All received ≥ 2 courses of RTX. Data on serum immunoglobulins (Ig), serious infections and DAS28 were collected, with maximum follow-up being 24 months for the 6 months fixed group and 156 months for the non-fixed group). Statistics for non-parametric analysis were applied.

Results: The percentages of patients developing low IgG or IgM did not differ between groups after the 3rd cycle, but those with non-fixed retreatment tended to be higher. After 4 cycles, median IgM levels were significantly lower in both groups compared with pretreatment ($p<0.05$). Only patients in the fixed retreatment group receiving 4 cycles of treatment showed a significant drop in median IgG level ($p<0.05$). IgA levels remained within the normal range. Withdrawals due to infections per 100 patient years (py)s in patients with low IgG were higher after 3 Cycles in patients within the fixed retreatment group (4.60/100py *vs* 1.36/100py, CI: 0.59, 6.23). DAS28 did not differ between cohorts after multiple cycles.

Conclusions: Although the percentage of RA patients developing low IgG tended to be higher in the non-fixed group, median IgG level was significantly lower after 4 Cycles of RTX in the fixed regimen group. The fixed retreatment group also had more patients discontinuing rituximab over a shorter period of time (24 months compared with 156 months), with no significant differences in median DAS28 after multiple Cycles. If multiple cycles of RTX are to be instituted, non-fixed regime may allow the opportunity to control the disease with a lower incidence of withdrawal due to low Igs and infections.

Keywords: Rituximab; Hypogammaglobulinaemia; DAS28; Infections

Abbreviations: RTX: Rituximab Rituxan; Ig: Immunoglobulin; DMARD: Disease Modifying Anti-Rheumatic Drug

Background

In patients with RA, the rationale of B cell depletion therapy (BCDT) based on Rituximab (RTX) was to eliminate autoreactive B cell clones, as precursors of autoantibody secreting cells, while minimizing the period of impact on normal B cells and protective antibody production [1]. Edwards et al. defined a retreatment strategy for patients (retreatment with any deterioration) [2] considering observations of the clinical response to RTX–based therapy [3] international treatment-to-target guidelines, would advise patients to be retreated from six months if patients did not reach (or are no longer) in remission or at least low disease activity [4,5]. Nevertheless, the optimal retreatment regime with RTX has not been fully determined and it includes treatment-to-target as above, treatment on flare (as in earlier randomized clinical trials), regular retreatment, for example, every 6 months, and retreatment with any deterioration.

When levels of CD19 depletion (<0.1%) are attained in the circulation after RTX, clinical benefit can last for months or in some cases, years [3,6]. An important early observation was that clinical relapse followed B cell repopulation, and in up to 50% of patients in the initial cohort, it occurred several months after B cell return. Reconstitution of memory B cells (CD27+) following RTX in RA is often slow [7] and although falls in total immunoglobulin levels following single cycles of BCDT based on RTX are modest, there is evidence for progressive decrease with repeated cycles [3,8,9]. Pooled analysis of safety data from the global clinical trial program from Roche and Genentech, showed that the proportion of patients with low IgM at 6 months post-RTX increased with each additional course from 10% of patients after 1st cycle to up to 40% following 5 cycles. The proportion of patients with low IgG by course remained relatively stable, from 3%–6% [8] although in clinical practice a progressive fall has been reported [9]. The percentage of patients with low IgA did not decrease from baseline in any scenario, being <1% for multiple courses. The practical application of results obtained in clinical trials, where patients are by definition selected for admission, to the treatment of consecutive patients attending clinics can be confusing.

As part of an on-going prospective study of the effect of B cell depletion therapy on immunological parameters, we investigated

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Received December 04, 2012; **Accepted** January 17, 2013; **Published** January 24, 2013

Citation: de la Torre I, Leandro MJ, Gerona D, Valor L, Carreno L, et al. (2013) Impact of Non-Fixed Versus 6 Month Fixed Retreatment Schedules on Serum Immunoglobulins Following Rituximab in Patients with Rheumatoid Arthritis. J Clin Cell Immunol S6: 005. doi:10.4172/2155-9899.S6-005

the impact of two different treatment regimes based on RTX on immunoglobulin levels and their relationship with infections and the withdrawals because of serious infections from RTX-based treatment programmes.

Methods and Patients

73 patients from Hospital Gregorio Marañon (HGUGM) (all receiving 6 month fixed retreatment) and 63 patients from University College London Hospitals (UCLH) (non-fixed retreatment) with active RA who fulfilled the revised American College of Rheumatology/EULAR criteria [10,11], and retreated with 2 or more cycles of RTX, were included in the study. In the 6 month fixed treatment group, 73 patients received 2 cycles, 57 patients received 3 cycles, and 40, 4 cycles. In the non-fixed regime group, 63 patients received 2 cycles, 37 received 3 and 25 a 4th cycle. After the 4th cycle, follow up was completed only up to the 6 month time point, so for the non-fixed group, as that cycle would not be completed, part of the follow up time in this cycle would have been lost. In the fixed cohort, 7/73 (9.6%) patients were seronegative for rheumatoid factor and/or anti-citrullinated peptide antibodies and in the non-fixed group, 1/63 (1.6%) were seronegative. Induction of B-cell depletion was the same for all patients, consisting of two infusions of 1g RTX 1-2 weeks apart, each preceded by 100mg intravenous methylprednisolone. The study was approved by both Hospital Ethics Committees and all patients gave informed consent.

As part of a non-randomised, observational and prospective follow up study, routine clinical data and blood samples were obtained at baseline and at least every 3/4 months. In order to perform comparisons, and due to different retreatment times in both groups, we collected data on Ig levels (g/L), total lymphocyte count and DAS28 at baseline, i.e. before infusion of drug in each cycle, up to the fourth cycle, and at 6 months after each cycle, regardless of therapy regime. Data was collected on a common database, in use at both centres. Ig levels were measured by nephelometry and normal ranges were defined as: IgG: (7-16.0 g/L), IgM: (0.4-2.3 g/L), IgA: (0.7-4.0 g/L). Serious infections (defined as events that were fatal, immediately life-threatening or requiring hospitalisations due to specific therapy requirements) and whether occurring in the presence or absence of low Igs in any class, and causing interruption/withdrawal of therapy were also collected retrospectively.

Patients receiving a regular 6 months fixed regimen were treated following international guideline recommendations [4]. Patients treated at UCLH on the non-fixed regimen based on tight control strategy [2], namely patients were retreated when there was any return of symptoms of RA with or without rise in C-reactive protein (CRP) following an original fall of at least 50% in CRP during the previous course of B-cell depletion therapy in relation with DAS28>2.6 or DAS28 increase>1.2 from minimum achieved.

Statistical analyses

Summary statistics were calculated for comparisons of 6 month fixed and non-fixed treatments using non-parametric tests and 95% Confidence Interval (CI) (Newcombe test). Incidence of serious infections in patients with low Ig causing therapy withdrawal was calculated as number of events/100 treated patients per year (py). All data management and analyses were done using GraphPad Prism 5.

Results

Demographic data

As shown in Table 1, median disease duration was significantly longer in the UCL cohort, but there were no other differences related to demographic data including baseline age, pre-RTX values for DAS28 and baseline Ig levels for both cohorts. However, all patients had at least 2 years history of RA. Also, as RTX has been approved as an option after anti-TNF failure, the majority of patients in both cohorts had experienced continuous synthetic and biological drug failures. We therefore suggest that patients were comparable between centers in relation to the objectives analyzed here, i.e. immunoglobulin dynamics and infections. In Table 2, the number of patients retreated and median times to retreatment are shown for both cohorts. Only patients who clearly responded to the first cycle of treatment and received a second cycle were included. In the 6 month fixed treatment cohort, over four cycles, 9 patients (12.3%) withdrew due to partial/total lack of response, 7 (9.5%) experienced serious adverse events and 4 were lost to follow up (5.4%). 54.7% of patients receiving the fixed regimen (n=40) continue on therapy and were followed up to the 4th cycle and 18% (n:13), undergoing the therapy were not followed-up for long enough to enable data collection after 4 Cycles due to the study end time point.

Of the patients treated with at least 2 cycles within the non-fixed group, 2 (3.1%) withdrew because of partial/total lack of response, 3 (4.7%) with serious adverse events and 3 (4.7%) were lost to follow up. 36.5% of patients in the Non-fixed Group (n=23) continue on therapy

(Median, p25-p75)	HGUGM cohort Fixed 6 months retreatment	UCL cohort Non fixed retreatment
Age (years)	57 (35-68)	53 (32-75)
Disease duration (years)	12 (2-20)	21 (8-35)*
Previous DMARDs	3 (1-3)	3 (1-5)
Previous anti-TNF	1.5 (1-2)	1.5 (1-3)
Baseline DAS28	5.3 (2.8-7.0)	6.0 (5.2-8)
Baseline IgG (g/L)	10.1 (8.8-13.2)	12.5 (10.2-15.5)
Baseline IgM (g/L)	1.1 (0.8-1.9)	1.4 (0.8-18)
Baseline IgA (g/L)	2.6 (1.8-3.8)	3.3 (2.5-4.3)

*p<0.05, Mann Whitney U-test

Table 1: Demographic data.

	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
Treatment Regime	Fixed	Non fixed	Fixed	Non fixed	Fixed	Non fixed	Fixed	Non fixed
N (patients in each Cycle)	73	63	63	63	57	37	40	25
Months to retreatment (Median and range)	6 (5-7)	15 (7-48)	6 (5-7)	15 (7-48)	6 (5-7)	16 (7-48)	6 (5-7)	20 (7-32)

Table 2: Shows number of patients treated per cycle in each retreatment group and the median and range for each course of treatment in each cycle.

Parameters after 3 cycles of RTX	Fixed retreatment n:57	Non Fixed n:37	Relative risk (95% confidence intervals)
% patients with low IgG	4.3	15.3	3.08 (0.48-8.65)
% patients with normal IgG and infections	5.26	10.81	2.05 (0.07-8.19)
% patients with low IgG and infections	3.50	2.70	0.77 (0.07-8.19)
Patients with low IgG and withdrew because of infections	4.6/100 p/y	1.36/100 p/y	(0.59-6.23)

Table 3: Relationship between the presence or absence of low IgG levels with infections and with withdrawal from the study.

and were followed up to the 4th cycle, however, 50.7% (32) were not followed up after the 4th cycle, as described for the fixed group. (A lower % of patients within the non-fixed group were followed up to the 4th cycle because of the extended period until retreatment when compared to the 6 month fixed group).

Median Ig levels and maximum percentage change

There was no significant difference between median Ig levels at baseline and at the 6 month time points after each cycle between the treatment groups within each cycle (Wilcoxon paired analysis) (Figure 1). Of the patients who completed 4th cycles, there was a significant fall in IgM levels from initial pre-RTX to 6 months after the 4th cycle using both regimens (fixed regimen, p=0.009; non-fixed regimen, p=0.03, Wilcoxon paired analysis) (Figures 1A and D), with IgG decreasing significantly only in the 6 month fixed group (p=0.05) (Figure 1C). The decrease in IgM and IgG levels after the 4th cycle was therefore significantly greater in the 6-month fixed treatment cohort, despite the shorter period of therapy compared to the non-fixed cohort. As shown in Figure 2, this was indeed the case, where percentages of maximum increase between 6 month values to the following pre-cycle determination for patients in the non-fixed cohort were apparent for all Ig classes. In Figures 3A and 3B, % of maximum decrease in Ig isotypes is plotted against months of follow-up to the 6 month point after the 3rd cycle. Maximum decreases were similar between groups

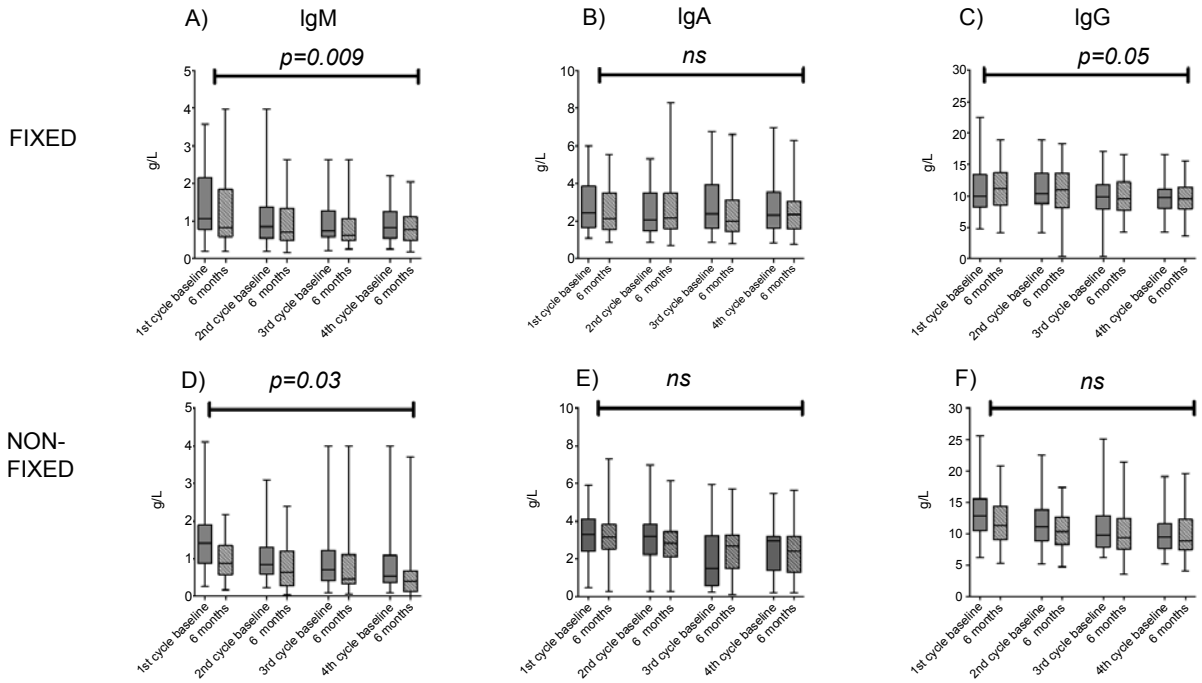

Figure 1: Box and whiskers plots (median and range) and 6 month levels of IgM, IgA and IgG respectively in patients with RA receiving either a 6 month fixed retreatment (A), (B), (C) or a non-fixed retreatment protocol (D), (E), (F,). P values shown were calculated using Wilcoxon matched pairs test for non-parametrically distributed data comparing patients before the first cycle of RTX with those remaining in the study 6 months after 4th cycle.

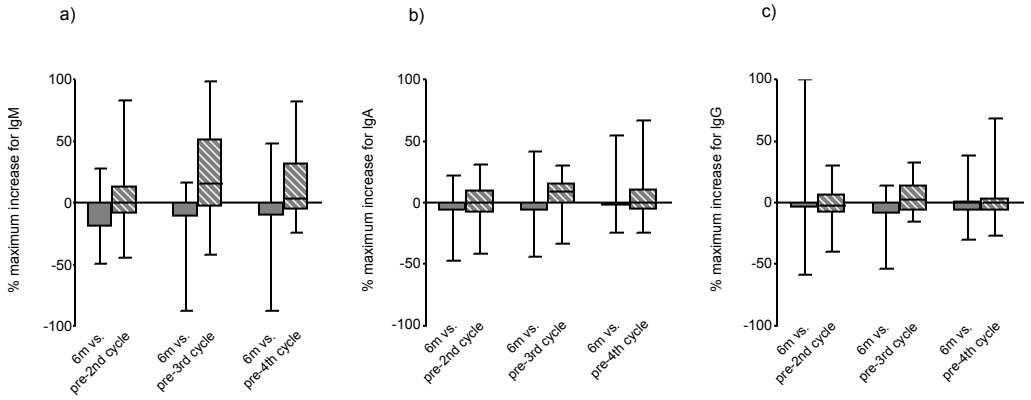

Figure 2: Patients receiving non-fixed retreatment protocol. Box and whiskers (median and range) plots showing % maximum decrease in Ig levels between pre-cycle to 6 month time points in each cycle and then from the 6 month time points up until the beginning of the following cycle of RTX for IgM (A), IgA (B) and IgG (C).

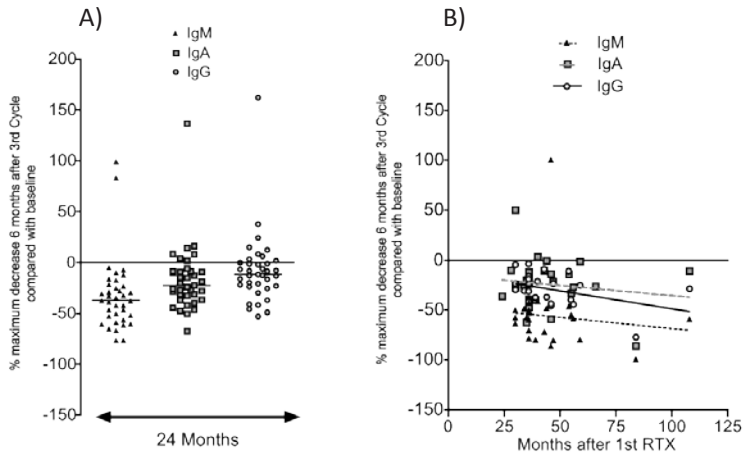

Figure 3: (A) Shows the percentages of maximum decrease for each patient at 6 months following the 3rd cycle of RTX in the 6 month fixed cohort. (B) Shows the percentage maximum decrease of Ig levels 6 months after the 3rd cycle of RTX therapy in the non-fixed retreatment cohort plotted against time after start of first cycle of RTX. Linear regression lines are shown but there was no significant correlation between time and %maximum decrease for any Ig class.

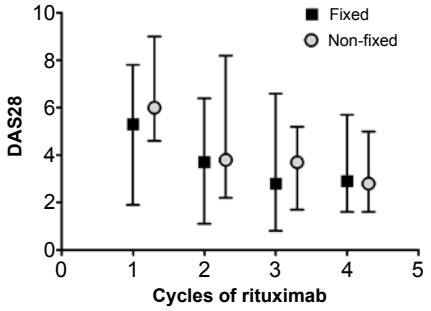

Figure 4: Median and range of DAS28 scores at the 6 month time point after each RTX cycle for patients receiving either the fixed or the non-fixed retreatment protocol.

despite the differences in time over which the 3 courses of treatment were delivered (24 months for the fixed retreatment cohort and 112 for non fixed cohort). There was no correlation between % of maximum decrease and time in the non-fixed group (linear regression; $r^2<0.25$ for all 3 Ig classes).

Relationship of Ig levels with infections and withdrawal from study

Even though the proportion of new patients developing low IgG (<7 g/L) tended to be higher without reaching statistical significance for the non-fixed group after multiple cycles (Table 3) (after 3rd cycle : 15.3 *vs.* 4.3%, CI: -0.38,0.08, ns) the number of patients with serious infections with IgG levels remaining within the normal range was higher than those with low IgG in both cohorts (Table 3). However, withdrawals due to serious infections in patients with low IgG were significantly higher after the 3rd cycle in patients within the 6 months fixed regimen, compared to those in the non-fixed group (4.6/100 py *vs.* 1.36/100 py, CI: 0.59, 6.23, p<0.05). Infections of the respiratory tract requiring intravenous antibiotics were the main cause of serious infectious episodes. Two of the patients from the 6 month fixed regimen required monitoring due to cardiovascular failure. Incidence of renal or serious skin infections was <1%. Any infections due to opportunistic microorganisms were collected, although some infections were recurrent due to antibiotic resistance. The percentage of patients with low IgM after the 3rd cycle was greater in the non-fixed group (25.0 vs. 8.3%, CI: -0.46, -0.03, p<0.05), but there were no correlations with infection independent of low IgG. The proportion of patients with low IgA was similar for both groups and per cycles.

DAS28 after multiple cycles

Both strategies tended to decrease Ig levels. It could be suggested that in order to preserve clinical remission, patients should be treated with a 6 months-fixed regimen. DAS28 scores in fixed vs. non-fixed retreatment cohorts at the 6th month point following each cycle were therefore compared (Figure 4). Although after the 2nd and 3rd cycle, median DAS 28 tended to be lower within the 6 months fix group, they were not significantly different and median values were similar after the 4th cycle, fixed, 2.90 *vs.* non-fixed 2.80, p=0.8).

Discussion

In initial Phase IIa clinical trials of treatment of patients with RA with RTX, mean Ig levels were within the normal range [12], with an increased frequency of patients affected with hypogammaglobulinemia after multiple cycles [8,9]. Long lasting hypogammaglobulinemia following treatment with RTX (as monotherapy or in combination with chemotherapy) has been also seen in, for example, patients with post-transplant Epstein–Barr virus associated lymphoproliferative disorder [13], post autologous bone marrow transplantation [14] as well as in autoimmune cytopaenia [15]. Rituximab therapy has also been suggested to precipitate hypogammaglobulinaemia [16].

In this observational study, IgM and IgG levels below the normal range were found here in both cohorts. After multiple cycles, median decreases were seen more frequently within the non-fixed retreatment regimen than within the 6 month fixed regimen for both IgM and IgG, as shown in Figure 1. Much of the serum IgM is produced from short-lived plasmablasts and from pre-switch memory B cells. Regeneration of B cells is from naive B cell populations produced in the bone marrow. The finding that decreases in IgM were more common after repeat cycles in the fixed group, where retreatment was instituted without regard to B cell reconstitution, would result in the repeated removal of regenerating naive B cells, preventing the generation of plasmablasts producing IgM. As most serum IgG is produced from rituximab-resistant long-lived plasma cells, levels of IgG are more robust, but the more frequent removal of B cells capable of generating

'new' class-switched B cells in those on the fixed regime may explain the lower levels of IgG after 4 cycles in the fixed group. The extended period of time between retreatment with RTX in the non-fixed group might also therefore allow patients to recover IgG levels before entering the following cycle. However, low IgG, per se was not the cause of the higher proportion of patients with serious infection stopping therapy. As we showed in Figure 2, in the non-fixed retreatment group, levels of Igs were shown to increase in the interval before induction of the next cycle perhaps due to allowing better reconstitution and therefore time to possibly restore IgG levels. The higher proportion of patients with IgG within the normal range suffering infections may partly reflect caution in re-treatment of patients with progressive Ig falls after multiple cycles. A number of studies have now confirmed that protective antibodies are relatively preserved following multiple cycles of RTX-based therapy, whilst autoantibody-committed B cell clones and their daughter plasmablasts are relatively short-lived [17,18]. Repopulation of the memory B cell pool is delayed after RTX, but the reasons why some patients but not others suffer a relatively fast attrition of IgG-producing plasma cells, especially in the non-fixed group, is not clear. Low IgM levels develop in a higher proportion of patients after RTX, but are not usually associated with development of low IgG levels. Low IgM levels are especially common in patients with a longer gap between B cell repopulation and relapse and may relate to an underlying slow rate of B cell maturation and with persistently raised BAFF (B cell Activating Factor) levels in these patients [19].

Treating all patients with B-cell depleting therapies every six months, independently of their clinical and immunological state, may not to be the most appropriate strategy for at least a proportion of RA patients. Some patients may therefore be receiving extra cycles of RTX while still B cell depleted and thus the possible effect on the recovery of the B cell maturation process in individual patients is not being taken into account. Although it may be sensible to give two consecutive 6 months-cycles of RTX in order to achieve and optimize the initial clinical benefit, after the 3rd cycle, we should be cautious about which patients need to be retreated. This idea has been discussed recently in patients coming from clinical trials where a treatment to target strategy, rather than a regular fixed regimen, has been suggested as a better option for retreatment [5]. In support of this conclusion, we found that further fixed cycles every 6 months did not seem to reach a better clinical response (as shown by DAS28), but could produce and increase side effects with persistently low IgG and also with serious infections.

As far as we are aware, this is the first time that different and valid strategies for retreating patients with RTX (not coming from clinical trials) have been compared focusing on hypogammaglobulinaemia and serious infections. Although the study was not strictly randomized, the inclusion of two different reference centers each using only one strategy of treatment with RTX, tends to support consistency within retreatment regimens. In the clinic, these findings may have relevance to both the aim of preserving a good clinical response without adding serious side effects.

In conclusion, the cohort following a non-fixed course receiving fewer total doses of rituximab and had lower cases of serious infection, whilst maintaining comparable DAS28 scores. Although a clinical trial should be designed to address this question, once remission or low disease activity has been achieved, non-fixed retreatment strategy based on individual clinical response observations and aiming to retain clinical remission or low active disease (tight control) might be a logical option.

Key Messages

Fixed *vs*. non-fixed regimens are equally valuable to preserve clinical remission.

Serious infections in patients with hypogammaglobulinaemia leading to RTX withdrawal are less common if patients, once in remission, are treated with non-fixed regimen based on regular follow up.

Acknowledgements

We would like to thank Mr Jorge Ruiz, from Mixestat S.L for his support on realising the statistical analyses and Bryony Alderman for assistance with collating clinical data.

Conflicts of Interest

None

Funding

This work was supported by the Worshipful Company of Grocers of the City of London. Dr De La Torre was funded by the Alonso Martin Escudero Foundation, Spain.

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This article was originally published in a special issue, **Immunotherapies and Rheumatoid arthritis** handled by Editor(s). Dr. Hongkuan Fan, Medical University of South Carolina, USA