

Original article

Long-term persistence of rituximab in patients with rheumatoid arthritis: an evaluation of the UCL cohort from 1998 to 2020

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Abstract

Objectives. B cell depletion therapy based on rituximab in patients with RA was pioneered at University College London Hospitals/University College London in 1998. The objective of this study was to evaluate long-term persistence of rituximab and identify factors associated with discontinuation of treatment.

Methods. Retrospective review of medical records from all rituximab-treated RA patients followed up in a dedicated clinic (1998–2020). Data collected included gender, disease duration, previous DMARDs, autoantibody status, age and concomitant therapy at first cycle, length of follow-up, and number of cycles. Drug survival and factors associated with drug discontinuation were analysed using Kaplan–Meier survival curves, log-rank test and Cox regression analysis.

Results. A total of 404 patients were included. Median disease duration and age at time of first rituximab cycle were 10 and 57 years, respectively. Median total follow-up was 55 months and median number of cycles five. 93.1% of patients were seropositive. Overall, 31.2% of patients stopped rituximab, with the largest reason for discontinuing being primary inefficacy (42.1%). Comparison of Kaplan–Meier curves showed that rituximab drug survival was lower in seronegative patients and in patients who had previously failed at least one biologic DMARD (bDMARD). Cox regression analysis revealed that rituximab discontinuation was associated with a greater number of previous bDMARDs.

Conclusion. Many patients with RA achieve good control of their disease with repeated cycles of rituximab treatment. The most common reasons for treatment discontinuation were either primary or secondary inefficacy. Patients who were seronegative and who had previously failed other bDMARDs were more at risk of drug discontinuation.

Key words: rheumatoid arthritis, rituximab, drug survival, bDMARDs, B cells

Rheumatology key messages

- Seronegativity and previous treatment with biologic DMARDs were associated with lower treatment survival on rituximab.

Introduction

RA is a chronic systemic autoimmune inflammatory disease that predominantly affects diarthrodial joints. RA rarely goes into remission without treatment and patients usually require treatment with multiple different

DMARDs during the course of their illness. This is due to a combination of lack of or inadequate response during induction treatment (primary inefficacy) and/or development of side effects (intolerance), but also to loss of response following an initial period of benefit (secondary inefficacy). It is unclear what lies behind secondary loss of efficacy of DMARDs in RA.

The introduction of treatment with biologic DMARDs (bDMARDs) has remarkably improved patient outcomes. bDMARDs used in the treatment of RA include different classes of drugs such as anti-cytokine therapies targeting TNF or IL-6, a blocker of T cell interaction with antigen-presenting cells (CTLA4-Ig) and a B cell depleting agent (anti-CD20). However, treatment with

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bDMARDs is associated with secondary inefficacy, attributable, at least in part, to the development of anti-drug antibodies that either block drug interaction with target and/or increase drug clearance leading to sub-optimal drug levels. This has been well documented for the TNF inhibitors infliximab and adalimumab.

Nevertheless, secondary loss of efficacy can be observed with all drugs used in the treatment of RA, including those for which there is no known development of neutralizing anti-drug antibodies [1]. It is therefore presumed that changes in pathogenic mechanisms of disease perpetuation can drive, at least in part, secondary inefficacy to both bDMARDs and conventional synthetic DMARDs (csDMARDs).

Rituximab is a chimaeric anti-CD20 mAb that depletes B cells. It was first used to treat RA patients at University College London Hospitals (UCLH)/University College London (UCL) in an open-label study starting in 1998 and has been licensed since 2006 [2–5]. In patients who respond to treatment, continued control of RA disease activity is obtained with repeated cycles of treatment.

The aim of this study was to assess the long-term persistence of rituximab therapy and to investigate for potential predictors of drug discontinuation in patients with RA under the care of a dedicated clinic at UCLH from 1998 until 2020.

Methods

Patients

This study was a retrospective review of medical records, as part of a service evaluation of clinical care, of patients with RA who received treatment with rituximab under follow-up in a dedicated clinic at UCLH from November 1998 until March 2020. According to National Health Service Research Ethics Committee guidelines, no formal ethical approval was required [6]. Data evaluated included gender, autoantibody status (RF, anti-CCP and ANA), age and disease duration at the time of first rituximab cycle, previous treatment with csDMARDs and bDMARDs, and concomitant treatment with csDMARDs and oral CS (prednisolone) at the time of first rituximab cycle. Follow-up data collected included overall response to rituximab, total duration of follow-up while on rituximab, number of rituximab cycles and the time interval between cycles, reason for rituximab discontinuation defined as primary inefficacy (no response or insufficient response), secondary inefficacy (loss of response following initial response to treatment), side effects or other. For patients who continued on rituximab at the time of data cut-off (March 2020), data on concomitant medications at the time of last rituximab cycle and disease activity scores at last clinic visit expressed using the DAS based on 28 joints and ESR (DAS28ESR) were also collected. Responders were all patients who did not have primary inefficacy.

Rituximab treatment protocol at UCLH

Initially RA patients who responded to rituximab were retreated at the time of flare (on-demand retreatment); over time provisional retreatment was offered to patients approximately 1 month before they were expected to flare and not <6 months after their previous cycle. The initial 22 patients (who received their first cycle of treatment from November 1998 to June 2000) were treated as part of two open-label trials [3]. A total of 73 patients were initiated on rituximab before rituximab was licensed for RA in Europe in September 2006 and a further 7 patients until July 2007 when the National Institute for Health and Care Excellence approved rituximab for the treatment of RA in the UK and its use became part of routine clinical practice. Even though CYC was included in several of the initial treatment protocols as part of the open-label trials, its use was abandoned from 2001 once it was clear that it could not prevent disease flare with the associated need for retreatment with rituximab. Retreatments were in the large majority of cases with standard rituximab dose (two infusions of 1 g).

Statistical analysis

Descriptive statistics for categorical (number and percentages) and numerical [median and interquartile range (IQR)] variables were used to describe distribution of the data. Persistence on rituximab displayed as survival curve was calculated using the Kaplan–Meier method. Survival curves were compared using the log-rank test. Cox proportional hazard regression analysis was used to identify factors associated with drug discontinuation and quantify the risk. Statistical analysis was performed using IBM SPSS Statistics, Version 26 (Armonk, NY, USA).

Results

A total of 404 patients were included in the study and patient characteristics are described in [Table 1](#). Three hundred and twenty-seven patients were female (80.9%) and 77 male (19.1%). Median age at first rituximab cycle was 57 years (range 16–86) and median disease duration was 10 years (range 0–55). At UCLH rituximab treatment is considered mainly in seropositive RA and therefore 376/404 (93.1%) patients were seropositive for either RF or anti-CCP antibodies: 361/403 (89.6%) were RF positive and 324/393 (82.4%) were anti-CCP positive. One hundred and sixty-two of the 404 (40.1%) patients were ANA positive, including 11 of the 28 (39.3%) seronegative patients. Prior treatment included a median of 3 csDMARDs (range 1–6), and rituximab was the first biologic used in 108/403 (26.8%) patients. In the 295 patients who had previously tried other bDMARDs, the median number of previous bDMARDs was 2 (range 1–4).

Data on concomitant therapy at the time of the first rituximab cycle was available in 376/404 (93.1%)

TABLE 1 Characteristics of RA patients treated with rituximab

	Whole cohort	Responders
Total number of patients	404	351 (86.9)
Gender, female/male, <i>n</i> (%)/ <i>n</i> (%)	327 (80.7)/77 (19.1)	284 (80.9)/67 (19.1)
Age at first RTX cycle, median (IQR), years	57 (44–65)	57 (44–65)
Disease duration at first RTX cycle, median (IQR), years	10 (5–21)	10 (5–22)
Seropositive, <i>n</i> (%)	376/404 (93.1)	333/351 (94.9)
Total follow-up, median (IQR), months	55 (16–106)	63 (26–110)
Number of RTX cycles, median (IQR)	5 (4–10)	6 (3–11)
Interval between RTX cycles, median (IQR), months	NA	7.8 (6–11)
Previous csDMARDs, median (IQR)	3 (2–4)	3 (2–3)
Previous bDMARDs, median (IQR)	2 (1–2)	2 (1–2)
Previous bDMARDs, <i>n</i> (%)	294/393 (74.8)	255/350 (72.9)
Patients on concomitant csDMARDs at first RTX cycle, <i>n</i> (%)	238/376 (63.3)	204/327 (62.4)
Patients on concomitant oral prednisolone at first RTX cycle, <i>n</i> (%)	119/376 (31.6)	105/327 (32.1)

RTX: rituximab; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; NA, not applicable.

patients. Two hundred and thirty-eight (64.9%) of these patients were on concomitant csDMARDs, with the majority of the patients being on concomitant MTX (41.9%), followed by SSZ (17.0%) and HCQ (15.9%). Only 3.7% of patients were on concomitant LEF at the time of their first rituximab cycle. The majority of patients were on one csDMARD (41.7%), with 18.5% being on two and 7.7% on three.

One hundred and thirty-eight (37.6%) patients were not on a concomitant csDMARD at the time of their first rituximab cycle. Nearly one-third of these patients was on oral prednisolone (43/138, 31.2%), almost the same as the proportion of patients on concomitant oral prednisolone in the whole group, as shown in [Table 1](#).

Median total follow-up from first rituximab cycle was 55 months (range 5–248). Three hundred and fifty-one (86.9%) patients responded to rituximab. Responders were all patients who did not fail rituximab for primary inefficacy.

The median number of rituximab cycles in the whole cohort was 5 (range 1–22). Median interval between rituximab cycles was 7.8 months (range 6–74). [Table 1](#) includes patient characteristics in the responders.

At data collection cut-off date, 212 (52.5%) patients were on rituximab. Median (IQR) DAS28ESR at last follow-up visit was 2.4 (1.5–3.4). Median (IQR) swollen joint count was 0 (0–1), tender joint count was 0 (0–3), patient global visual analogue scale was 40 (20–60), ESR was 6 (2–14) and median (IQR) CRP was 3.2 mg/dl (1.3–5.6).

During the study duration 191 (47.3%) patients left the cohort, including 42 (10.4%) patients who died while on rituximab, 16 (4.0%) patients who were lost to follow-up (this included patients who moved their care to another hospital in the UK or who moved country), 6 patients (1.5%) who went into long-term remission and have not needed retreatment with rituximab or initiation of another bDMARD and 2 patients who stopped to try to conceive. Among the 42 patients who died while on rituximab, no cause of death was directly attributed to

TABLE 2 Reasons for discontinuing rituximab

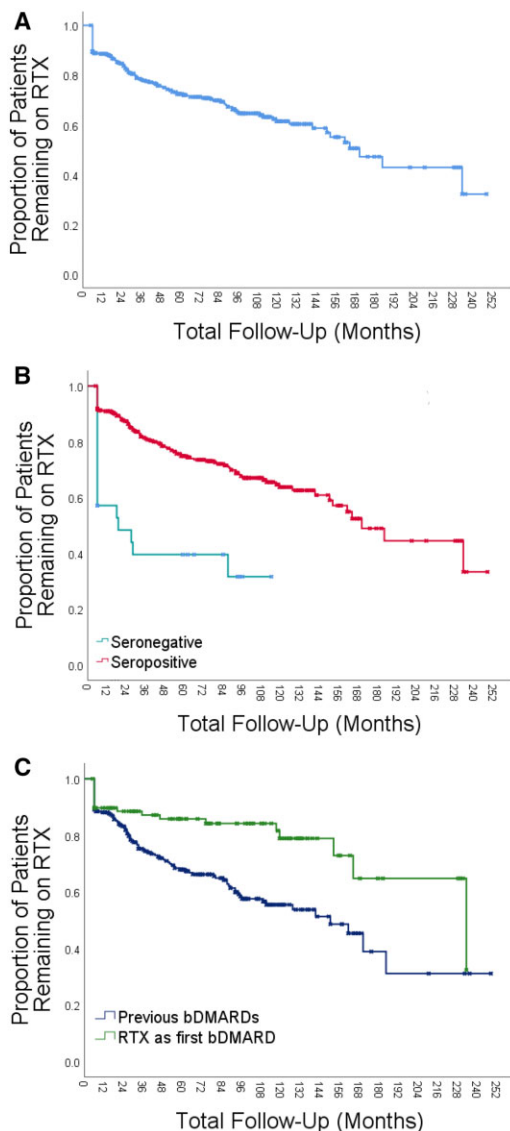
Total number of patients, <i>n</i> (%)	126/404 (31.2)
Reasons for stopping, <i>n</i> (%)	
Primary inefficacy	53 (42.1)
Secondary inefficacy	42 (33.3)
Adverse effects	37 (29.4)
Hypogammaglobulinaemia	14
Infections (chest/sinus)	12
Infusion reaction	12
Serum sickness reaction	1

treatment with the drug. However, six of the patients died of infection, and immunosuppression with rituximab is likely to have been a contributing factor ([supplementary Table S1](#), available at *Rheumatology* online).

Reasons for stopping rituximab in the other 126/404 (31.2%) patients are specified in [Table 2](#). Fifty-three of 404 patients (13.1%) stopped rituximab for primary inefficacy and 42/404 (10.4%) for secondary loss of response. Thirty-eight of 404 (9.4%) patients stopped rituximab because of side effects. A small number of patients (7/126) discontinued rituximab for more than one reason: two patients stopped for primary inefficacy (insufficient response) and adverse events (one infections, one infusion reaction); and five patients stopped for secondary inefficacy (loss of response) and adverse events (one neutropaenia, two infusion reactions, two infections). Three patients stopped for infections in the context of hypogammaglobulinaemia.

After one year of follow-up, 76.2% (308/404) of patients continued on rituximab. More than half of the patients ever treated with rituximab, 57.2% (231/404) continued treatment for ≥ 3 years, 46.0% (186/404) for ≥ 5 years and 16.6% (67/404 patients) continued for ≥ 10 years. Twelve (3.0%) patients were on rituximab for ≥ 15 years. One of the initial five patients treated with

Fig. 1 Kaplan–Meier treatment survival curves for rituximab in the UCLH/UCL RA cohort



(A) Kaplan–Meier curve showing probability of continuing rituximab for the whole cohort. (B) Kaplan–Meier curves showing probability of continuing rituximab for seronegative and for seropositive patients. (C) Kaplan–Meier curves showing probability of continuing rituximab in patients who had previously failed other bDMARDs and in patients who were treated with received rituximab as their first bDMARD. UCLH /UCL: University College London Hospitals/University College London; bDMARD: biologic DMARD.

rituximab at University College London in the late 1990s [1] was still on rituximab after 21 years.

Rituximab treatment survival for the 404 patients is shown in Fig. 1A. When looking at possible factors associated with earlier discontinuation of treatment, the Kaplan–Meier curves showed that treatment

continuation was lower in seronegative patients compared with patients who were seropositive (log-rank $P < 0.001$). Continuation on rituximab was also lower in patients who had previously failed at least one bDMARD compared with patients who had rituximab as their first biologic drug (log-rank $P = 0.03$) (Fig. 1B and C, respectively). No significant differences were found when other baseline characteristics such as gender, concomitant MTX, any concomitant csDMARDs, concomitant oral prednisolone, concomitant csDMARDs and oral prednisolone at the time of first rituximab cycle were analysed. In addition, no significant differences were found when Kaplan–Meier curves for patients who were ANA positive were compared with those who were ANA negative, both in the whole cohort (log-rank $P = 0.45$) and in the small group of patients that were seronegative for both RF and anti-CCP (log-rank $P = 0.27$) (supplementary Fig. S1, available at *Rheumatology* online).

Cox regression analysis showed the number of previous bDMARDs was significantly associated with an increased risk of rituximab discontinuation. No significant associations were found with age or disease duration at first rituximab cycle, with number of previous csDMARDs, concomitant medication at first cycle including csDMARDs or prednisolone, or with median interval between rituximab cycles over time. Table 3 includes the explanatory variables included in the Cox regression analysis and the analysis results.

Of the patients who discontinued rituximab for secondary failure, 6 (14.3%) were male and 36 (85.7%) were female. Median age at first rituximab was 56.5 years (range 36–81), median disease duration was 15.5 years (range 1–54), longer than the median of 10 years in the whole cohort. All but three patients were seropositive; the three seronegative patients were ANA positive. Patients had previously failed a median of 3 csDMARDs (range 1–5) and 33/42 (78.6%) patients had previously failed at least 1 bDMARDs with a median of 2 (range 1–3). Nineteen of 42 (45.2%) of patients were on concomitant csDMARD at the time of first rituximab cycle, lower than the 63.3% in the whole cohort. Median number of cycles before rituximab was discontinued was 3 (range 2–14). No clear changes in the interval between rituximab cycles or on concomitant therapies or differences in peripheral blood B cell depletion achieved (as measured by CD19 count in the central haematology laboratory at UCLH) were identified as possible mechanisms of secondary failure in this group of patients as a whole (data not shown). Clear insufficient B cell depletion following retreatment with rituximab (second cycle) was only observed in two patients.

Discussion

Our study reports on the long-term persistence on rituximab in a real-life cohort of 404 patients with RA followed up in a dedicated clinic at UCLH. The large majority of patients in this cohort had established disease before treatment, with a median disease duration

TABLE 3 Hazard ratios for risk factors of drug discontinuation in RA patients following initiation of treatment with rituximab (Cox regression analysis)

Risk factors	Hazard ratios point estimate (95% CI)
Female gender	0.905 (0.489, 1.675)
Age at first RTX cycle	1.003 (0.984, 1.021)
Disease duration at first RTX cycle	1.005 (0.983, 1.027)
Number of previous bDMARDs	1.612* (1.255, 2.072)
Number of previous csDMARDs	0.955 (0.784, 1.163)
Seronegative	1.759 (0.672, 4.604)
Median time between RTX cycles	0.999 (0.964, 1.035)
Concomitant therapies at first cycle (csDMARDs and/or prednisolone)	0.884 (0.601, 1.299)
On prednisolone at first cycle	1.020 (0.596, 1.746)

*Statistically significant ($P \leq 0.05$). RTX: rituximab; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD.

of 10 years at the time of their first rituximab cycle. Patients had previously tried a median of three csDMARDs and three-quarters had previously failed at least one other bDMARD. The large majority of patients had seropositive disease, reflecting the common clinical practice of using rituximab mainly in patients who have detectable RF and/or anti-CCP autoantibodies. Almost two-thirds of patients were on concomitant medication with at least one csDMARD, most commonly MTX. Almost one-third of patients were on concomitant oral prednisolone.

Median follow-up was 55 months (4.6 years). Slightly less than half of the patients were on rituximab for at least 5 years, with close to 17% continuing treatment with rituximab for 10 years or more. At most recent follow-up 212 patients were on rituximab with well controlled disease, as reflected by a median DAS28ESR of 2.4.

The most frequent reason for discontinuing rituximab was primary inefficacy at 42%, followed by loss of clinical response after an initial response to rituximab in one-third of patients and then by development of side effects in 29%. A small number of patients who discontinued rituximab did so for more than one reason. Six of the 42 patients who died while on rituximab died of infection and of the 37 patients who discontinued rituximab because of side effects, 12 did so because of infections.

When survival curves were compared using the log-rank test, patients who were seronegative and patients who had previously failed at least one bDMARD were more likely to discontinue rituximab than patients who were seropositive or than patients who had rituximab as their first bDMARD, respectively. In the Cox regression analysis only the number of previous bDMARDs was significantly associated with a shorter duration of

rituximab treatment; having seronegative disease was not, possibly due to the small number of patients.

No other variables evaluated in the study showed any significant association with an increased risk of discontinuing rituximab, including gender, age and disease duration at first rituximab cycle, number of previously failed csDMARDs and interestingly whether rituximab was used in combination with csDMARDs or not. One-third of patients treated with rituximab without any csDMARD were on low-dose oral prednisolone at the time of their first rituximab cycle. The median time between rituximab cycles was not associated with the risk of discontinuing treatment.

Other publications have also focused on drug survival on rituximab for patients with RA and on identifying factors associated with an increased risk of discontinuation of treatment. In the British Society for Rheumatology Biologics Register (BSRBR) report, which included >1300 patients, around 60% of patients continued rituximab at 4 years [7]. The most common cause for stopping treatment is usually inefficacy, but published studies do not usually report primary and secondary inefficacy separately.

Similar to the data here presented, most studies did not find any increased risk of treatment discontinuation in association with patients' age or gender [7–11]. Only one study found a higher risk of drug discontinuation with increasing age, but with a very low hazard ratio of 1.02 [12]. No influence of smoking status on treatment survival was noted in the BSRBR report [7]. Disease characteristics at baseline such as disease duration, baseline DAS28 and baseline HAQ have also not been found to be associated with treatment duration. Only one study showed an increased risk of 1.045 of stopping rituximab with the number of swollen joints [11]. All studies found that patients who were seronegative had a higher risk of stopping treatment with rituximab [7, 9, 10, 13]. Several studies have found that patients who had previously failed bDMARDs were at higher risk of stopping rituximab when compared with patients who received rituximab as the first biologic [9]. No such association was found in the BSRBR cohort, but the large majority of patients had previously failed bDMARDs (84%) [7]. Some studies have reported a higher risk of discontinuation of treatment in patients that received rituximab without MTX or other csDMARDs [10, 12, 13], but not others [7].

It is not known why patients do not respond to rituximab or stop responding. Possible reasons are pathogenic mechanisms independent of B cells, the presence of long-lived plasma cells producing pathogenic autoantibodies or insufficient B cell depletion. The latter is possible but rarely documented in RA patients within the limitations of standard B cell counts performed in routine laboratories. In our cohort, insufficient B cell depletion following retreatment with rituximab, likely to be associated with presence of anti-drug antibodies leading to rapid clearance of the drug, was only observed in two patients.

This study has several limitations, including its observational nature, involvement of a single centre, and the small number of seronegative RA patients included as early experience suggested no or poor response. In addition, patients were included over a long period of time, during which alternative available biologic treatments became available. However, the study by Orbis *et al.* [10] did not find any difference on persistence on rituximab when patients initiated on treatment up to 2008 were compared with patients started between 2009 and 2011 or between 2012 and 2014.

In conclusion, rituximab is an effective treatment in RA and many patients will achieve good control of their disease with repeated cycles of treatment. The most common reasons for treatment discontinuation are either primary or secondary inefficacy. Patients who are seronegative and who have previously failed other bDMARDs are more at risk of drug discontinuation.

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Data availability statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of patients included in the study.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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