Serum rituximab levels and efficiency of B cell depletion: differences between patients with rheumatoid arthritis and systemic lupus erythematosus

Sir, Variability in clinical response to rituximab-induced B cell depletion therapy (BCDT) is well described in both RA and SLE [1, 2]. Recent evidence suggests that an inadequate depletion is associated with poor clinical response in both RA and SLE [3, 4]. Importantly, it was shown that clinical response depended on the degree of depletion and not the dose of rituximab in RA [4].

In a study of patients with RA, the majority of inadequate responders (IRs) to the first cycle of rituximab treatment had a greater number of circulating plasmablasts at baseline, with 90% not achieving adequate depletion, defined as CD19+ B cells <0.0001 × 10^9/l [using highly sensitive flowcytometry (HSFC)], when compared with 60% of responders. Importantly, 72% of the first-cycle IRs subsequently showed a clinical improvement following a second cycle of rituximab given 6 months after the first cycle [5]. In SLE, an initial Phase II dose-escalation study of rituximab employing three dosing regimens found that serum rituximab levels and the degree of B cell depletion were highly variable between patients regardless of the dose used [6]. Vital et al. [3] reported that in SLE, poor clinical response (as measured by BILAG 2004 score) was associated with an inadequate degree of depletion (>0.0001 × 10^9 CD19+ B cells/l determined using HSFC at 2 weeks after the second dose of 1 g rituximab), which occurred in all IRs. Thus, inadequate depletion appears to be clinically relevant, but the underlying causes remain elusive. It is worth noting that earlier studies of BCDT in RA and SLE defined complete depletion as a CD19+ B cell count ranging from <0.005 to 0.01 × 10^9/l. We hypothesized that the levels of rituximab reached in the serum might be lower in patients with SLE, in whom inadequate depletion is more frequent, than in patients with RA.

To test our hypothesis, we undertook a retrospective study that investigated (i) the relationship between rituximab levels and CD19+ B cell count and (ii) whether there were any differences in the levels of rituximab in patients with RA and SLE receiving their first cycle of rituximab (thereby, although not absolutely, minimizing the confounding effect of human anti-chimeric antibodies). This study had ethical approval from the local research ethics committee (University College London Hospitals research ethics committee). We included 15 patients with SLE and 23 with RA, of whom, at 1 month after the second dose of 1 g rituximab, 6 patients in each disease category had >0.005 × 10^9 CD19+ B cells/l (defined as non-depleted patients) and the others had <0.005 × 10^9 CD19+ B cells/l (defined as well-depleted patients). Two patients with SLE who had vital organ involvement also received a single dose of 750 mg of cyclophosphamide. At 1 and 3 months post-treatment, rituximab levels were measured with a capture ELISA using sera diluted at a concentration of 1/40,000 and CD19 counts were determined by flow cytometry. Data on serum rituximab levels between the two groups were analysed using Mann-Whitney U test. Correlation between serum rituximab levels and CD19+ B cell counts were analysed using Spearman r test.

Median CD19+ B cell counts were similar between RA and SLE at all time points. The levels of rituximab were significantly lower in patients with SLE when compared with RA, at both 1 and 3 months after treatment (Fig. 1A), with the median rituximab level at 1 month for SLE being 43.07 ng/ml (range 0.777) and for RA 391.9 ng/ml (range 1.3–2500) (P = 0.0008) and at 3 months 0 ng/ml (range 0.54) for SLE and 2.6 ng/ml (range 0–1153) for RA (P = 0.008). In well-depleted patients, rituximab levels were significantly lower in patients with SLE compared with those with RA at both 1 (P = 0.003) and 3 months (P = 0.008) (Fig. 1B). No such difference was found in non-depleted patients. The levels of rituximab correlated inversely with the absolute numbers of CD19+ B cells in patients with RA (r^2 = 0.63, P = 0.006) and SLE (r^2 = 0.51, P < 0.05) (data not shown) only at 3 months. Six patients with SLE had LN, but the presence of LN did not influence the levels of rituximab or the degree of depletion in this small group of patients (data not shown). Furthermore, there was a significant difference in rituximab levels between well-depleted and non-depleted patients at both 1 and 3 months in RA but not in SLE. Also we noted an interindividual variability in rituximab levels within each disease category (Fig. 1B).

In conclusion, patients with SLE had markedly (>9-fold, at 1 month) lower serum levels of rituximab than patients with RA at both 1 and 3 months, regardless of the level of depletion. Factors such as reduced serum half-life of IgG, impaired recycling of IgG through FcRn and internalization and destruction of rituximab by target B cells as noted in lymphoma [7] might occur more frequently in SLE and contribute to the low levels of rituximab in SLE. Interestingly, the absence of an inverse correlation between serum rituximab levels and CD19+ B cell counts at 1 month might suggest an intrinsic resistance of B cells to rituximab-induced depletion.

Rheumatology key message
Rituximab is rapidly consumed in patients with SLE when compared with patients with RA.

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References


