The Journal of Rheumatology 2021;xx:xxxx
doi:10.3899/jrheum.210361
First Release September 15 2021

The Journal of Rheumatology

Dose-dependent Pharmacological Response to Rituximab in the Treatment of Antineutrophil Cytoplasmic Antibody-associated Vasculitis

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ABSTRACT. ***Objective.*** Rituximab (RTX) is effective in the induction and maintenance of remission in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). However, uncertainty remains regarding the optimal maintenance dosing regimen. This work evaluates the relationship between variability in RTX dosing and pharmacological response in AAV.

Methods. A prospective cohort of patients with AAV (n = 28) with either granulomatosis with polyangiitis (n = 23) or microscopic polyangiitis (n = 5) receiving maintenance RTX therapy were followed in a single tertiary care academic medical center over a 2-year period. Patient demographics, RTX dosing information, and trough plasma RTX levels were collected along with laboratory measures of pharmacologic response, including B cell counts and ANCA titers.

Results. RTX dosing information from 94 infusions with 59 trough samples were collected with a mean ± SD dose of 640 ± 221 mg, dosing interval of 210 ± 88 days, and trough plasma RTX concentration of 622 ± 548 ng/mL. RTX trough concentrations were associated with RTX dose ($\rho = 0.60$, $P < 0.0001$) and dosing interval ($\rho = -0.55$, $P < 0.0001$). RTX dosing intensity (mg/d) was associated with RTX trough concentrations ($\rho = 0.57$, $P < 0.0001$). Higher dosing intensities were associated with undetectable B cell repopulation ($P < 0.0001$), but not negative ANCA titers ($P = 0.60$). Stratification of dosing intensities based on the standard dosing regimen of 500 mg every 6 months (2.4–3.3 mg/d) demonstrated that this regimen was associated with B cell repopulation in 8 of 17 doses (47%) compared to 0 of 23 doses (0%) with the high-dose regimen (> 3.3 mg/d; $P < 0.0001$).

Conclusion. RTX maintenance dosing of 500 mg every 6 months may be inadequate to maintain B cell depletion in the treatment of AAV.

Key Indexing Terms: ANCA-associated vasculitis, B cells, granulomatosis with polyangiitis, microscopic polyangiitis, pharmacokinetics, rituximab

Rituximab (RTX) has been shown to be effective for both induction of remission[1] as well as maintenance of remission[2–5] in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). In 2014, Guillevin and colleagues demonstrated that after cyclophosphamide induction therapy, an RTX maintenance dosing regimen of 500 mg every 6 months for 24 months was superior to a tapering dose of azathioprine (AZA) in the prevention of major relapses.[2] A subsequent trial demonstrated that after RTX induction therapy, an RTX maintenance dosing regimen of 1000 mg every 4 months was superior to fixed doses of AZA at 24 months in the prevention of relapses.[5] To date, there have been no head-to-head trials comparing different maintenance fixed-dosing regimens of RTX.

In practice, maintenance therapy is commonly initiated based on the established standard dosing regimen of 500 mg every 6 months and escalated or deescalated based on clinical and laboratory measures of response, resulting in a large variation in RTX dose and interval under real-world treatment conditions. However, the optimal dose and interval to maximize efficacy and minimize toxicity remain to be established. In addition, while the pharmacokinetics of RTX for the treatment of induction have been explored,[6,7] there are few data regarding the pharmacokinetics of maintenance RTX therapy during remission. The objective of this work was to evaluate the relationship between variability in RTX dosing in our real-world cohort of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and pharmacological response.

Support for this work was provided by a Clinical and Translational Science Awards grant from the National Center for Advancing Translational Sciences awarded to the University of Kansas for Frontiers: University of Kansas Clinical and Translational Science Institute (# UL1TR002366 and #KL2TR00236), and by a COBRE grant from the National Institute for General Medical Sciences awarded to the Kansas Institute for Precision Medicine (# P20GM130423).

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The authors report no financial conflicts of interest relevant to this article.

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Accepted for publication July 14, 2021.

METHODS

Study design and patients. Patients were recruited from a single tertiary referral center and written informed consent was collected from all participants in accordance with approval guidelines from the University of Kansas Medical Center Institutional Review Board (IRB #141788). All patients met either the 1990 American College of Rheumatology classification criteria for GPA or the 2010 Chapel Hill Consensus Criteria for MPA. All patients were in remission (defined as a Birmingham Vasculitis Activity Score version 3 = 0), were currently receiving RTX maintenance therapy, and received RTX in the 8 months prior to recruitment. The RTX maintenance dosing regimen was not fixed and was determined by the treating physician (JMS). As per the standard practice of the treating physician, decisions about RTX dosing were not made based on B cell counts or ANCA titers, but rather on clinical variables. Blood collection was completed at the trough of RTX therapy (i.e., just prior to the next RTX infusion). The median follow-up was 15.3 months (SD 4.4). B cell depletion was defined as undetectable B cells by flow cytometry (defined by CD19 expression). ANCA was measured by both indirect immunofluorescence and enzyme immunoassay (EIA) at RTX troughs; however, ANCA negativity was defined as the absence of detectable ANCA by EIA.

Plasma RTX analysis. Blood samples were collected in tubes containing K2-EDTA immediately prior to RTX infusion. Blood samples were kept on ice and processed within 2 hours of collection. Plasma was isolated by centrifugation of whole blood at 1000 × g for 10 minutes. The resulting plasma samples were aliquoted and stored at –80 °C until analysis. Samples were thawed at 4 °C prior to analysis and were not subjected to any repeat freeze-thaw cycles. RTX concentrations in plasma were determined using the commercially available BioSim ELISA (#E4371, BioVision). The RTX quantitation range for the assay was 3–300 ng/mL with an intra- and inter-assay coefficient of variation < 30%. RTX plasma samples and blank plasma standards were diluted 1:10 in assay buffer prior to analysis. RTX was detected for samples and standards by a horseradish peroxidase-conjugated probe using the chromogenic substrate 3,3′,5,5′-tetramethylbenzidine. Absorbance at 450 nm and 650 nm was measured for each sample and the ratio of optical densities (450:650 nm) was fit to a 4-parameter logistic curve. Plasma RTX concentrations were interpolated based on the 5-point standard curve and corrected based on the dilution factor.

Statistical analysis. Spearman rank correlation analysis was used to evaluate associations between continuous variables. Unpaired grouped analyses were conducted by *t* test analysis or Wilcoxon rank-sum testing, as appropriate. Data analysis and statistical testing were conducted using JMP software v11 (SAS Institute). Statistical significance is considered for $P < 0.05$.

Ethics. Informed consent was collected from all participants in accordance with approval from the University of Kansas Medical Center Institutional Review Board (IRB #141788).

RESULTS

RTX dosing intensity and trough plasma concentrations. Patient demographics and RTX dosing information are summarized in Table 1. A total of 59 samples were drawn at the time of RTX trough (i.e., just prior to RTX infusions). A median of 2 trough samples per patient was collected, with a range of 1–4 samples per patient. The dose and dosing interval associated with each trough sample is provided for each of the 28 patients (Figure 1A). RTX dose ranged from 500 to 1000 mg and the dosing interval ranged from 120 to 565 days. Corresponding trough plasma RTX concentrations following these doses ranged from 106.1 to 2571.2 ng/mL. Plasma trough levels were evaluated for their relationship with RTX dose (Figure 1B) and dosing interval (Figure 1C). Higher trough plasma concentrations were significantly associated with both higher RTX dose and a shorter dosing interval. As a result, dosing intensity was calculated as the RTX dose normalized to dosing interval (mg/d) and was significantly correlated with RTX trough plasma concentrations (Figure 1D). RTX plasma concentrations were also evaluated for associations with measures of body mass, including weight, body surface area (BSA), and BMI. Interestingly, BMI was the only measure significantly associated with plasma trough RTX concentrations ($\rho = 0.27$, $P = 0.04$). Normalization of dose intensity based on BSA (i.e., mg/m^2/d) did improve the correlation of dose intensity with plasma RTX trough concentrations ($\rho = 0.60$, $P < 0.0001$). However, RTX maintenance therapy is not commonly dosed based on measures of body mass in AAV and was not considered further in our stratification based on dosing intensity.

Table 1. Patient demographics and RTX dosing information.

	Values
Demographics	
Patients, n	28
Age, yrs	60 (± 14)
Female	19 (68)
Height, cm	170 (± 10)
Weight, kg	95 (± 28)
Diagnosis	
GPA	23 (82)
MPA	5 (18)
ANCA by EIA	
PR3-ANCA	13 (46)
MPO-ANCA	14 (50)
Negative	1 (4)
RTX maintenance therapy	
Trough samples, n	59
Duration, yrs	2.2 (± 1.2)
Dose, mg	640 (± 221)
Interval, d	210 (± 88)
Trough, ng/mL	622 (± 548)

Values are expressed as mean (± SD) or n (%) unless otherwise indicated. ANCA: antineutrophil cytoplasmic antibody; EIA: enzyme immunoassay; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; RTX: rituximab.

RTX dosing intensity and pharmacological response. B cell count data at the time of trough were available for 65 of the doses with negative B cell counts in 47 (72%), ANCA titers at the time of trough were available for 46 of the doses with negative titers in 36 (78%), and both B cell count data and ANCA titers for 44 of the doses, with double negativity in 16 (36%). Differences in RTX dosing intensity were compared based on B cell detection and ANCA positivity, alone and in combination (Figure 2). Undetectable B cells measured at the time of trough were observed to have a significant (i.e., 93%) higher mean RTX dosing intensity compared to patients with a detectable repopulation of their B cells (median [IQR]: 2.8 [2.2–7.3] vs 2.3 [2.0–2.7] mg/d; Figure 2A). Negative ANCA titers at the time of trough failed to demonstrate any significant difference in

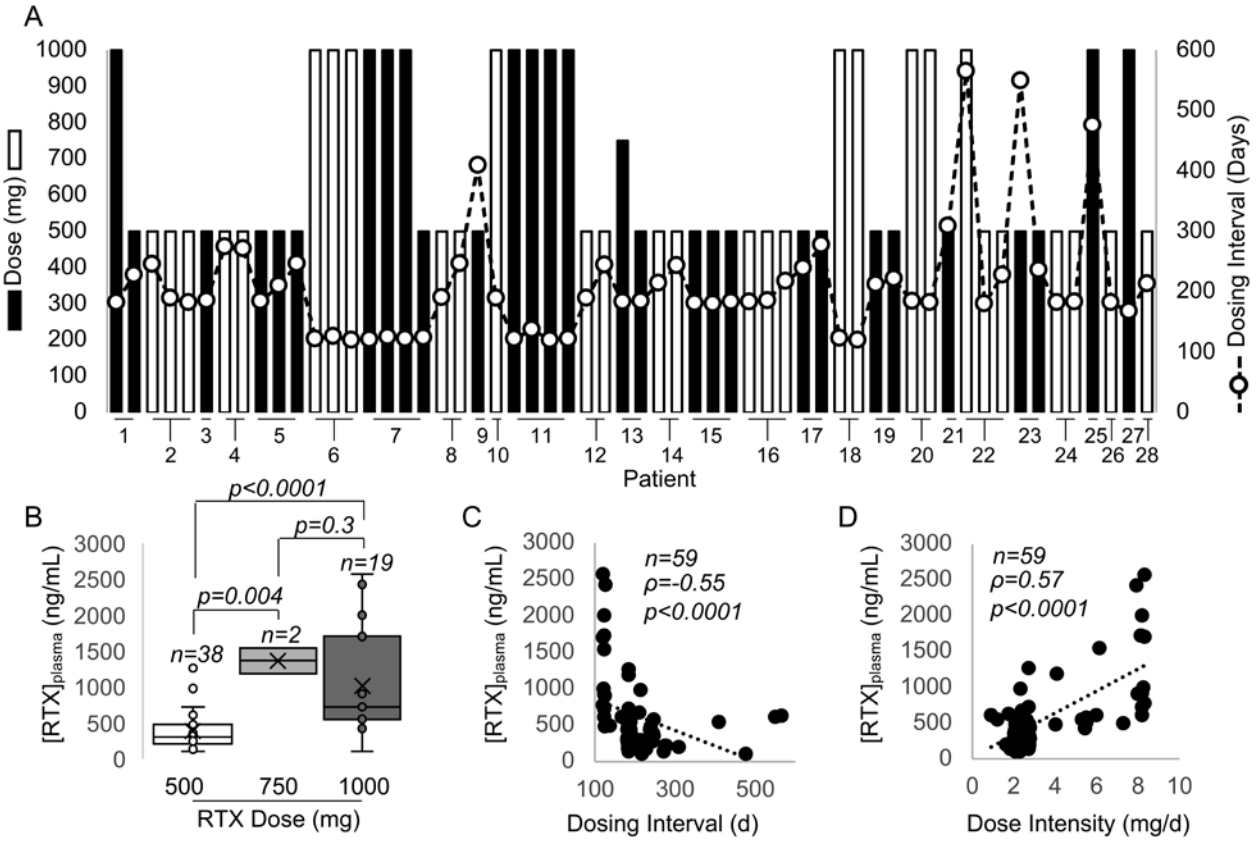

Figure 1. Trough RTX plasma concentrations as a function of dosing intensity. The graphical data represent (A) the doses and dosing intervals associated with each plasma trough sample collected for RTX analysis (alternating black and white bars to visually separate patients); (B) the plasma RTX concentration as a function of absolute dose; (C) the RTX plasma concentration as a function of interval between dosing; and (D) the linear correlation between RTX plasma concentration and dose intensity in mg/day. RTX: rituximab; $[RTX]_{plasma}$ = trough plasma RTX concentration.

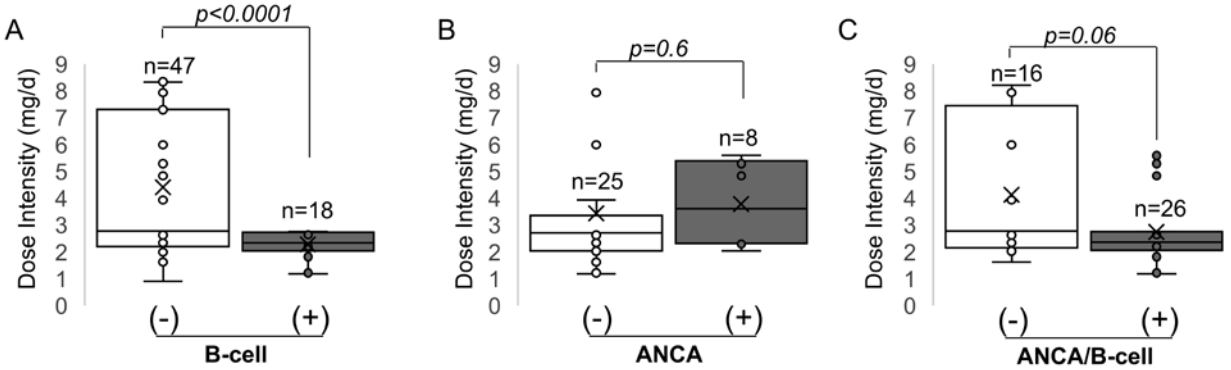

Figure 2. RTX dose intensity based on B cell depletion and ANCA positivity (by EIA). (A) Comparison of dose intensities in patients with undetectable B cells (-) to those with detectable B cells (+). (B) Comparison of dose intensities in patients with undetectable ANCA serologies (-) to those with detectable ANCA serologies (+). (C) Comparison of dose intensities in patients who had both undetectable B cells and ANCA negativity (-) to those with either detectable B cells or ANCA serologies (+). ANCA: antineutrophil cytoplasmic antibodies; EIA: enzyme immunoassay; RTX: rituximab.

mean RTX dosing intensity compared to those with positive ANCA titers (Figure 2B). However, combination of undetectable B cell repopulation and negative ANCA titers at the time of trough were observed to have a higher (i.e., 50%) mean RTX dosing intensity compared to those with either detectable B cell repopulation or a positive ANCA titer (median [IQR]: 2.8 [2.2–7.4] vs 2.4 [2.1–2.7] mg/d), but failed to reach statistical significance (Figure 2C).

Antidrug antibody positivity was also compared based on dose intensity and no difference in median [IQR] dose intensities were observed between trough plasma samples positive for antidrug antibodies (2.7 [2.2–8.0] mg/d) and those negative for antidrug antibodies (2.8 [2.2–5.8] mg/d; $P > 0.99$).

Stratification by RTX dosing intensity. Based on the standard dosing regimen of 500 mg every 6 months, equating to a calculated dose intensity of 2.8 mg/day, patient clinical data were stratified by dose intensity as being associated with low-, standard-, or high-dose RTX (Figure 3). The standard-dose intensity was defined as receipt of a dose intensity equivalent to 500 mg with a dosing interval between 5–7 months to account for the real-world variation in prescribed vs observed times between doses (i.e., 2.4–3.3 mg/d). Doses below this window were labeled as low-dose intensity and those above were labeled as high-dose intensity (Figure 3A). As a result of collecting multiple samples per patient, 11 of the 28 patients received RTX doses that resulted in representation in > 1 dosing intensity group. An RTX dose of 500 mg was received for 20 of 20 doses (100%) from patients receiving the standard dosing intensity, 28 of 30 doses (93%) from patients receiving the low-dose intensity, and only 2 of 21 doses (8%) from patients receiving the high-dose intensity (Figure 3B). The majority of doses for patients receiving the high-intensity dosing were either 750 mg (n = 2, 8%) or 1000 mg (n = 21, 84%). Comparison of the time since the last dose (Figure 3C), which is representative of the dosing interval, demonstrated that standard-intensity doses were associated with a mean interval of 183 days (range 164–190 days), whereas the low-intensity doses were associated with a mean interval of 282 days (range 210–565 days), and high-intensity doses were associated with a mean interval of 146 days (range 120–207 days).

RTX dosing intensity and pharmacological response. RTX trough plasma concentrations were compared based on dosing intensity (Figure 4A). Mean trough plasma concentrations were not found to significantly differ based on low- or standard-intensity RTX doses. However, the high-intensity doses were observed to be associated with mean trough plasma concentrations 3.0-fold and 2.7-fold higher than low- and standard-dose intensities, respectively. Comparison of B cell counts (measured at the time of trough) based on dosing intensity demonstrated a progressive reduction in B cell counts with increasing dose intensity (Figure 4B). Evaluation of the relationship of dose intensity as a continuous variable with B cell counts further demonstrated the association of higher dosing intensity with a reduction in B cell counts (Figure 4C). Based on the resulting plot, high-dose intensity (i.e., > 3.3 mg/d) is associated with the lowest risk of B cell repletion.

The proportion of doses associated with undetectable B cell repopulation, negative ANCA titers, and both undetectable B cell repopulation and negative ANCA titers were compared based on RTX dosing intensity (Figure 5). With high-intensity doses, 23 of 23 (100%) doses were associated with negativity for detectable B cell repopulation, compared to 15 of 25 (60%) and 9 of 17 (53%) of doses with low- and standard- intensity doses, respectively ($P < 0.0001$; Figure 5A). Negative ANCA titers were associated with 10 of 10 (100%) doses with standard-intensity dosing compared to 9 of 13 (69%) and 6 of 10 (60%) of the low- and high-intensity doses, respectively ($P = 0.03$; Figure 5B). The combination of undetectable B cell repopulation and negative ANCA titers were not found to be significantly different based on dosing intensity ($P = 0.21$; Figure 5C). However, a trend toward a higher incidence of undetectable B cells and ANCA negativity was observed with higher dosing intensity from 5 of 19 (26%) with low-intensity dosing, to 5 of 13 (38%) with standard-intensity dosing, and to 6 of 10 (60%) with high-intensity dosing. Similar to the observed relationship of higher dose intensity with higher B cell/ANCA negativity, it was also observed that B cell/ANCA negativity was associated with higher plasma trough RTX concentrations (mean ± SD: 730 ± 702 vs 380 ± 210 ng/mL, $P = 0.09$; data not shown).

DISCUSSION

Prior to RTX, standard therapies for the maintenance of remission in GPA and MPA consisted of either methotrexate (MTX), AZA, or mycophenolate mofetil (MMF).[8] In 2014 a direct comparison of RTX to tapered dosing of AZA showed RTX to

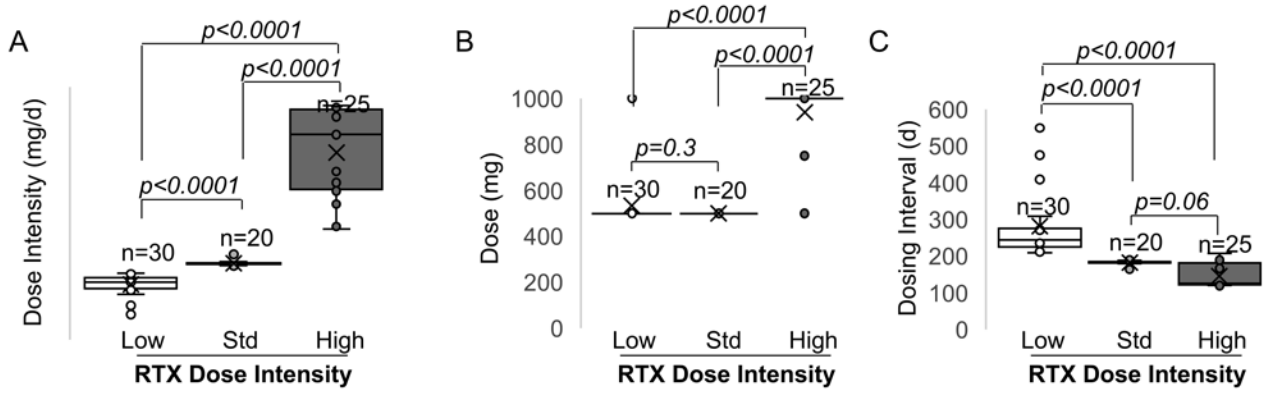

Figure 3. Stratification of RTX dosing intensity. Patients receiving a dosing regimen of 500 mg every 5–7 months (2.4–3.3 mg/d) were labeled as "standard"-intensity dosing. Patients labeled as "low" or "high" were below or above this standard, respectively. (A) Comparison of absolute dose intensities between each stratified group. (B) Comparison of absolute dose (in mg) between each stratified group. (C) Comparison of dosing interval (in days) between each of the stratified groups. RTX: rituximab; Std: standard.

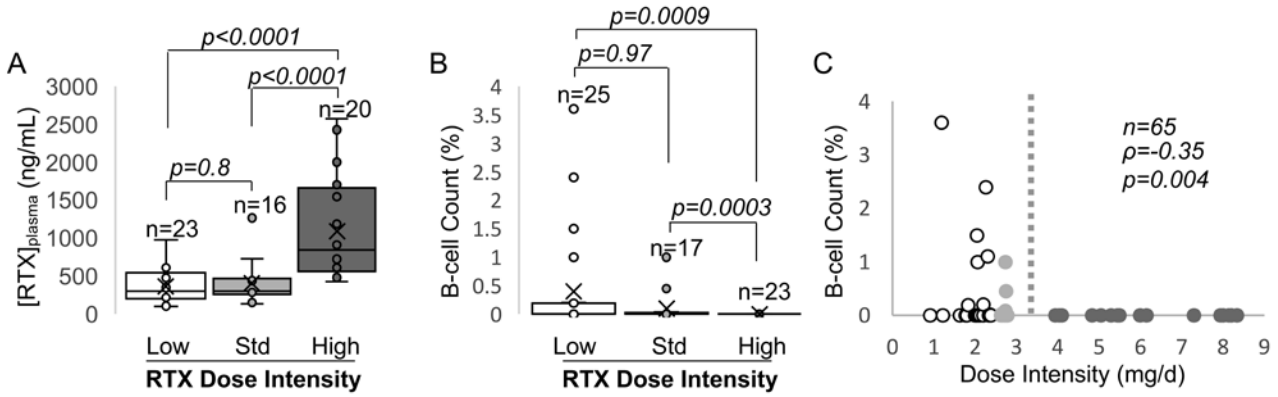

Figure 4. Dose intensity and pharmacological response. (A) Peripheral plasma concentrations of RTX between stratified dose intensities. (B) Peripheral B cell counts between stratified dose intensities. (C) B cell counts based on dose intensity (in mg/d). An absolute cut-off at 3.3 mg/d is shown, in which all patients above this dose intensity had undetectable B cells. RTX: rituximab; $[RTX]_{plasma}$ = trough plasma RX concentration; Std = standard.

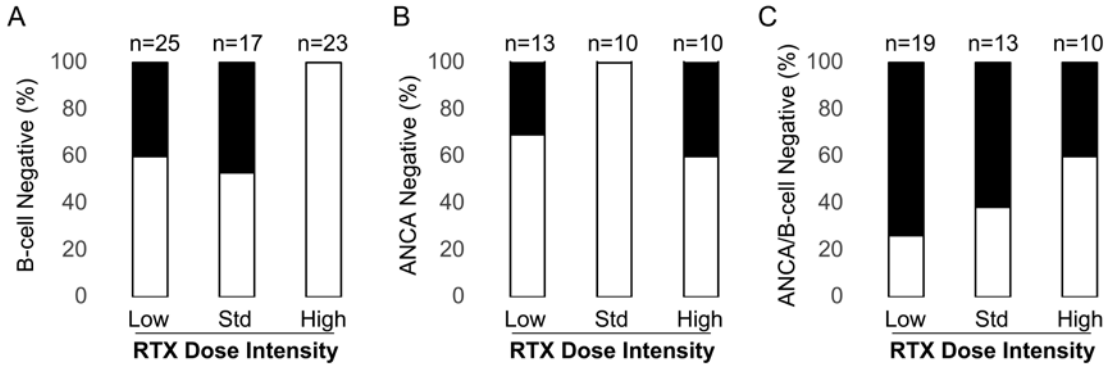

Figure 5. Relationship between dose intensity with B cell depletion and ANCA negativity. (A) Comparison of percentage of patients with undetectable B cell between stratified RTX dose intensities. (B) Comparison of percentage of patients with undetectable ANCA serologies between stratified RTX dose intensities. (C) Comparison of percentage of patients with both undetectable ANCA serologies and B cells between stratified RTX dose intensities. ANCA: antineutrophil cytoplasmic antibodies; RTX: rituximab, Std: standard.

be superior in the prevention of major relapses at 28 months.[2] There have been no head-to-head trials comparing RTX to either MTX or MMF; however, neither MTX nor MMF has been shown to be superior to AZA.[9,10] Thus, RTX has emerged as a dominant maintenance agent in GPA and MPA. Many of the clinical trials have utilized a standard maintenance RTX dose of 500 mg every 6 months.[2,4] To date there has been only 1 clinical trial utilizing a different RTX maintenance regimen (1000 mg every 4 months).[5] Since there have been no head-to-head studies comparing these fixed-dosing regimens, it is unclear which is optimal. Further, it may be possible that the optimal dose may not be uniform across the AAV patient population and that dosing practices require individualization based on pharmacokinetic and/or pharmacodynamic metrics to best optimize clinical outcomes.

The pharmacokinetics of RTX during maintenance therapy has not been clearly defined. Pharmacokinetic studies after induction therapy (375 mg/m^2 over 4 doses) have found that higher RTX exposure was associated with longer B cell depletion and a delayed reduction in ANCA levels.[6,7] However, RTX serum levels after induction dosing failed to demonstrate a relationship with either achieving complete remission, time to relapse, or risk of relapse over an 18-month follow-up period, ultimately resulting in the conclusion that RTX drug level monitoring was not a useful therapeutic monitoring tool for RTX induction dosing. However, these studies were done only for induction therapy to evaluate whether drug levels after induction predicted clinical outcomes. With the evolving use of RTX as chronic maintenance therapy and the practice of tailoring RTX therapy to maintain B cell depletion and avoid hypogammaglobulinemia, our group recently evaluated trough plasma RTX levels in patients with AAV in remission on RTX maintenance therapy.[11] Our work demonstrated that repopulation of B cells was associated with lower RTX trough plasma concentrations and that the development of hypogammaglobulinemia was associated with higher RTX trough plasma concentrations. Based on our data, we identified a target trough plasma RTX concentration between 550 and 1000 ng/mL during maintenance therapy to maximize maintenance of B cell depletion and minimize the risk of hypogammaglobulinemia.[11] We suspect the

pharmacokinetics of RTX differ between states of active disease and remission, likely related to differences in drug clearance, as has been demonstrated with other biologic therapies used in the treatment of autoimmunity, such as infliximab.[12]

Our present study provides important information about the relationship between RTX dose and plasma trough levels of RTX during remission and shows a direct comparison of different RTX dosing intensities. A significant association between RTX dosing intensity and trough RTX plasma concentrations was observed. However, based on the variance in the relationship, it is unlikely that plasma trough concentrations can be predicted with a reasonable level of confidence based on RTX dosing intensity alone. Maintenance of B cell depletion and ANCA negativity have been found by others to be associated with a low risk of relapse.[13] Therefore, these were the important surrogate outcomes on which we focused. Normalization of RTX dosing based on dosing intensity (mg/d) allowed us to make important comparisons between different RTX dosing regimens that varied by both dose and dosing interval. When looking at a dosing intensity equivalent to the maintenance regimen used in most trials (500 mg every 5–7 months or 2.4–3.3 mg/d), we found that almost half of doses administered at this standard dosing intensity were associated with the inability to maintain B cell depletion. The average trough peripheral RTX levels associated with these doses (under 500 ng/mL) were below the therapeutic window of 550–1000 ng/mL previously identified by our group.[11] Taken together, this suggests that standard RTX maintenance dosing may not be optimal for a significant number of patients. Further, the observed variance in the relationship between RTX dosing intensity and trough RTX plasma concentrations suggest the need for additional studies to explore therapeutic monitoring of trough RTX concentrations as a means for dose modification and individualization. As described in our previous work, a direct relationship between RTX plasma trough levels and pharmacodynamic markers (i.e., B cell count and IgG levels) has been demonstrated.[11]

Compared to the standard RTX dosing regimen of 500 mg every 6 months used in most clinical studies, our data support the need for a higher dose intensity of RTX to maintain B cell depletion. Specifically, at a dose intensity of at least 3.3 mg/day, all patients were able to maintain undetectable B cell repopulation. There was a linear correlation between peripheral RTX levels and dose intensity. Utilizing this relationship between dose and exposure, the previously identified therapeutic window for RTX peripheral trough levels would correlate with a dose intensity of 3.7–5.0 mg/day. The 2 dosing strategies that have been utilized in clinical trials, including 500 mg every 6 months and 1000 mg every 4 months, would be expected to result in trough levels either below or above this therapeutic window. Rather, a maintenance dosing regimen of 500 mg every 4 months or 750 mg every 6 months would fall within our therapeutic window. These data provide a bridge between RTX dosing and important serological outcomes.

Our study has several weaknesses that should be recognized. First, we did not measure relapse rate and rate of severe adverse events as outcomes. This was beyond the scope of this study; however, our data provide important information for the design of future clinical trials utilizing RTX maintenance therapy. Second, we did not look at important covariates in determining the relationship between dosing and response. Covariates, such as sex and BSA, have been identified as important during induction therapy by other groups. Exploration of body mass as a covariate for trough plasma RTX levels failed to demonstrate an association with weight or BSA but did interestingly demonstrate a positive correlation with BMI. The basis for this relationship is not understood but may reflect a bias toward higher absolute RTX dose in overweight patients.

There are several strengths to this study. First, this was a real-world experience without a protocolized approach to RTX maintenance therapy. RTX maintenance dosing regimens were at the discretion of the treating physician. The inter- and intra-individual variability in dosing regimens was advantageous for the scope of this trial. Further, to our knowledge, this is also the first study that has utilized a normalization of dosing to make direct comparisons between RTX regimens, which represents a function of the 2 variables commonly used clinically to either intensify or deintensify therapy (i.e., dose and dosing interval).

In conclusion, an RTX maintenance regimen of 500 mg every 6 months (equivalent to a dosing intensity of 2.7 mg/d) is inadequate for maintaining B cell depletion in almost half of the patients. A target dosing intensity of at least 3.3 mg/day is required to adequately maintain B cell depletion. However, it is important to recognize that higher intensities of RTX may be associated with a higher risk of infections, which was outside of the scope of the current study. Future studies are needed to explore individualized dosing in combination with dose adjustments based on therapeutic drug monitoring as a strategy to optimize RTX maintenance therapy in AAV.

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