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BRIEF REPORT

# Low-dose rituximab as induction therapy for ANCA-associated vasculitis

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## Abstract

Administration of four once-weekly doses of 375 mg/m$^2$ rituximab (RTX) is commonly used as remission induction therapy for ANCA-associated vasculitis (AAV). Low-dose RTX has been recently shown to produce closely similar results to conventional treatments in other autoimmune diseases. However, the therapeutic potential of this approach in AAV remains largely unknown. Here, we analyzed the efficacy and tolerability of high- and low-dose regimens of RTX in patients with AAV. We retrospectively examined AAV patients who met the classification algorithm of Watts et al. from 2006 to 2016. Patients were divided into high- (HD) and low-dose (LD) RTX groups. HD-RTX was the original regimen while LD-RTX consisted of two once-weekly doses of 375 mg/m$^2$. Cumulative complete remission (CR) rates for 1 year were compared, and serial changes in peripheral B cell counts and serious adverse events were monitored. Apart from a higher percentage of elderly patients in the LD group ($p < 0.01$), the 17 patients with HD-RTX and 11 patients with LD-RTX showed no significant differences in clinical characteristics, including Birmingham Vasculitis Activity Score (BVAS), Vasculitis Damage Index (VDI), and the initial dose of glucocorticoid. On 1-year observation, cumulative CR rates did not significantly differ ($p = 0.20$). Further, peripheral B cell counts and incidence of serious adverse events also did not differ. Cumulative CR rate did not significantly differ between LD and HD groups. Further study is warranted to confirm these results.

**Keywords** ANCA-associated vasculitis · High dose · Low dose · Rituximab

## Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitis (AAV) is a group of heterogeneous systemic vasculitis diseases that include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Since mortality is as high as 90% if untreated, aggressive initial immunosuppression is generally required for generalized AAV [1, 2]. Initial immunosuppressive therapy in GPA and MPA typically consists of glucocorticoids (GC) combined with either cyclophosphamide (CY) or rituximab (RTX) [3]. This strategy was based on the results of two randomized trials conducted in Europe and America [4, 5]. RTX is an effective alternative to CY for the initial treatment of patients who have newly diagnosed disease or relapsed disease following treatment with CY or other immunosuppressive therapy [4, 5]. The therapeutic dose of RTX for AAV was determined based on the regimen for CD20-positive B cell non-Hodgkin's lymphoma (four once-weekly doses of 375 mg/m$^2$), however, an appropriate dose for AAV has yet to be determined [6, 7]. Recently, low-dose RTX was shown to provide results which were closely similar to the successful results provided by conventional regimens in other autoimmune diseases, including rheumatoid arthritis (two doses of 500 mg), immune thrombocytopenia (100 mg weekly for 4 weeks), and kidney transplantation (single dose of 50–100 mg/m$^2$) [8–10]. Here, we comprehensively analyzed the efficacy and safety of high- and low-dose RTX regimens in patients with AAV.

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## Materials and methods

### Patients

The study was conducted under a retrospective design in 104 cases of AAV with life-threatening organ manifestations which were treated with CY/RTX for remission induction at our hospital from 2006 to 2016. The diagnosis of AAV was confirmed on the basis of the classification algorithm of Watts et al. for EGPA, GPA, and MPA [11]. We selected all patients treated with RTX during the observation period. We then excluded those treated with a single dose of RTX 500 mg or two doses of RTX 1000 mg. Of the remaining 35 cases, we excluded further seven patients who received an irregular dose of RTX. Finally, 28 patients were subject to analysis. This study was approved by the ethics committee of our hospital (approval number 2145). Because the study had a retrospective cohort design that did not conduct any investigations/interventions beyond those for regular clinical purposes, written informed consent was not required. This study was carried out as per routine clinical care and RTX was initiated at the attending physician's discretion.

### Data collection

Patient data before initial treatment were collected, including age, gender, and clinical manifestations. Patients were divided into two groups, a high-dose (HD) RTX group which received 375 mg/m$^2$ of body surface area once weekly for 4 weeks and a low-dose (LD) RTX which received 375 mg/m$^2$ of body surface area once weekly for 2 weeks. Serum samples were tested at diagnosis for C-ANCA and P-ANCA by immunofluorescence, and for proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA by a direct enzyme-linked immunosorbent assay (ELISA). Disease activity was measured on the basis of the Birmingham Vasculitis Activity Score version 3 (BVAS) [12] and the physician's global assessment at 0, 2, 4, 8, 12, 24, 36, and 48 weeks after RTX initiation was collected. Disease- or treatment-related adverse outcomes were scored according to the Vasculitis Damage Index (VDI) at year 1 [13]. The peripheral blood B cell counts were measured by flow cytometry at weeks 0, 2, 4, 8, 12, 24, and 48. Complete remission (CR) was defined as an absence of clinical disease activity in the prednisolone (PSL) tapering process, as indicated by a BVAS of zero that was maintained for 4 weeks [4, 5]. A disease relapse was defined as more than one-point increase of BVAS [4, 5]. All adverse events for 1 year were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3 (CTCAE), including deaths (from all causes); malignant conditions; grade 2 or higher leukopenia, anemia, or thrombocytopenia; grade 2 or higher infection; stroke; hospitalization; and infusion reactions [14].

### Statistical analysis

Quantitative variables are presented as the mean ± standard deviation (SD). Continuous data were analyzed using the Mann-Whitney *U* test. The Fisher's test was used to compare categorical data. The cumulative complete remission (CR) rate was calculated using the Kaplan-Meier method, and differences between the two groups were tested using the log-rank test. $p < 0.05$ was considered to indicate statistical significance.

## Results

### Clinical characteristics of high- and low-dose RTX groups at baseline

The 28 patients were divided into two groups according to the dose of RTX initiated, namely 11 with LD-RTX and 17 with HD-RTX. The clinical characteristics at baseline are shown in Table 1. Gender, AAV type, newly diagnosed, disease-assessment score, organ involvement, ANCA phenotype, GC dose, methylprednisolone pulse therapy, serum creatinine level, and estimated glomerular filtration rate did not significantly differ between the two groups. Older patients were more frequently included in LD-RTX than HD-RTX ($p < 0.01$). Although not significant, patients with HD-RTX tended to have a higher incidence of nodules or cavities in the lung ($p = 0.07$), sensory peripheral neuropathy ($p = 0.07$), and a lower incidence of interstitial lung disease ($p = 0.09$) and myeloperoxidase-ANCA positivity ($p = 0.06$) than those with LD-RTX. All patients received induction therapy with GC at an initial dose of 0.5–1.0 mg prednisolone (PSL) equivalent/kg/day for 2–4 weeks. GC was then tapered by 10% of the last dose or 10 mg, as determined by the attending physician. Initial PSL dose did not markedly differ between the two groups ($p = 0.47$). All patients did not receive additional immunosuppressants including RTX, during at least 6 months after the initial administration of RTX.

### Cumulative complete remission rate over 1 year and association between BVAS at month 6 and AAV disease type or ANCA phenotype

Cumulative CR rates were compared between the two groups (Fig. 1A). There was no significant difference in CR rate for 1 year between the groups (HD-RTX 88.2% vs LD-RTX 90.9%, $p = 0.20$). Furthermore, there was no significant difference in cumulative relapse rate for 1 year between the groups (HD-RTX 13.3% vs. LD-RTX 20.0%, $p = 0.66$). We next focused on the association between AAV

**Table 1** Comparison of clinical characteristics at baseline between high-dose and low-dose rituximab groups

| Characteristic | High-dose RTX ($n = 17$) | Low-dose RTX ($n = 11$) | $p$ |
|---|---|---|---|
| Age (years) | 52.2 ± 18.0 | 75.4 ± 14.8 | < 0.01 |
| Female, *n* (%) | 10 (58.8) | 7 (63.6) | 0.80 |
| AAV type (%) | | | |
| GPA | 10 (58.8) | 4 (36.4) | 0.24 |
| MPA | 6 (35.3) | 7 (63.6) | 0.14 |
| EGPA | 1 (5.9) | 0 (0.0) | 0.48 |
| Newly diagnosed, *n* (%) | 8 (47.1) | 8 (72.7) | 0.18 |
| Disease assessment scores | | | |
| BVAS version 3 | 13.3 ± 7.0 | 12.7 ± 8.3 | 0.43 |
| VDI | 2.8 ± 2.4 | 1.9 ± 1.4 | 0.11 |
| Organ involvement | | | |
| Eye involvement, *n* (%) | 3 (17.6) | 2 (18.2) | 0.74 |
| Ear involvement, *n* (%) | 4 (23.5) | 3 (27.3) | 0.94 |
| Nose involvement, *n* (%) | 8 (47.1) | 3 (27.3) | 0.29 |
| Pulmonary involvement, *n* (%) | | | |
| Alveolar hemorrhage | 1 (5.9) | 1 (9.1) | 0.75 |
| Nodules or cavities | 9 (52.9) | 2 (18.2) | 0.07 |
| Interstitial lung disease | 4 (23.5) | 6 (54.5) | 0.09 |
| Endobronchial lesions | 3 (17.6) | 0 (0.0) | 0.21 |
| Renal involvement, *n* (%) | 7 (41.1) | 5 (45.5) | 0.82 |
| Neurologic involvement, *n* (%) | | | |
| Motor mononeuritis multiplex | 2 (11.8) | 3 (27.3) | 0.30 |
| Sensory peripheral neuropathy | 7 (41.1) | 1 (9.1) | 0.07 |
| Cutaneous involvement, n (%) | 3 (17.6) | 4 (36.4) | 0.26 |
| ANCA-positive at diagnosis (%) | | | |
| By immunofluorescence | | | |
| C-ANCA | 50.0 | 37.5 | 0.30 |
| P-ANCA | 37.5 | 50.0 | 0.54 |
| By ELISA | | | |
| Proteinase 3-ANCA | 52.9 | 36.4 | 0.39 |
| Myeloperoxidase-ANCA | 35.3 | 72.7 | 0.06 |
| CD19+ B cell counts (cells/mm$^3$) | 175.9 ± 148.6 | 192.5 ± 63.5 | 0.36 |
| Dose of PSL (mg/day) | 35.1 ± 15.8 | 34.5 ± 23.4 | 0.47 |
| mPSL pulse therapy, *n* (%) | 5 (29.4) | 7 (63.6) | 0.12 |
| Serum Cr level (mg/dL) | 0.76 ± 0.27 | 1.12 ± 1.32 | 0.19 |
| eGFR at base line (mL/min) | 75.3 ± 30.1 | 73.0 ± 39.2 | 0.43 |

Data are expressed as either *n* (%) or value ± SD. The chi-square test or Fisher's exact test was used to compare categorical data, and the Mann-Whitney U-test was used to analyze continuous data

*RTX* rituximab, *ANCA* antineutrophil cytoplasmic autoantibody, *AAV* ANCA-associated vasculitis, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *BVAS* Birmingham Vasculitis Activity Score, *VDI* Vasculitis Damage Index, *ELISA* enzyme-linked immunosorbent assay, *CD19+ B cell*: peripheral-blood CD19+ B cell, *PSL* prednisolone, *mPSL* methylprednisolone, *Cr* creatinine, *eGFR* estimate glomerular filtration rate

disease type or ANCA phenotype and BVAS score at 6 months (Fig. 1B). On comparison by AAV disease type, no patients with MPA experienced BVAS ≥ 1 at month 6. Although one patient in the LD-RTX group and two in the HD-RTX experienced BVAS ≥ 1 in GPA, no significant difference was observed in the percentage of patients with BVAS ≥ 1 at month 6 between the LD-RTX and HD-RTX groups. Results for ANCA phenotype were the same as those for AAV disease type: only patients with C/PR3-ANCA had BVAS ≥ 1 and no significant difference was seen in the percentage of patients who experienced BVAS ≥ 1 at 6 months after induction therapy.

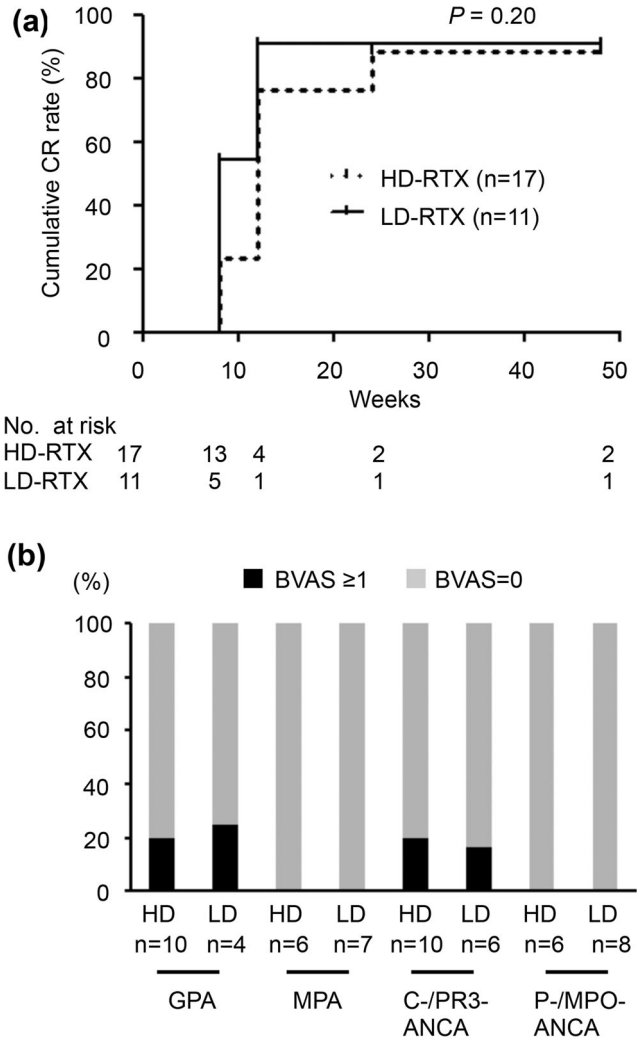


**Fig. 1** Cumulative complete remission rate over 1 year and association between BVAS at month 6 and AAV disease type or ANCA phenotype. **a** Cumulative complete remission rate for 1 year after induction therapy between patients with HD-RTX and LD-RTX. **b** Association between AAV disease type or ANCA phenotype and BVAS score at 6 months. HD-RTX: high-dose rituximab, LD-RTX: low-dose rituximab, BVAS: Birmingham Vasculitis Activity Score, HD: high dose, LD: low dose, GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis, ANCA: Antineutrophil cytoplasmic autoantibody, AAV: ANCA-associated vasculitis

## Peripheral blood B lymphocyte counts and disease-assessment scores

Serial changes in peripheral blood CD19+ B cell counts in the two groups were compared for 1 year after RTX initiation (Fig. 2A). Although the period of complete depletion of CD19+ B cell counts was longer in the HD-RTX than LD-RTX group, we found no significant difference in counts at any point during the observation period. We next compared serial changes in BVAS (Fig. 2B). Mean BVAS decreased remarkably by week 12, with similar changes in the two groups. Finally, we compared VDI for 1 year (Fig. 2C). A higher percentage of patients with a more than one point increase in VDI was observed in the HD-RTX than LD-RTX group, although the difference was not significant ($p = 0.69$).

## Adverse events

Adverse events during 1 year after RTX initiation are summarized in Table 2. There were no significant differences between the groups in the number of serious adverse events. Infection developed in 9 (52.9%) and 7 (63.6%) patients treated with HD-RTX and LD-RTX, respectively. Anemia and hypogammaglobulinemia were frequently observed. Four patients in the HD-RTX group and 3 in the LD-RTX required

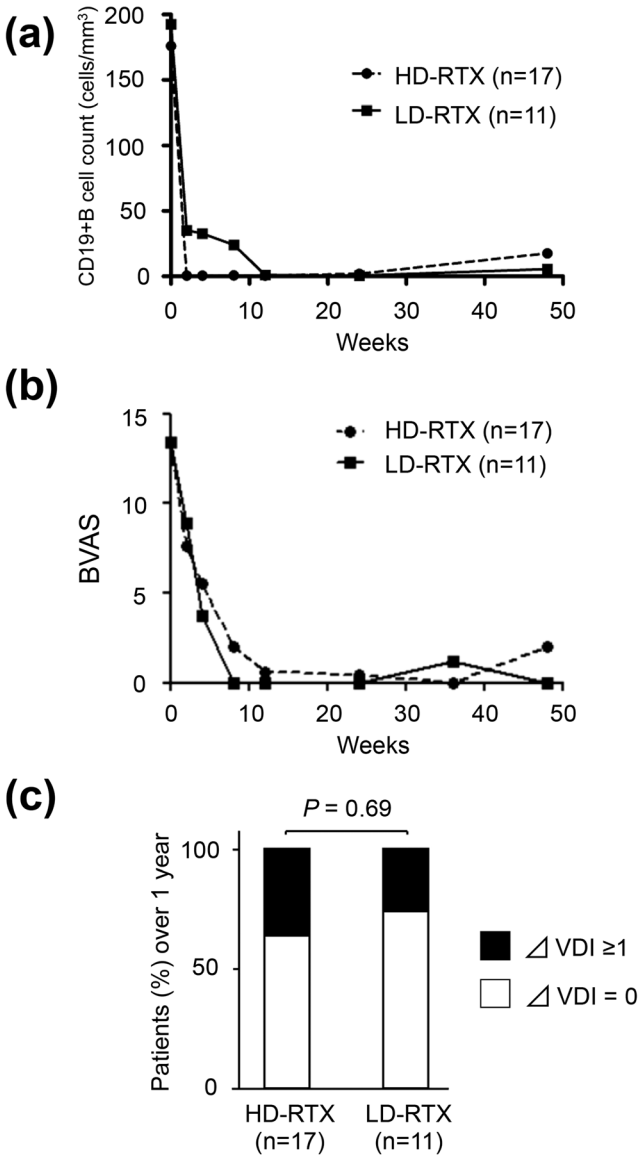


**Fig. 2** Peripheral-blood B lymphocyte count and disease-assessment score. Serial changes in peripheral-blood CD19+ B cell counts (**a**), BVAS (**b**) and VDI (**c**) in the two groups for 1-year after RTX initiation were compared. BVAS: Birmingham Vasculitis Activity Score, VDI: Vasculitis Damage Index, RTX: rituximab

hospitalization, 1 in the HD-RTX group due to cerebral aneurysm and the remaining 3 due to bacterial infection, whereas all 3 patients in the LD-RTX group were hospitalized due to bacterial infection. No cancers occurred during the observation period.

## Discussion

In this study, we found no significant difference in CR rate or serious adverse events for 1 year between patients taking low and high doses of RTX for AAV. Our findings suggested that low-dose treatment with RTX might be an alternative choice for elderly patients with MPA or positive result of MPO-ANCA as an induction therapy.

The proposed pathogenic mechanism of vascular inflammation in AAV involves ANCA-induced activation of primed neutrophils in association with activation of the alternative complement pathway [15]. The central role of B cells in the pathogenesis of AAV has been highlighted by identification of the association between B cell activation status and disease activity and the efficacy of RTX as a treatment for patients with AAV. Indeed, the use of RTX, a chimeric anti-CD20 monoclonal antibody, as a new therapy for AAV is the most important development in this field since the introduction of CY 40 years ago [16]. Favorable results of RTX treatment have been reported in two randomized control studies, the Rituximab Versus Cyclophosphamide for AAV (RAVE) trial [4] and Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) trial [5]. In both trials, the RTX group received induction therapy with RTX (375 mg/m2 of body-surface area) once per week for 4 weeks as induction therapy. Results showed no inferiority in efficacy compared with CY.

Recently, a new strategy for remission maintenance therapy using rituximab was reported in the MAINRITSAN 2 trial [17]. In this trial, a non-significant trend towards more frequent relapse was seen with lower RTX exposure in the biomarker-based group, indicating that some patients may experience RTX overdosing when fixed doses are used to prevent disease flare. Although the question of whether the incidence of infection increases in a RTX dose-dependent manner has been poorly investigated, appropriate dose of RTX and depletion of B cells might be safe. Furthermore, since RTX is expensive ($4912.79 in the USA, €830.561 in France or \157,855 in Japan, per 500 mg), the lowest dose of RTX for preventing disease flare or suppressing disease activity is socioeconomically preferable.

To our knowledge, this is the first report to compare the efficacy of HD-RTX and LD-RTX in induction therapy of AAV. Low-dose RTX has recently shown closely similar results to those successful results obtained with conventional regimens in a number of other autoimmune diseases, including rheumatoid arthritis (two doses of 500 mg), immune thrombocytopenia (100 mg weekly for 4 weeks), kidney transplantation (single dose of 50–100 mg/m$^2$), and mixed cryoglobulinemia vasculitis (MC) (two doses of 250 mg/m$^2$) [8–10, 18]. In patients with RA, no significant difference was seen in the percentages of patients who achieved a European League Against Rheumatism good response (18.4% vs 17.3%, $p = 0.36$) at 6 months between high- (two doses of 1000 mg) and low-dose RTX groups (two doses of 500 mg) [8]. Visentini et al. reported that patients with MC showed no significant difference in CR rate (86% vs 81%, $p = 0.50$), relapse rate (32% vs 41%, $p = 0.32$), or adverse events (19.9%

**Table 2** Adverse events at 1 year

| Variable | High-dose RTX ($n = 17$) | Low-dose RTX ($n = 11$) | $p$ |
|---|---|---|---|
| Total number of selected adverse events | 23 | 18 | – |
| ≧ 1 selected adverse event, $n$ (%) | 13 (76.5) | 5 (45.5) | 0.20 |
| Specific selected adverse events, $n$ (%) | | | |
| Death | 0 (0.0) | 1 (9.1) | 0.39 |
| Cancer | 0 (0.0) | 0 (0.0) | 1.0 |
| Leukopenia (≧ grade 2[a]) | 1 (5.9) | 1 (9.1) | 1.0 |
| Thrombocytopenia (≧ grade 2[a]) | 0 (0.0) | 1 (9.1) | 0.39 |
| Anemia (≧ grade 2[a]) | 3 (17.6) | 4 (36.4) | 0.38 |
| Hypogammaglobulinemia (≦ 500 mg/dl) | 4 (23.5) | 2 (18.2) | 0.65 |
| Infection (≧ grade 2[a]) | 9 (52.9) | 7 (63.6) | 0.87 |
| All infusion reactions | 2 (11.8) | 0 (0.0) | 0.51 |
| Cerebrovascular accident | 1 (5.9) | 0 (0.0) | 1.0 |
| Hospitalization due to disease or treatment | 4 (23.5) | 3 (27.3) | 0.82 |

All values for both groups indicate $n$ (%)

[a] The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3

vs 11.5%, $p = 0.13$) for 1 year between high- (four doses of 375 mg/m$^2$) and low-dose RTX groups (two doses of 250 mg/m$^2$) [18]. The pharmacokinetics of RTX was highly variable among patients with AAV despite a dosing protocol that adjusted for the body surface area, and higher RTX exposure was not associated with important clinical outcomes, such as achieving CR, relapse risk, or time to relapse [19]. These findings support our finding that HD-RTX is not necessary for all the AAV patients and some could be treated with LD-RTX.

This study was a small single-center study conducted under a retrospective design in a Japanese population. As patients were selected retrospectively, a degree of selection bias was present, as follows: induction therapy was at the discretion of the attending physician and only patients who could be observed for 1 year were enrolled. Accordingly, our findings require confirmation in a larger multi-center, prospective study.

In conclusion, we found that LD-RTX may be effective in induction therapy for AAV, particularly in MPA and MPO-ANCA-positive patients. This LD-RTX regimen may improve the cost/benefit profile of RTX therapy for AAV.

## Compliance with ethical standards

**Disclosures** None.

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