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ORIGINAL ARTICLE

Immunoglobulin levels and infection risk with rituximab induction for anti-neutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Background: Rituximab (RTX), a B cell–depleting anti-CD20 monoclonal antibody, is approved for treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Low immunoglobulin (Ig) levels have been observed surrounding RTX treatment. The association between the degree of Ig deficiency and infection risk is unclear in AAV patients.

Methods: AAV patients treated with RTX for remission induction at a single center (2005–15) with serum Ig measurements were included. Patient characteristics; serum IgG, IgM and IgA levels and occurrence of infections were collected retrospectively. Low IgG was defined as mild (376–749 mg/dL) or severe (>375 mg/dL). Logistic regression models were adjusted for age at RTX administration, estimated glomerular filtration rate (eGFR) and race to examine the association of degree and type of Ig deficiency and infection risk.

Results: Our cohort of 30 patients had a mean age of 63 (SD 7) years, 23 were women, 16 had granulomatosis with polyangiitis and 13 were PR3 ANCA positive. Nine patients received concomitant cyclophosphamide. The mean IgG level was 625 mg/dL (SD 289), mean IgM level was 55 mg/dL (SD 41) and mean IgA level was 133 mg/dL (SD 79). In this cohort, 20 patients had low serum IgG levels (<750 mg/dL) following RTX treatment. During the follow-up period, four individuals developed infections requiring hospitalization. In unadjusted logistic regression analysis, an IgG level ≤ 375 mg/dL was associated with 23 times higher odds of hospitalized infection [95% confidence interval (CI) 1.8–298.4; P = 0.02]. After adjustment for age, race and eGFR, results were similar [odds ratio (OR) 21.1 (95% CI 1.1–404.1) P = 0.04]. Low IgA was also associated with an increased risk of infections requiring hospitalization after adjusting for age, race and eGFR [OR 24.6 (95% CI 1.5–799.5) P = 0.03]. Low IgM was not associated with a higher risk of infections requiring hospitalization.

Conclusions: Severe hypogammaglobulinemia was associated with increased odds of infection requiring hospitalization in this cohort. Further investigation is warranted given our study is limited by small sample size, concomitant cyclophosphamide use and variable timing of Ig measurement.

Key words: ANCA, immunoglobulin level, infection risk, rituximab, vasculitis

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Introduction

Rituximab (RTX), a chimeric, monoclonal antibody directed against the CD20 antigen on B cells, has demonstrated efficacy in the treatment of B cell non-Hodgkin's lymphoma, rheumatoid arthritis, systemic lupus erythematosis (SLE), idiopathic thrombocytopenia and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [1–6]. The rationale for its use in these diseases stems from the role of B cells in each disease process. In AAV, the pathogenicity of ANCA, the role of B cells as precursors of ANCA-producing plasma cells and elevated titers of activated B cells and B cell–activating factor of the tumor necrosis factor (TNF) family (BAFF) in patients with active AAV point to the central role of B cells in this disease [7–10].

RTX causes B cell depletion through antibody-dependent cytotoxicity, complement-dependent cytotoxicity and direct induction of apoptosis [11]. Although mature plasma cells lack CD20 expression and are not direct targets of RTX therapy, decreased immunoglobulin (Ig) levels can occur with RTX use due to a reduction in plasma cell precursors [12].

It is unclear whether a reduction in Ig levels corresponds to a higher risk of infection. Retrospective evidence suggests no link between IgG levels and infection risk, although in one study, patients with a reduction in more than one Ig subtype were more likely to have an infection [12–15]. The contribution of RTX to infection risk is confounded by complex underlying disease processes in addition to prior and ongoing exposure to other immunosuppressants.

This study aims to examine the association between low Ig levels and infection risk in individuals treated with RTX for induction of remission of AAV.

Materials and methods

AAV patients from a single university center treated with RTX for induction of remission between 2005 and 2016 with available Ig titers were included. All patients received pulse methyl prednisone 1000 mg/day for 3 days followed by oral prednisone 1 mg/kg/day. Prednisone was tapered every 2 weeks to a maintenance dose of 5 mg/day by month 6. Patients were allowed to be treated with plasmapheresis or concomitant oral cyclophosphamide. Approval for the study was obtained from the university's Institutional Review Board.

The diagnosis of AAV required documentation of a compatible syndrome and/or biopsy-proven pauci-immune vasculitis and a positive serum assay for cytoplasmic or perinuclear ANCA. Patients were classified as having microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) or eosinophilic granulomatosis with polyangiitis (EGPA) based on the Chapel Hill Consensus Conference [16] .

Information regarding patient age, race, gender, AAV type, ANCA type, estimated glomerular filtration rate (eGFR) at entry, vasculitis activity at entry, remission, RTX dosage, concomitant immunosuppression, remission, adverse events with RTX, immunoglobulin (IgG, IgM and IgA) levels and types of infection were recorded retrospectively. If any patients had Ig levels measured on more than one occasion, only the earliest measured values following RTX administration were utilized for this analysis. GFR was estimated using the Modification of Diet in Renal Disease formula [17]. Vasculitis activity was calculated using the Birmingham Vasculitis Activity Score for Wegener's granulomatosis (BVAS/WG) [18]. Remission was defined as a BVAS/WG score of zero. The primary outcomes of this study were to assess the severity of Ig reduction in patients treated with RTX and how levels of Ig correlate with infection risk.

Baseline patient characteristics were compared by IgG levels (IgG $>$ 375 mg/dL and IgG $\leq$ 375 mg/dL) using Fisher's exact tests and *t*-tests. Logistic regression was used to evaluate the relationship between Ig level and risk of infection. The lower limits of normal for IgG, IgM and IgA in our laboratory are 751 mg/dL, 46 mg/dL and 82 mg/dL, respectively. Low IgG was defined as mild (376–749 mg/dL) or severe ($>$375 mg/dL). The IgG level was dichotomized as $>$375 mg/dL and $\leq$375 mg/dL and the IgM level as $>$23 mg/dL and $\leq$23 mg/dL, as there were more infections requiring hospitalization among patients with IgG and IgM below these cutoffs. The IgA level was categorized as $>$66 mg/dL and $\leq$66 mg/dL—this cutoff was used due to the small number of patients with very low IgA levels. Multivariable analyses were adjusted for race (Caucasian versus other) and age at RTX administration. Analyses were not adjusted for gender, as infections requiring hospitalizations only occurred among women. Statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX, USA).

Results

Of the 30 patients who fulfilled inclusion criteria, the mean age was 63 years (SD 14), 7 were men and 16 carried a diagnosis of GPA. Twenty-six patients carried a new diagnosis of AAV. Among the four patients with relapsing disease, three had prior exposure to cyclophosphamide. The median interval from last cyclophosphamide exposure to RTX administration in these three patients was 58 months (range 22–84). Thirteen patients were PR3 ANCA positive. All patients had renal involvement and 28 of these were biopsy proven. The mean estimated GFR at entry was approximately 28 (SD 17) mL/min/1.73 m^2. The mean BVAS/WG score was 5.1 (SD 2.1). Twenty-eight patients were treated with RTX induction dosed at 375 mg/m^2 weekly for four doses and two patients received 1000 mg every 2 weeks for two doses. Nine patients received concomitant cyclophosphamide. Six patients received seven sessions of plasma exchange over a 2-week period. All but two patients received *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis after receiving RTX. B cell count was not tested in all patients and B cell depletion was documented in all 28 patients who were tested. One patient had refractory vasculitis and the remaining 29 patients achieved remission after a mean of 65 (SD 42) days. Remission maintenance immunosuppression included RTX every 6 months in 15 patients, azathioprine in 2 patients, leflunomide in 1 patient and 12 patients were not on maintenance therapy at the time of the last follow-up.

During the follow-up period [mean follow-up 711 days (SD 631], 17 (57%) patients developed a total of 23 infections and 5 (17%) of these patients developed more than one infection. Of these infections, five were bacterial pneumonia, one was PJP, one was cytomegalovirus (CMV) viremia, one was *Clostridium difficile* colitis, one was cellulitis, five were sinusitis requiring antibiotics, one was viral tracheitis, one was tinea versicolor and seven were herpes zoster. The single patient with PJP developed the infection 40 months after her RTX infusion while she was on maintenance therapy with low-dose azathioprine and was not on PJP prophylaxis. Four (13%) patients developed eight infections requiring hospitalizations. One patient died of *Clostridium difficile* colitis. The median daily prednisone dose at the time of infection was 5 mg. Of the nine patients who received concomitant cyclophosphamide treatment, two patients required hospitalization for bacterial pneumonia. Of the six patients who received plasma exchange, one patient required hospitalization for PCP pneumonia that developed 40 months after the initial presentation.

Ig levels were drawn an average of 206 days after RTX administration. The mean IgG level was 625 mg/dL (SD 289), mean IgM level was 55 mg/dL (SD 41) and mean IgA level was 133 mg/dL (SD 79). There were no differences in baseline characteristics between patients with IgG > 375 mg/dL and those with IgG ≤ 375 mg/dL (Table 1).

Twenty patients had IgG levels below the lower limit of normal in our laboratory (< 751 mg/dL), 15 had IgM levels below the lower limit of normal (< 46 mg/dL) and 11 had IgA levels below the lower limit of normal (< 82 mg/dL). Among the 11 patients with low IgA levels, all had low IgG, with 5 patients having severe hypogammaglobulinemia, and 7 had low IgM. Follow-up Igs in seven patients who developed hypogammaglobulinemia and did not get RTX for remission maintenance revealed normalization of Ig levels at a median of 168 days (range 56–809).

There was no association between an IgG level ≤ 375 mg/dL and overall infection {odds ratio [OR] for unadjusted analysis 5.0 [95% confidence interval (CI) 0.5–49.4] P = 0.17}. Similarly, IgM level ≤ 23 mg/dL [unadjusted OR 1.8 (95% CI 0.4–9.3); P = 0.47] and an IgA level ≤ 66 mg/dL [unadjusted OR 3.7 (95% CI 0.4–37.9); P = 0.27] were also not associated with overall infection. However, lower Ig levels were associated with infections requiring hospitalization (Table 2). In unadjusted logistic regression analysis, an IgG level ≤ 375 mg/dL was associated with 23 times higher odds of hospitalized infection (95% CI 1.8–298.4; P = 0.02) (Table 3). After adjustment for age and race, results were similar [OR 24.3 (95% CI 1.4–420.6); P = 0.03]. The addition of eGFR to the model did not change results substantially [OR 21.1 (95% CI 1.1–404.1); P = 0.04].

For IgM ≤ 23 mg/dL, there was a lesser association with infections requiring hospitalization, with an unadjusted OR of 10 (95% CI 0.9–114.7; P = 0.06) and an adjusted OR of 19.2 (95% CI 1.0–356.9; P = 0.048). IgA ≤ 66 mg/dL was significantly associated with hospitalized infections, with an unadjusted OR of 36.0 (95% CI 2.5–527.1; P = 0.009). Results remained statistically significant after adjustment for age and race [OR 38.4 (95% CI 1.9–760.3); P = 0.02] as well as eGFR [OR 24.6 (95% CI 1.5–799.5); P = 0.03].

Table 1. Baseline characteristics by IgG level

Characteristic	IgG > 375 mg/dL (*n* = 24)	IgG ≤ 375 mg/dL (*n* = 6)	P-value
Female, *n* (%)	17 (70.8)	6 (100.0)	0.29
Caucasian, *n* (%)	18 (75.0)	5 (83.3)	1.00
Diagnosis, *n* (%)			
GPA	14 (58.3)	2 (33.3)	0.47
MPA	8 (33.3)	4 (66.7)	
EGPA	2 (8.3)	0 (0.0)	
ANCA type, *n* (%)			
c-ANCA	12 (50.0)	1 (16.7)	0.19
p-ANCA	11 (45.8)	4 (66.7)	
ANCA negative	1 (4.2)	1 (16.7)	
Age at RTX, years (SD)	61.7 (3.0)	68.7 (4.8)	0.30
Estimated GFR (SD)	30.8 (4.3)	20.2 (2.6)	0.23
Cyclophosphamide use, *n* (%)	6 (25.0)	3 (50.0)	0.33
RTX maintenance, *n* (%)	12 (50.0)	4 (66.7)	0.66
B cell depletion, *n* (%)	21 (95.5)[a]	4 (66.7)	0.11

[a]Two patients in the IgG > 375 mg/dL group were not checked for B cell depletion.

Discussion

This single-center retrospective study demonstrates that hypogammaglobulinemia is common in AAV patients treated with RTX. IgG levels return to baseline after RTX is stopped. Our study examines the risk of infection related to the severity of hypogammaglobulinemia and demonstrates a higher risk of infections requiring hospitalization in patients with severe hypogammaglobulinemia in AAV.

RTX depletes pre-plasma B cells and this may lead to decreased repopulation of plasma cells resulting in decreased production of Igs. RTX-induced hypogammaglobulinemia is rare in rheumatoid arthritis patients [19]. In contrast, hypogammaglobulinemia occurs in >50% of AAV patients treated with RTX [20]. This difference may be related to older age, concomitant use of other immunosuppressive medications or uncharacterized B cell dysfunction in AAV. Low baseline Ig level, prior cyclophosphamide exposure and glucocorticoid therapy have been shown to be risk factors for RTX-induced hypogammaglobulinemia [12, 21]. Low IgG levels complicate ongoing use of RTX due to the association of low IgG levels with infection risk. This is an important consideration, given the increasing role of RTX not only for induction of remission in AAV, but also for maintenance of remission.

Literature describing the effect of RTX on Ig levels and infection risk in AAV is sparse. In the 18-month follow-up of the Rituximab in ANCA-Associated Vasculitis trial, there was no significant difference in IgG levels between patients treated with RTX and cyclophosphamide, and although IgG levels decreased in both arms, there was no association between IgG level and infection risk [22]. In 179 patients with AAV and SLE treated with RTX, of which 69% had prior cyclophosphamide exposure

Table 2. Infections requiring hospitalizations by Ig level

IgG level and number of infections requiring hospitalization, *n* (%)			P-value[a]
≥750 mg/dL	376–749 mg/dL	0–375 mg/dL	
(*n* = 10)	(*n* = 14)	(*n*=6)	
1 (10%)	0 (0%)	3 (50%)	0.01
			0.10
≥46 mg/dL	24–45 mg/dL	0–23 mg/dL	
(*n* = 16)	(*n* = 5)	(*n*=9)	
1 (6%)	0 (0%)	3 (33%)	
			<0.001
≥82 mg/dL	41–81 mg/dL	0–41 mg/dL	
(*n* = 19)	(*n* = 8)	(*n*=3)	
1 (5%)	0 (0%)	3 (100%)	

[a]Fisher's exact *t*-test.

Table 3. Odds ratios for infections requiring hospitalization by Ig subclass

	OR (95% CI); P-value		
Model	IgG level $\leq$ 375 mg/dL	IgM level $\leq$ 23 mg/dL	IgA level $\leq$ 66 mg/dL
Unadjusted	23.0 (1.8–298.4); 0.02	10.0 (0.9–114.7); 0.06	36.0 (2.5–527.1); 0.009
Adjusted for age and race	24.3 (1.4–420.6); 0.03	19.2 (1.0–356.9); 0.05	38.4 (1.9–760.3); 0.02
Adjusted for age, race and eGFR	21.1 (1.1–404.1); 0.04	17.7 (0.9–340.5); 0.06	24.6 (1.5–799.5); 0.03

and 58% were on concomitant immunosuppression, 23% developed *de novo* hypogammaglobulinemia [12]. In another study of 55 AAV patients treated with RTX following cyclophosphamide, RTX lowered all Ig levels further than what was seen with cyclophosphamide. Greater cumulative exposure to RTX may result in lower Ig levels, although this finding was not reproduced by Marco *et al.* [12–14, 23]. In a study by Venhoff *et al.* [19], there was a decline in IgG and IgM concentrations in AAV patients who received cyclophosphamide followed by RTX. Twenty-one percent of patients were started on Ig replacement because of severe broncho-pulmonary infections and serum IgG concentrations <500 mg/dL. Their study indicated that in patients with AAV who were previously treated with cyclophosphamide, RTX can lead to a further decline in Ig concentrations, but the infection risk was not analyzed against the Ig levels [19]. In another study by Roberts *et al.* [20], moderate to severe hypogammaglobulinemia was common but transient in the majority of cases after RTX treatment. Hypogammaglobulinemia after RTX administration was also noted in the study by Chocova *et al.* [24], but the infectious complications did not correlate with IgG levels.

In our study, 57% of patients experienced an infection and 13% of patients developed infections requiring hospitalization. We found a significant association of infections requiring hospitalization with the lowest levels of IgG and IgA. In prior studies, although low IgM and IgA levels were noted after RTX, there was no association with infection [12]. The association of low IgA level with hospitalized infection risk in our cohort may be related to the overall degree of plasma cell dysfunction since all patients had severe hypogammaglobulinemia. Seven (23%) of our patients experienced herpes zoster. An increased risk of herpes zoster due to reactivation of herpes virus has been described in patients receiving TNF-α antagonists [25], but the incidence of herpes zoster in RTX-treated patients is not known and needs further study.

Intravenous Ig has been used for the treatment of RTX-induced hypogammaglobulinemia, but the data are very limited. The threshold for initiation of Ig replacement varies in the absence of formal guidelines. In addition to the severity of hypogammaglobulinemia, functional antibody deficiency can be an indicator of impaired immune response and has been used to guide Ig replacement [26]. Roberts *et al.* [20] describe 12 of 288 RTX-treated patients with autoimmune disease who were treated with Ig replacement [20]. Of the 12 patients who received Ig replacement therapy, 6 had moderate hypogammaglobulinemia and 4 had mild hypogammaglobulinemia. Functional antibody deficiency was present in all six patients who were tested. All 12 patients had recurrent or severe infection. Intravenous Ig replacement decreased the incidence and severity of infection in these patients. None of our patients were treated with intravenous Ig.

Limitations of this study include the small sample size, retrospective design, lack of baseline Ig levels prior to RTX administration and the variable timing of Ig measurements following RTX administration. Since Ig levels were not measured consistently prior to the administration of RTX, we are unable to conclude whether RTX is responsible for low Ig levels in this group.

The statistical power of our study does not allow us to draw valid conclusions. Nonetheless, our data suggest that hypogammaglobulinemia is common after RTX therapy for AAV, and IgG levels $\leq$ 375 mg/dL may be associated with an increased risk of infections requiring hospitalization. RTX has emerged as an effective agent for remission induction in AAV. Given the high incidence of hypogammaglobulinemia and increased infection risk, it is of utmost importance to identify not only the risk factors for infection but also to validate the scoring tools used to guide Ig replacement therapy [26] in a larger cohort.

Conflict of interest statement

None declared.

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