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Rituximab-associated hypogammaglobulinemia: Incidence, predictors and outcomes in patients with multi-system autoimmune disease

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ABSTRACT

Rituximab is a B cell depleting monoclonal antibody used to treat lymphoma and autoimmune disease. Hypogammaglobulinemia has occurred after rituximab for lymphoma and rheumatoid arthritis but data are scarce for other autoimmune indications. This study describes the incidence and severity of hypogammaglobulinemia in patients receiving rituximab for small vessel vasculitis and other multi-system autoimmune diseases. Predictors for and clinical outcomes of hypogammaglobulinemia were explored. We conducted a retrospective study in a tertiary referral specialist clinic. The severity of hypogammaglobulinemia was categorized by the nadir serum IgG concentration measured during clinical care. We identified 288 patients who received rituximab; 243 were eligible for inclusion with median follow up of 42 months. 26% were IgG hypogammaglobulinemic at the time that rituximab was initiated and 56% had IgG hypogammaglobulinemia during follow-up (5–6.9 g/L in 30%, 3–4.9 g/L in 22% and <3 g/L in 4%); IgM ≤0.3 g/L in 58%. The nadir IgG was non-sustained in 50% of cases with moderate/severe hypogammaglobulinemia. A weak association was noted between prior cyclophosphamide exposure and nadir IgG concentration, but not cumulative rituximab dose. IgG concentrations prior to and at the time of rituximab correlated with the nadir IgG post rituximab. IgG replacement was initiated because of recurrent infection in 12 (4.2%) patients and a lower IgG increased the odds ratio of receiving IgG replacement. Rituximab is associated with an increased risk of hypogammaglobulinemia but recovery of IgG level can occur. IgG monitoring may be useful for patients receiving rituximab.

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1. Introduction

Rituximab is an anti-CD20 chimeric monoclonal antibody that depletes pre-plasma B-cells. It is approved treatment for rheumatoid arthritis (RA) and anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) [1–4]. Rituximab use is increasing for the treatment of these and other autoimmune diseases, and the relapsing nature of AAV has led to repeat rituximab courses with high cumulative exposure [5,6].

The proposed mechanisms of action of rituximab include altered B-cell signaling and/or a decrease in production of pathogenic autoantibody. Rituximab depletes pre-plasma B-cells which may subsequently reduce re-population of antibody-secreting plasma cells, leading to decreased production of immunoglobulins G and M (IgG and IgM). This may predispose to hypogammaglobulinemia and associated infection.

Prolonged hypogammaglobulinemia is reported post-rituximab, particularly following treatment of lymphoma with combination chemotherapy and/or stem cell transplantation [7–17]. In a series of 211 patients with lymphoma the initial IgG concentration was normal in 179 patients and 39% of these developed hypogammaglobulinemia (<6 g/L), and 6.6% required IgG replacement therapy

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for recurrent infections of the upper respiratory tract [18]. However, hypogammaglobulinemia is a feature of active lymphoma [19] which complicates the interpretation of these studies.

Hypogammaglobulinemia has not been reported in RCTs in patients with other autoimmune diseases, although it has been noted subsequently and the incidence is poorly defined. A registry study reported severe infections in 5% of RA patients treated with rituximab; 16% of these had IgG <6 g/L before rituximab, compared to 3.9% without severe infection [20]. The incidence of hypogammaglobulinemia (IgM and IgG) may increase with higher doses of rituximab in RA and lymphoma patients; IgA is variably affected and does not appear to be a major risk factor for infection [18,21–23].

Of concern, a recent retrospective study reported that seven (21%) of 33 patients who received cyclophosphamide and rituximab for AAV required IgG replacement for severe bronchopulmonary infections in the context of serum IgG concentration <5 g/L [24]. Another retrospective study in 35 patients with AAV receiving cyclophosphamide followed by rituximab reported that five patients (14%) required IgG replacement therapy after receiving rituximab [25]. More data are required to validate these observations of severe outcomes and explore the effect of dose in populations other than RA or lymphoma.

This study describes the incidence and severity of hypogammaglobulinemia in patients receiving rituximab for AAV and other multi-system autoimmune diseases. Potential predictors for, and clinical outcomes of, hypogammaglobulinemia are explored.

2. Material and methods

This retrospective study was conducted in a specialist Lupus and Vasculitis Clinic in a tertiary hospital. A subset of data on 177 patients in this cohort, until 2010, has been previously reported [26]. Patients receiving rituximab were identified from existing databases and demographic, diagnostic and previous treatment data were extracted.

Decisions regarding immunosuppressive therapies were made by treating physicians. Serum IgG concentrations measured as part of routine clinical care between 26th July 1995 and 1st March 2013 were reviewed. IgG concentrations obtained within three months of IgG therapy (for disease control) or within one month after plasmapheresis were excluded. Inclusion criteria was a minimum of three serum IgG concentrations over at least six months after receiving rituximab, similar to that used by others [24].

Hypogammaglobulinemia is variably defined, including IgG <5 g/L [21,27,28], <6 g/L [18,20,22,29], or 6.7 g/L [23], but the lower limit of normal may be up to 8 g/L depending on patient age, comorbidity and the assay [27,30]. We graded hypogammaglobulinemia on the basis of the nadir serum IgG concentration as follows: mild (at risk) 5–6.9 g/L, moderate 3–4.9 g/L and severe < 3 g/L. The lower limit of normal for IgM is 0.4–0.45 g/L [21,22].

Renal involvement was defined as an abnormal urinalysis (microscopy, proteinuria) or renal biopsy, or an elevated serum creatinine concentration (reference range 35–125 μmol/L) due to the diagnosis.

The associations between the nadir IgG concentration and potential risk factors were determined by univariate analyses and p-value <0.05 was considered significant. The goodness of fit (r^2) of statistically significant correlations was determined using linear regression. The odds ratio of receiving IgG replacement according to the severity of hypogammaglobulinemia was calculated relative to patients who did not develop hypogammaglobulinemia. For all statistical tests, if data normality was not confirmed by the D'Agostino and Pearson omnibus normality test then nonparametric tests were used, notably the Mann Whitney and Spearman r correlation tests. All regressions and statistics were conducted using GraphPad Prism version 5.03 for Windows, GraphPad Software, San Diego CA USA.

This was a quality assurance project and in accordance with National Health Research Ethics Committee guidelines, formal ethical approval was not required because it comprises retrospective data and all treatment decisions were made prior to our review.

3. Results

We identified 288 patients who had received rituximab and 243 of these fulfilled inclusion criteria. Patients were administered the first dose of rituximab between 2002 and 2012 (Table 1). The majority were women, the mean age was 50 years, granulomatosis with polyangiitis (GPA, Wegener's) was the most common diagnosis; renal involvement was noted in 47% of the cohort. The disease duration prior to rituximab was median 48 (IQR 21-108) months and more than half of the patients had received at least 6 g of both cyclophosphamide and rituximab. Prophylactic sulphamethoxazole-trimethoprim was routinely administered to patients receiving cyclophosphamide, but not rituximab.

3.1. Development of hypogammaglobulinemia

IgG data were available for 223 patients at rituximab initiation and hypogammaglobulinemia was mild in 34 (15%), moderate in 13 (6%) and severe in 2 (1%) of patients. This increased following rituximab, being mild in 72 (30%), moderate in 53 (22%) and severe in 10 (4%).

In the 15 patients in whom the nadir IgG was noted within 6 months of commencing rituximab, this was followed by an upwards trend in IgG concentration over the following 6–12 months (Fig. 1).

Of those who developed severe hypogammaglobulinemia (7 systemic vasculitis, 1 systemic lupus erythematosus (SLE), 2 other diagnoses), this was transient in five, all of whom spontaneously

Table 1
Characteristics of the study population ($n = 243$).

Sex	
Female (n, %)	164, 67%
Male (n, %)	79, 33%
Age at first dose of rituximab (median; IQR, range)	51; 39–62, 14–84 years
Diagnosis (n, %)	
GPA	116, 48%
MPA	20, 8%
EGPA	24, 10%
SLE	44, 18%
Other	39, 16%
Disease duration prior to rituximab (median; IQR, range)[a]	48; 21–108, 0–396 months
Renal injury	
Present during disease course	47%
Creatinine concentration at first dose of rituximab (median; IQR, range)	81; 66–121, 41–758 μmol/L
Prior cyclophosphamide dose (Median; IQR, range)[b]	6; 0–15, 0–163 g
Total rituximab dose (median; IQR, range)	6; 3–8, 1–23 g
Serum IgG concentration at the time of the first dose of rituximab (Median; IQR, range)[c]	9.1; 7.2–11.3, 1.5–55.1 g/L
IgG data after first dose of rituximab	
Duration (median; IQR, range)	42; 22–74, 6–121 months
Number of samples (median; IQR, range)	16; 9–27, 3–58

[a] Known in 242 patients.
[b] Cyclophosphamide dosage known in 240 patients, 158 of whom received this treatment.
[c] Known in 223 patients.

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