Rituximab-induced hypogammaglobulinaemia in patients affected by idiopathic inflammatory myopathies: a multicentre study

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Abstract

Objective

Rituximab (RTX) is an anti-CD20 chimeric monoclonal antibody recommended as off-label treatment in patients with idiopathic inflammatory myopathies (IIM). The present study aimed to evaluate changes in immunoglobulin (Ig) levels during RTX-treatment and their potential association with infections in a cohort of IIM patients.

Methods

Patients evaluated in the Myositis clinic belonging to the Rheumatology Units of Siena, Bari and Palermo University Hospitals, and treated for the first time with RTX were enrolled. Demographic, clinical, laboratory and treatment variables, including previous and concomitant immunosuppressive drugs and glucocorticoid (GC) dosage were analysed before (T0) and after 6 (T1) and 12 (T2) months of RTX treatment.

Results

Thirty patients (median age, IQR 56 (42-66); 22 female) were selected. During the observational period, low levels of IgG (<700 mg/dl) and IgM (<40 mg/dl) occurred in 10% and 17% of patients, respectively. However, no one showed severe (IgG<400 mg/dl) hypogammaglobulinaemia. IgA concentrations were lower at T1 than T0 (p=0.0218), while IgG concentrations were lower at T2 compared to those at baseline (p=0.0335). IgM concentrations were lower at T1 and T2 than T0 (p<0.0001), as well at T2 than T1 (p=0.0215). Three patients suffered major infections, two others had paucisymptomatic COVID-19, one suffered from mild zoster. GC dosages at T0 were inversely correlated with IgA T0 concentrations (p=0.004, r=- 0.514). No correlation was found between demographic, clinical and treatment variables and Ig serum levels.

Conclusion

Hypogammaglobulinaemia following RTX is uncommon in IIM and is not related to any clinical variables, including GC dosage and previous treatments. IgG and IgM monitoring after RTX treatment does not seem useful in stratifying patients who require closer safety monitoring and prevention of infection, due to the lack of association between hypogammaglobulinaemia and the onset of severe infections.

Key words

rituximab, myositis, hypogammaglobulinaemia

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Introduction

Rituximab (RTX) is a chimeric monoclonal antibody that binds the CD20 molecule on the surface of B cells and leads to B cell depletion (1). RTX is widely used in the treatment of B-cell lymphomas (2) and several autoimmune conditions (3), including rheumatoid arthritis (RA) (4) and anti- neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (5). Moreover, RTX is also recommended by the European Alliance of Associations for Rheumatology (EULAR) as third-line treatment in systemic lupus erythematosus and it is used off-label in patients with other connective tissue diseases (CTD) including idiopathic inflammatory myopathies (IIM): in the latter, RTX is commonly employed in patients suffering from severe disease (6, 7), not responding to conventional synthetic immunosuppressants and in severe lung (8) and skin involvement.

Typically, after 6–9 months post-RTX infusion, a B cell reconstitution occurs mainly skewed toward naïve B cells (1). However, a relapsing-remitting disease course often requires repeated drug infusions leading to high cumulative doses. The CD20 surface molecule is lost prior to B-cell differentiation into plasma cells which are the major source of circulating immunoglobulin G (IgG) (9). Although effects on gammaglobulin production after short courses of RTX are rare and were not considered a major concern in early reports, the real-world experience has shown that hypogammaglobulinaemia occurring early after anti-CD20 treatment can be multifactorial, due to active disease and/or the effect of other drugs (*e.g.* glucocorticoids, cyclophosphamide (CYC) or mycophenolate mofetil (MMF)) and usually transient, with a minimal increase in the risk of infections (10). It is generally recommended to measure serum immunoglobulin levels prior to initiating RTX and before repeating cycles of RTX, though there are no consensus guidelines regarding screening for hypogammaglobulinaemia in autoimmune patients (11-15). Risk factors for the development of hypogammaglobulinaemia appear to reflect differences in dose and schedule, concomitant therapies, and underlying disease state (16).

To date, only one paper, detailing only four IIM patients from a larger cohort of CTD patients, investigated hypogammaglobulinaemia after RTX (17).

The present study aimed to characterise the rate of RTX-associated hypogammaglobulinaemia, its determinants and its potential association with infection in a cohort of IIM patients in a real-life setting.

Methods

Patients evaluated treated with RTX in the Myositis clinic belonging to the Rheumatology Units of Siena, Bari and Palermo University Hospitals, were retrospectively enrolled. Inclusion criteria were as follows: (i) fulfilment of disease-specific classification criteria 2017 EULAR criteria and/or Peter and Bohan criteria for dermatomyositis (DM) and polymyositis (PM) (18), (ii) positivity of anti-synthetase antibody and typical clinical features for anti-synthetase syndrome (ASSD) (19) and (iii) the measurement of serum Ig levels at baseline (T0) (maximum 2 weeks before RTX administration), 6 (T1) and 12 (T2) months later, accordingly to previous studies (3). Immunoglobulin serum levels, measured by standard nephelometry (normal ranges: IgG 700–1600 mg/dL, IgM 40–240 mg/dL, IgA 70–400 mg/dL), were assessed as part of routine clinical care. Hypogammaglobulinaemia was defined as moderate (serum IgG <600 mg/dL) and severe (IgG <400 mg/dL), as previously reported (17).

RTX induction scheme consisted of two 1000 mg intravenous (IV) infusions administered two weeks apart, and then every 6 months as maintenance treatment.

Demographic, clinical, laboratory and treatment variables, including previous and concomitant immunosuppressive drugs and glucocorticoid dosage were recorded. Laboratory parameters included CRP, CPK and ESR assessed as part of routine clinical care.

Infection was defined as severe when requiring hospitalisation and/or IV antibiotics.

The study was conducted according to the Declaration of Helsinki guidelines

Table I. Clinical and serological features of patients at baseline.

	Total IIM (n=30)
Mean age	56 (42-66)
M:F	8:22
Diagnosis	
ASSD	14 (46.6%)
DM	9 (30%)
IMNM	5 (16.6%)
PM	1 (3.3%)
IBM/ASSD	1 (3.3%)
Organs involved	
Muscle	23 (76.6%)
Lung	22 (73.3%)
Skin	22 (73.3%)
Joints	12 (40%)
GI tract	6 (20%)
Previous immunosuppressants	
MTX	20 (66.6%)
MMF	10 (33,3%)
IvIg	9 (30%)
CsA	7 (23.3%)
AZA	7 (23.3%)
CYC	5 (16.6%)
Mean serological values at baseline	
IgA (mg/dl)	236.06 ± 102.08
IgM (mg/dl)	1147.25 ± 281.53
IgG (mg/dl)	114.06 ± 48.76
CRP (mg/dl)	1.12 ± 1.5
CPK (UI/l)	402.47 ± 1293.62
Mean GCs dosage at baseline (PDN, mg)	7.02 ± 4.16
Concomitant immunosuppressants at baseline	
MTX	9 (30%)
MMF	4 (13.3%)
AZA	2 (6.6%)
CsA	2 (6.6%)
IVIG	2 (6.6%)

ASSD: anti-synthetase syndrome; AZA: azathioprine; CRP: C-reactive protein; CsA: cyclosporin A; DM: dermatomyositis; GCs: glucocorticoids; GI: gastrointestinal tract; IBM: inclusion body myositis; IVIG: intravenous immunoglobulins; MMF: mycophenolate mofetil; MTX: methotrexate; PM: polymyositis.

and was approved by the Ethics Committee (Comitato Etico Area Vasta Sud Est, Tuscany, Markerlung 17431, Rhelabus 22271). Informed consent was obtained from all subjects involved in the study.

Statistical analysis

Data are expressed as median and interquartile ranges for continuous variables, if not stated otherwise, and as number (%) for categorical ones. Chi-squared test or Fisher's exact test were used to compare differences in proportions. Wilcoxon's rank sum test was used to compare data before and after treatment. Spearman test correlation was used to evaluate strength and direction of association between two ranked nonparametric variables. *P*-value <0.05 was considered statistically significant. Data were analysed using GraphPad Prism 9.4 and XLSTAT 2021 software.

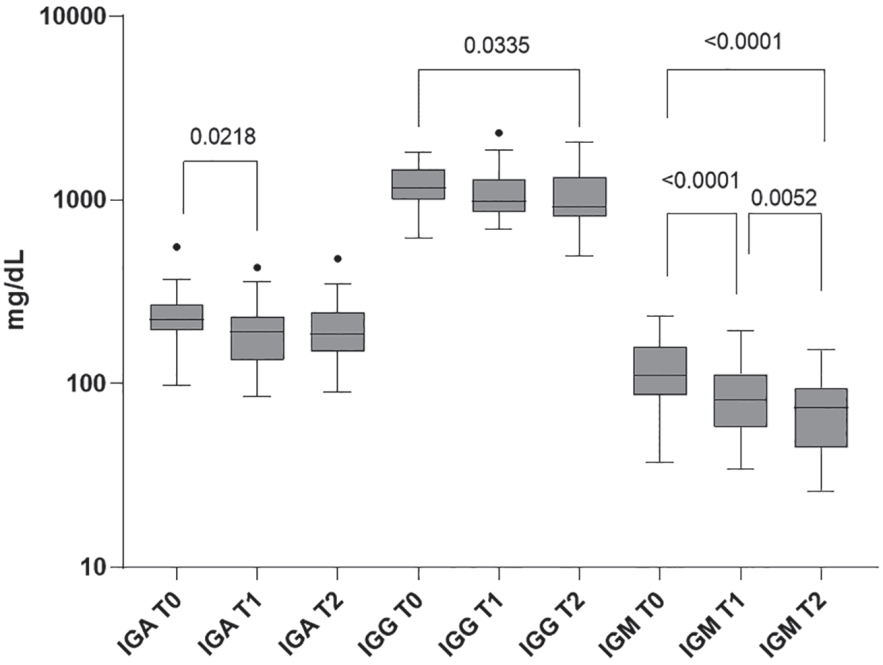

Fig. 1. Immunoglobulin trend in idiopathic inflammatory myopathies patients before (T0) and after 6 (T1) and 12 (T2) months of rituximab treatment.

Results

Thirty patients (median age, IQR 56 (42-66); 22 female) were enrolled. Fourteen of them had a diagnosis of ASSD, nine DM, five immune-mediate necrotizing myopathy (IMNM), one overlap ASSD-IBM and one PM. Nine patients showed anti-Jo1-positivity, eight anti-MDA5-positivity, two anti-Mi2-positivity, two anti-PM/Scl-positivity, one anti-TIF1-gamma-positivity, one anti-PL7- positivity (20), one anti-PL-12 positivity, one anti-Ku-positivity, one anti-HMGCR-positivity, while two only isolated ANA-positivity. All patients had at least two organs involved, and 17 out of 30 (57%) suffered from interstitial lung disease. Before starting RTX treatment, all patients were treated with at least oral GCs and all but one underwent synthetic immunosuppressants (Table I). Figure 1 reported the trend of immunoglobulins in IIM patients before (T0) and after 6 (T1) and 12 (T2) months of RTX treatment.

IgA concentrations were lower at T1 than T0 (p=0.0218). IgG concentrations were statically lower at T2 compared to those at baseline (p=0.0335) (Fig. 1). None of them showed severe hypogammaglobulinaemia. Similarly, IgM concentrations significantly decreased at T1 and T2 compared to those at baseline (p<0.0001), as well as at T1 than T0 (p=0.0215) (Fig. 1). An overall low level of IgG and IgM occurred in 10% and 17% of patients, respectively, while none showed severe hypogammaglobulinaemia.

Three patients experienced major infections (fungal pneumonia and severe zoster with post-herpetic neuralgia) after 8.66±3.51 months from the first infusion of RTX, two had paucisymptomatic COVID-19 (one of them was tested positive twice), three had urinary tract infection and one suffered from mild zoster, promptly resolved after the administration of antiviral agents and not leading to post-herpetic neuropathy. GCs dosages at T0 were inversely correlated with IgG T0 concentrations (p=0.004, r=-0.514).

No statistically significant correlation was evidenced between IgA, IgG and IgM serum levels at T0, T1 and T2 and

Table II. Note. Model coefficients.

Predictor	Estimate	95% Confidence interval		SE	Z	*p*	Odds ratio
		Lower	Upper				
Intercept	-105.8096	-3.76e−6	3.76e+6	1.92e+6	-5.52e−5	1.0000	1.12e-46
IGA T0	0.2233	-11359	11359	5796	3.85e-5	1.0000	1.250
IGA T1	-0.0849	-7964	7964	4063	-2.09e−5	1.0000	0.919
IGA T2	0.1362	-12088	12089	6168	2.21e-5	1.0000	1.146
IGG T0	0.0195	-1996	1996	1018	1.91e-5	1.0000	1.020
IGG T1	0.0126	-1888	1888	963	1.30e-5	1.0000	1.013
IGG T2	-0.0131	-2544	2544	1298	-1.01e−5	1.0000	0.987
IGM T0	-0.4738	-41219	41218	21030	-2.25e−5	1.0000	0.623
IGM T1	0.3753	-28829	28830	14709	2.55e-5	1.0000	1.455
IGM T2	-0.1711	-72362	72362	36920	-4.64e−6	1.0000	0.843
Disease duration (months)	-0.0386	-62090	62090	31679	-1.22e−6	1.0000	0.962
GC dosage	-0.3001	-59034	59033	30120	-9.96e−6	1.0000	0.741
DMARDS (0 none, 1, 2,3)	5.5660	-166363	166394	84889	1.83e-4	0.9999	5.76e0+6

Infection (0=minor; 1=major).
Estimates represent the log odds of "Infection (0=minor; 1=major) = Major" *vs*. "Infection (0=minor; 1=major) = Minor".

Table III. Model coefficients.

Predictor	Estimate	95% Confidence interval		SE	Z	*p*	Odds ratio
		Lower	Upper				
Intercept	0.63465	-4.0222	5.2915	2.3760	0.26711	0.7894	1.886
Disease duration (months)	-0.00293	-0.0550	0.0492	0.0266	-0.11008	0.9123	0.997
GC dosage	0.02163	-0.0883	0.1315	0.0561	0.38570	0.6997	1.022
DMARDS (0 nessuno, 1, 2,3)	0.08883	-0.8782	1.0558	0.4934	0.18004	0.8571	1.093
number of organs involved	-0.21891	-1.4327	0.9948	0.6193	-0.35349	0.7237	0.803
Infection (0=minor; 1=major)	-1.14704	-4.4329	2.1388	1.6765	-0.68420	0.4938	0.318
IMM subtype:							
ASS – DM	0.68193	-2.0429	3.4067	1.3902	0.49052	0.6238	1.978
PM – DM	18.49848	-5696.1407	5733.1376	2915.6858	0.00634	0.9949	1.08e+8
IMNM – DM	-0.04218	-2.6273	2.5430	1.3190	-0.03198	0.9745	0.959

Hypogamma: 0: no, 1: yes.
Estimates represent the log odds of "hypogamma 0: no, 1: yes = no" *vs*. "hypogamma 0: no, 1: yes = yes".

the onset of minor or major infections (Table II). Similarly, none of the clinical variables included in the study (disease duration, GCs dosage, DMARDs, number of organs involved, IIM subtype) were significantly associated with the onset of hypogammaglobulinaemia.

Discussion

The present study evaluated RTX-associated hypogammaglobulinaemia in a real-life cohort of IIM patients, aiming to assess whether any correlation exists with clinical and serological features of patients, including current and previous treatments.

During the therapeutic course, a statistically significant reduction of IgA, IgG and IgM serum levels was evidenced at T1 and T2. However, no patients showed severe hypogammaglobulinaemia.

Only three of our patients suffered from major infections after 12-months of RTX and an inverse correlation was observed between glucocorticoids dosage and IgG.

The burden of hypogammaglobulinaemia following RTX treatment in rheumatic diseases has not yet been fully elucidated (10, 11, 16, 17). Although hypogammaglobulinaemia following RTX is uncommon in CTD patients, few study have evaluated the effects on serious infection events (SIEs) in patients affected by ANCA-associated vasculitis (AAV) (17), systemic lupus erythematosus, systemic sclerosis and rheumatoid arthritis (16, 17). Such findings have highlighted a need for increased awareness of the role of immunoglobulin measurement at baseline and before maintenance doses of RTX, especially in patients with AAV and steroid exposure, to identify patients at risk of SIEs (5, 17). All Ig subtypes play a role in the monitoring of RTX effects and low levels of IgG, IgA and IgM, although in variable percentages (16, 17, 21), are commonly retrieved after the administration of anti-CD20 agents, despite notable differences according to the different diseases taken into account (22-24).

Individualised risk-benefit assessment should be therefore undertaken in those with lower IgG as this is a consistent SIEs predictor.

Marco *et al*. demonstrated a weak negative correlation between total oral prednisolone exposure and IgG concentrations in multisystem autoimmune disease, however the authors did not include any patients affected by IIM (16). To date, only one of the abovementioned papers (17) included four pa-

tients affected by IIM; nevertheless, this study, presumably due to the limited numerosity, did not differentiate these patients from the ones suffering from other CTDs nor evidenced any specific determinant of hypogammaglobulinaemia in IIM.

It should be remarked that our cohort, despite being small, was composed by patient with an aggressive disease, treated with medium-high dosage of GCs and not responding to at least one conventional immunosuppressant. This represents a specific sub-type of CTD patients theoretically more prone to suffer from any infective adverse event.

Indeed, 3 out of 30 (10%) suffered from major infections. The numbers in our study are low, but this is a higher infectious hazard than reported in other biologic drugs trials and real-life studies, as well as in cohorts of patients suffering from different CTD.

On the other hand, only a minority of the subjects included in our study presented low levels of IgG, IgA and/or IgM, while no one of them displayed a severe hypogammaglobulinaemia. Therefore, mild hypogammaglobulinaemia alone is not a suitable marker in the stratification of IIM patients who are more prone to develop severe infections, which are presumably driven by other factors. Similarly, in our cohort, no correlation was evidenced between low Ig serum levels and any of the clinical features of our patients.

In this regard, given the overall higher infective hazard of these patients, prophylaxis with antibacterial agents against *P. jirovecii* should always be performed, as well as the vaccination against COVID-19 and Herpes Zoster virus, eventually keeping in mind the possibility of a reduced response to vaccination. Although all our patients were fully vaccinated against COVID-19, two suffered from this condition, although mild, and one was tested positive twice in line with Daniel *et al*. (25). Conversely, one of them, despite the prophylaxis scheme with Trimethoprim-sulfamethoxazole, suffered from *P. jirovecii* pneumonia.

Despite the contribution of these results to our understanding of the usefulness of immunoglobulins for monitoring IIM patients undergoing RTX treatment, our study has some limitations. First, our data were up to 12 months of follow up. Secondly, it would be worthwhile validating these results in other antibody-positive IIM patients by means of multicentric prospective studies with a centralised dosage of Ig levels starting from thawed samples, which was not performed in our study.

Conclusion

Hypogammaglobulinaemia following RTX is uncommon in IIM and is not related to any clinical variables, including GCs dosage and previous treatments after RTX treatment does not seem useful in stratifying patients who require closer safety monitoring and prevention of infection, due to the lack of association between hypogammaglobulinaemia and the onset of severe infections.

Take home messages

- Hypogammaglobulinaemia after RTX treatment is uncommon.
- IgG and IgM monitoring 6 months after RTX treatment does not seem useful in stratifying patients who require closer safety monitoring and prevention of infection.

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