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Hypogammaglobulinaemia after rituximab treatment—incidence and outcomes

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Summary

Background: Rituximab, a chimeric monoclonal antibody against CD20, is increasingly used in the treatment of B-cell lymphomas and autoimmune conditions. Transient peripheral B-cell depletion is expected following rituximab therapy. Although initial clinical trials did not show significant hypogammaglobulinaemia, reports of this are now appearing in the literature.

Methods: We performed a retrospective review of patients previously treated with rituximab that were referred to Clinical Immunology with symptomatic or severe hypogammaglobulinaemia. Patient clinical histories, immunological markers, length of rituximab treatment and need for intravenous immunoglobulin replacement therapy (IVIG) were evaluated. An audit of patients receiving rituximab for any condition in a 12-month period and frequency of hypogammaglobulinaemia was also carried out.

Results: We identified 19 post-rituximab patients with persistent, symptomatic panhypogammaglobulinaemia. Mean IgG level was 3.42 ± 0.4 g/l (normal range 5.8–16.3 g/l). All patients had reduced or absent B-cells. Haemophilus Influenzae B, tetanus and Pneumococcal serotype-specific antibody levels were all reduced and patients failed to mount an immune response post-vaccination. Nearly all of them ultimately required IVIG. The mean interval from the last rituximab dose and need for IVIG was 36 months (range 7 months–7 years). Of note, 23.7% of 114 patients included in the audit had hypogammaglobulinaemia.

Conclusion: With the increasing use of rituximab, it is important for clinicians treating these patients to be aware of hypogammaglobulinaemia and serious infections occurring even years after completion of treatment and should be actively looked for during follow-up. Referral to clinical immunology services and, if indicated, initiation of IVIG should be considered.

Introduction

Rituximab, a chimeric monoclonal antibody binding CD20, is increasingly used in the treatment of B-cell lymphomas[1,2] and autoimmune conditions such as rheumatoid arthritis,[3] systemic lupus erythematosus[4] and autoimmune cytopenias.[5,6]

Rituximab causes a rapid depletion of CD20-expressing B-cell precursors and mature B-cells, which remain at very low or undetectable levels for 6–9 months before returning to pre-treatment levels.[7] Rituximab can lead to a state of immunosuppression through B-cell depletion, and also through the development of late onset neutropenia and hypogammaglobulinaemia.[8–11] Furthermore, reports also suggest that rituximab increases the risk of viral infections including hepatitis B and cytomegalovirus reactivation and JC virus leading to progressive multifocal leucoencephalopathy.[12–15]

Impaired humoral immune responses with less robust B-cell proliferation to simple haptens and recall antigen challenge suggest an adverse effect on memory B-cells.[16,17]

Although initial clinical trials did not show significant hypogammaglobulinaemia or associated increased risk of severe infections with rituximab use,[18,19] literature describing this has recently been appearing.[20,21] In patients with lymphoma, rituximab maintenance is also considered to generally be well tolerated and maintenance beyond 2 years is not associated with increased toxicity.[22,23] However, this evidence conflicts with meta-analyses of randomized controlled trials showing significantly increased rates of infections in patients who had received rituximab maintenance therapy compared with those who had not.[24,25]

In autoimmune diseases, association of infection and rituximab treatment is not considered to be a significant issue and has only been described in case reports and cohort studies.[26,27] A large longitudinal safety report from an international rituximab rheumatoid arthritis clinical trial programme in 3194 patients with 11 962 patient-years of follow-up, found that rituximab was generally well tolerated over multiple courses. The overall serious infection event rate was 3.94/100 patient-years which was comparable with placebo and methotrexate. Serious opportunistic infections were rare. About 22.4% of rituximab-treated patients developed low IgM and 3.5% low IgG levels for $\geqslant 4$ months after one or more course. Serious infection rates were similar before and during/after development of low immunoglobulin (Ig) levels; however, in patients with low IgG, rates were higher than in patients who never developed low IgG.[28] In this report, we will first present a series of patients previously treated with rituximab for lymphoma and autoimmune disorders that developed hypogammaglobulinaemia and clinically significant infections requiring intravenous immunoglobulin replacement therapy (IVIG). In order to obtain an estimate of the number of patients for whom rituximab is prescribed and to assess the extent of the problem of post rituximab hypogammaglobulinaemia, we carried out an audit on rituximab use by all specialities in one hospital over a 1-year period. The results of this audit will also be presented.

Methods

We performed a retrospective review of patients with symptomatic or severe hypogammaglobulinaemia referred to Clinical Immunology departments of four London hospitals. Patients having been previously treated with rituximab for any condition including malignancy, autoimmune haemolytic anaemia, rheumatoid arthritis and systemic lupus erythematosus were identified.

Patient demographics, clinical histories, previous immunosuppressive treatments, number and types of confirmed infections were analysed. Immunological markers including white cell count, IgG, IgM and IgA levels, IgG subtypes and lymphocyte subsets were reviewed. Haemophilus influenzae B, tetanus and Pneumococcus total and specific serotype antibodies and responses to immunization were assessed. The length of treatment with rituximab and the time interval between the last rituximab infusion and need for intravenous immunoglobulin replacement therapy were evaluated.

The audit on the use of rituximab was performed at King's College Hospital. The pharmacy 'off tariff' medication invoices covering a period from May 2011 to April 2012 (inclusive) in the hospital were used to identify all patients for whom rituximab was prescribed in that time period. This list was used to search the electronic patient record (EPR) system to obtain the blood results for globulin, albumin, IgG, IgA and IgM levels. Patients who had low albumin were excluded from this audit as the cause of low IgG in these cases may have been renal or gastrointestinal loss. In addition, electronic in-patient notes were accessed to identify the indication for rituximab. The patient identifying information was removed once the link between blood results and diagnosis was made.

Case Series Results

Patient characteristics

Our review identified 19 patients previously treated with rituximab with persistent, symptomatic

hypogammaglobulinaemia. In total, 12 patients were treated with rituximab as well as combination chemotherapy for non-Hodgkin's lymphoma (NHL) (diffuse large B-cell lymphoma=3, follicular =6, marginal zone B-cell =2, high grade transformation of NHL = 1), four for seropositive rheumatoid arthritis, two for systemic lupus erythematosus and one for autoimmune haemolytic anaemia. Mean age was 54.3 years (range 24–78). The majority of the patients were female (63.2%) (Table 1).

Infections

Patients developed a variety of bacterial, viral and/or fungal infections mainly prior to referral to Clinical Immunology. They were not neutropenic at the time when they suffered the infections.

The majority of infections affected the respiratory tract such as bronchitis, pneumonia and sinusitis. Organisms identified as causing these included *Haemophilus influenzae*, *Pseudomonas aeruginosa, Streptococcus pneumoniae* and *Klebsiella* species. Other bacterial infections included conjunctivitis, ear infections, urinary tract infections, *Campylobacter* diarrhoea and *Staphylococcus aureus* osteomyelitis. Some patients were affected by viruses such as herpes zoster, varicella zoster and cytomegalovirus. Of note, three patients developed enteroviral meningoencephalitis confirmed with cerebrospinal fluid PCR (polymerase chain reaction). Unfortunately, one of these patients did not survive despite treatment with IVIG. A small proportion of patients developed fungal infections (oesophageal candidiasis $n=1$, lung aspergillosis $n=1$) (Table 2). Some patients had episodes of the same organism affecting different sites, for example, *Haemophilus* causing conjunctivitis and sinusitis whereas other patients were affected by different organisms, one patient having *Staphylococcus aureus* osteomyelitis and aspergillosis.

The IgG level in this cohort of patients was decreased with a mean of 3.42 ± 0.4 g/l (normal range 5.8–16.3 g/l) at presentation to the immunology clinic. The median was 64.7% below the lower limit of normal. The IgG subclasses found to be decreased in these patients were IgG1 and IgG2. The mean IgG1 was of 2.62 g/l (normal range 3.20–10.20 g/l) and mean IgG2 0.73 g/l (normal range 1.20–6.60 g/l). IgM was below the normal range in all but one patient with a markedly reduced mean of 0.29 ± 0.05 g/l (normal range 0.7–3.50 g/l). The mean IgA level was within the lower end of the normal range at 0.67 ± 0.20 g/l (normal range 0.5–2.40 g/l). In 61.1% of the patients IgG, IgM and IgA were all decreased (Table 3).

Lymphocyte analysis revealed that CD19+ B-cells were reduced with a mean of 74.97 ± 19.84 (normal range 100–500 cells/μl). Nine of the patients had absolute CD19 counts which were undetectable or below 50. There was no significant reduction in mean CD4, CD8 and CD56 absolute cell counts (Table 3).

The mean *Haemophilus Influenzae* B (Hib) antibody levels were below the accepted long-term protective level of 1.0 mg/ml at 0.63 ± 0.15 mg/ml. In 75% of the patients anti-tetanus antibodies were below 0.11 IU/ml. Median level was 0.02 IU/ml. Total Pneumococcal IgG antibodies were reduced in the 17 patients that these were measured in with a mean level of 7.80 ± 1.82 U/ml. The serotype-specific pneumococcal responses were all <0.35 g/ml (protective value >1.3) in all patients that these were measured in. Furthermore, patients who received Pneumococcal, tetanus or Hib vaccination failed to mount an immune response.

The length of rituximab treatment ranged from 1 month to 4 years. Persistent B-cell depletion was seen in patients regardless of the number of courses. The mean interval from the last dose of rituximab and need for IVIG was 35.98 ± 6.05 months. This ranged from 7 months to 7 years.

Treatment

Of these patients, 18 were treated with IVIG therapy for infections. IVIG doses of 200–300 mg/kg were given every 3 or 4 weeks. One patient is currently under monitoring after being started on prophylactic antibiotics.

Of note, prior to starting treatment with immunoglobulin replacement therapy, the majority of these patients were treated with prophylactic antibiotics. However, these clinically failed to control infections and initiation of IVIG was deemed appropriate.

The majority of patients have responded to IVIG with reduction in frequency of infections and prevention of further hospital admissions. One patient who suffered with enteroviral encephalitis passed away after 3 months of IVIG treatment. The rest of the patients are still receiving regular IVIG.

Post-rituximab hypogammaglobulinaemia audit

The number of patients who received rituximab at King's College Hospital over a 12-month period was 117. Some of these patients had commenced their treatment during the 12-month period covered; others had started treatment with rituximab in

Table 1 Patient demographics and treatments received

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Age	78	55	74	65	51	68	37	70	46	63	33	45	53	57	61	52	24	53	47
Gender	F	F	F	F	F	F	F	F	F	M	M	M	F	F	F	M	M	M	M
Condition	RA	RA	RA	SLE	SLE	RA	DLBCL	FL	FL	MZL	DLBCL	FL	FL	FL	MZL	FL	AHA	DLBCL	High-grade transformation of NHL
Interval b/w last rituximab dose and IVIG (months)	–	–	36	24	84	N/A	18	60	48	16	50	24	48	24	22	7	17	12	84
Rituximab	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fludarabine										+				+	+	+			
Cyclophosphamide					+		+	+	+		+	+	+		+	+		+	+
Chrorambucil							+							+		+			
Vincristine							+	+	+		+	+	+		+			+	+
Prednisolone	+	+		+	+	+		+	+	+	+	+	+				+	+	+
Doxorubicin							+				+							+	
Methotrexate							+												+
Cytarabine							+		+				+						+
Etoposide							+		+				+						
Etanarcept		+																	
Adalimumab		+																	
Abatacept						+													
Other							ifosfamide		cisplatin				Cisplatin lomustine Infliximab daclizumab						dexamethasone

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; AHA, autoimmune haemolytic anaemia; NHL, non-Hodgkin's lymphoma; (–) exact date missing.

Table 2 Type of infections

Bacterial	(*n* = 30)	Viral	(*n* = 9)	Fungal	(*n* = 2)
Sinusitis	6	Herpes zoster	3	Oesophageal candidiasis	1
Bronchitis/Pneumonia	10	Varicella zoster	2	Aspergillosis	1
Conjunctivitis	2	Cytomegalovirus	1		
Otitis	3	Enterovirus (meningoencephalitis)	3		
Urinary tract infection	3				
Osteomyelitis	1				
Enteritis	1				

Table 3 Immunological markers at presentation of the 19 case series patients

Investigations (normal range)	Mean ± SE
IgG (5.8–16.3 g/l)	3.42 ± 0.4
IgM (0.7–3.50)	0.29 ± 0.05
IgA (0.5–2.40)	0.67 ± 0.19
IgG1 (3.20–10.20 g/l)	2.62 ± 0.36
IgG2 (1.20–6.60)	0.73 ± 0.18
IgG3 (0.20–1.90)	0.31 ± 0.08
IgG4 (0.00–1.30)	0.05 ± 0.03
CD4 (300–1400)	513.16 ± 86.9
CD8 (200–900)	619.78 ± 139.03
CD56 (90–600)	225.78 ± 43.93
CD19 (100–500)	74.97 ± 19.48

Table 4 Summary of audit showing indications for rituximab and number of patients with low IgG

Indication	Number of patients *n* (%)	Number of patients with low IgG (i.e. <5.8 g/l) (%)
Haematological	75 (65.8)	25 (92.6)
Connective tissue disease	27 (23.7)	2 (7.4)
Hepatological, including two cases of PTLD post hepatic transplantation	7 (6.1)	0 (0.0)
Neurological	4 (3.5)	0 (0.0)
Glomerulonephritis	1 (0.9)	0 (0.0)
Total	114 (100)	27 (100)

PTLD, post-transplantation lymphoproliferative disorder.

previous years. Three sets of patient data had to be excluded as they did not have the minimal required information.

In the 114 patients analysed, 75 (65.8%) received rituximab for a haematological indication, 27 (23.7%) for autoimmune diseases and the rest for other diseases. Of the 75 haematology patients, 72 were treated with rituximab for haematological malignancies and 3 for idiopathic thrombocytopenic purpura or autoimmune haemolytic anaemia. 27 (23.7%) had hypogammaglobulinaemia with IgG <5.8 g/l (Table 4). Of note, all patients with hypogammaglobulinaemia had normal immunoglobulins prior to commencement of rituximab. The majority of patients with hypogammaglobulinaemia were patients with haematological malignancies (92.6%). Among the 27 patients with hypogammaglobulinaemia, 7 (25.9%) had IgG <3 g/l for 3–66 months, 5 (18.5%) patients had IgG 3–3.9 g/l for 5–19 months, 15 (55.6%) had IgG 4–5.7 g/l for 3–58 months. Of the 27 patients, 20 (74%) had low IgG (<5.8 g/l) persisting for over 4 months.

Discussion

Our findings demonstrate that B-cell depletion and hypogammaglobulinaemia may persist for a long time after discontinuation of rituximab treatment. This can be associated with bacterial, viral and/or fungal infections that can be recurrent and severe requiring immunoglobulin replacement therapy.

A majority of our patients also suffered from haematological malignancy, which may have contributed to some bias as these patients also received treatment with other chemotherapeutic agents. It has been suggested that individuals previously treated with a fludarabine–rituximab combination have a much higher cumulative incidence of non-neutropenic infections than those treated with non-fludarabine-rituximab regimens.[20,24] Furthermore, patients may have a degree of immunocompromise associated with their underlying disease and the use of other immunomodulatory drugs. Therefore, it is difficult to quantify the risk of infection. In addition, persistent hypogammaglobulinaemia has been

observed after autologous stem cell transplantation.[29,30] In our case series, three patients had also undergone this treatment.

Our finding of low IgG as well as IgM levels in the case series is in agreement with other studies.[20,28] Rituximab and immunosuppressants affect the short-lived memory B-cells and not the long-lived memory B-cells that reside in the bone marrow after they have transformed to long-lived plasma cells. This may be one mechanism for the progressive decline in total serum immunoglobulins and also may explain why IgM levels fall off earlier before class switched memory B cells.

Interestingly, a retrospective review of 211 patients treated with rituximab for B-cell lymphoma found that after rituximab use, 38.54% of patients with initially normal serum IgG developed hypogammaglobulinaemia. The risk was greater in patients who received maintenance rituximab. Furthermore, symptomatic hypogammaglobulinaemia that required IVIG administration occurred in 6.6% of patients.[31] In rheumatoid arthritis, a recent study has found that patients with lower baseline serum immunoglobulin levels tended to develop persistent IgM and IgG hypogammaglobulinaemia, resulting from an accumulation of incremental decreases after repeat cycles. This was not due to lower numbers of returning B-cells in those developing low serum immunoglobulins.[32] Unfortunately, as it is currently not standard practice, the levels of serum immunoglobulins prior to starting rituximab treatment were not measured in all our case series patients, whereas all audit patients with hypogammaglobulinaemia had normal immunoglobulins prior to commencement of rituximab.

The observation of poor response to immunization in our patient group is in accordance with previous findings in patients with rheumatoid arthritis.[33] In one study, humoral responses to influenza vaccination were lower among patients treated with rituximab compared with rheumatoid arthritis patients who had received non-biological disease-modifying anti-rheumatic drugs and healthy controls. Previous influenza vaccination in rituximab-treated patients increased pre- and post-vaccination titres.[34] Furthermore, another study found that rituximab-treated patients had decreased responses to pneumococcal polysaccharide vaccine and to neoantigen (keyhole limpet haemocyanin) vaccine compared with patients treated with methotrexate alone. The authors concluded that patients with rheumatoid arthritis treated with rituximab can be effectively and safely vaccinated, but to maximize response, polysaccharide and primary immunizations should be administered before initiating rituximab treatment.[35]

Rituximab has been shown to be an effective drug for a number of haematological malignancies and autoimmune conditions. However, some patients who receive this treatment may develop sustained suppression or absence of B-cell function, hypogammaglobulinaemia and infections which can be recurrent and in some cases severe. It is important for clinicians to be aware that these immunological defects may present even years after the last course of treatment and especially in patients receiving multiple courses. B-cells play an important role in antigen presentation and return to virulence of polio and other enteroviridae may be seen in these patients; specific advice should therefore be given on exposure to live vaccines and about recognition of new neurological signs and symptoms.

The management of secondary immunodeficiency resulting from lymphoproliferative and autoimmune disease and their treatment has recently been thoroughly reviewed.[36] The authors highlighted the relevance of monitoring gammaglobulins prior to starting rituximab and note that hypogammaglobulinaemia is more likely to occur in patients treated for haematological malignancy, older patients and patients taking higher doses of glucocorticoids. No studies have demonstrated that immunoglobulins should be administered to patients who develop hypogammaglobulinaemia with rituximab. In the absence of such evidence, pragmatically we would recommend that a trial of immunoglobulin replacement be considered on a case-by-case basis in patients with low IgG following rituximab treatment, who have ongoing infections despite the use of appropriate prophylactic antibiotics. In general, the need for this treatment would be reviewed on a regular basis, and withdrawn if no benefit was derived, or if there was evidence of recovery in natural immunoglobulin production.

In conclusion, it is advisable that all patients have a baseline measurement of serum immunoglobulins prior to initiation of rituximab treatment and levels are monitored for long-term changes during follow-up. In addition, immunization should be considered prior to rituximab administration and vaccine responses should be monitored. Furthermore, if hypogammaglobulinaemia is detected, referral to clinical immunology services and, if indicated, initiation of immunoglobulin replacement therapy should be considered.

Conflict of interest: H.L. and members of her department have received funding to attend conferences and other educational events, donations to her departmental fund and/or have participated in clinical trials with the following immunoglobulin

manufacturers: BPL, CSL Behring, Octapharma, Baxter, Grifols and LFP. She has been a member of the medical advisory panel for Baxter and CSL. M.B. has received payment for consultancy for Shire and Octopharma and sponsorship for meetings by Viropharma. The rest of the authors have no conflicts of interest.

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