

Letter to the Editor

Continuing IgG replacement therapy for hypogammaglobulinemia after rituximab—for how long?

To the Editor:

Rituximab is an anti-CD20 chimeric mAb that depletes CD20-expressing B cells in lymphoid tissue and in circulation. Rituximab and other biologic immunotherapies are an important treatment option for autoimmune conditions such as rheumatoid arthritis¹ and for oncologic conditions such as non-Hodgkin's lymphoma.² In patients with these conditions, it is challenging to distinguish between lasting effects of rituximab therapy and primary immunodeficiency, especially given that patients with common variable immunodeficiency (CVID) have an increased risk of autoimmune diseases, granulomatous disease, and malignancy. Autoimmune conditions such as idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia occur in up to 20% to 40% of the patients with CVID, and these manifestations can precede symptoms and diagnosis of immune deficiency.³

There have been increasing reports of hypogammaglobulinemia in patients receiving rituximab therapy.^{4,5} Peripheral B-cell depletion is expected after rituximab therapy. In patients treated with chemotherapy and rituximab, B-cell recovery can take up to 18 to 24 months, whereas B-cell depletion usually lasts for up to 6 months in rituximab treatment alone.² In 1 series, hypogammaglobulinemia was identified in 38.5% of the patients with lymphoma with initially normal serum immunoglobulin level after receiving rituximab therapy.⁶ These patients had symptomatic hypogammaglobulinemia, prompting IgG replacement in 6.6% of the patients.⁶ In another case series, IgG replacement was initiated in 4.2% of the patients who received rituximab for multisystem autoimmune disease.⁷ In these cases of hypogammaglobulinemia unmasked after rituximab therapy, it is often challenging to determine the duration of treatment with IgG replacement. In rheumatoid arthritis, relapse appears to be correlated with memory B-cell level, suggesting that targeting memory B cells may be a key to the mechanism of action of rituximab.⁸ This is a potential explanation for the particularly long-lasting effect on the memory B-cell compartment seen after rituximab therapy and highlights the importance of monitoring memory B cells for treatment, response, and the need for IgG replacement. We suggest that in patients with immunodeficiency after rituximab therapy, there are 2 groups of patients, one subset of patients who may have recovery of immunoglobulin levels and cell counts versus a subset of patients with long-lasting low or absent memory B cells after B-cell-depleting therapy that may represent underlying immune deficiency such as CVID.

We report a retrospective review of a series of 17 clinical cases of hypogammaglobulinemia noted after rituximab therapy in a large academic medical center. The patients' clinical history including indication for rituximab, cumulative amount of rituximab, immunological markers and flow cytometry, and need for continued IgG therapy were evaluated.

Of the 17 patients, there were 10 females and 7 males. These patients had a median age of 44 years (range, 2-71 years). These patients had received rituximab for a number of

conditions ranging from idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia to rheumatoid arthritis and Waldenstrom macroglobulinemia (Table I). All patients had reduced or absent B cells at some point. Titers for tetanus, pneumococcal, and *Hemophilus influenza* were reduced, and the patients failed to mount an immune response postvaccination. None of these patients had immunoglobulin levels sent before initiation of therapy. All patients except for 1 required IgG replacement for clinically significant infections. The average cumulative dose of rituximab was 5.8 g (range, 0.2-20 g).

In our series of patients, there were 2 of 16 patients who recovered IgG or B-cell counts to a level at which IgG replacement therapy could be discontinued. In the other subset, there were 14 of 16 patients in whom there has not yet been recovery in cell counts after a mean of 45 months (range, 5 months to 12 years). In these patients, IgG replacement therapy has continued and IgM and IgA levels as well as B-cell levels will continue to be trended. There was 1 of 17 patients who did not have clinically significant infections requiring intravenous immunoglobulin.

As the use of rituximab continues to increase, it is important for clinicians to be aware of hypogammaglobulinemia after rituximab therapy and routinely check immunoglobulin levels before initiation of therapy because these patients may be at an increased risk for prolonged hypogammaglobulinemia requiring IgG replacement therapy.

Most important, there was a subset of 5 patients (highlighted in Table I) who had recovery of peripheral B cells, but prolonged hypogammaglobulinemia and sustained absence or decreased switched or unswitched memory B-cell compartments. This subset of patients had an average duration of IgG replacement therapy of 83 months compared with 24 months for the other patients. There did not seem to be a correlation with the amount of cumulative rituximab received because this subset of patients had received an average cumulative dose of 4.8 g of rituximab compared with 6.3 g for the other patients. In patients with hypogammaglobulinemia after rituximab therapy, we recommend monitoring switched memory B cells in flow cytometry. This, in conjunction with recovery of other immunoglobulins (IgM and IgA), may be a possible indication for tapering and discontinuing IgG replacement therapy.

Of note, only 3 of the 17 patients in our cohort had undergone splenectomy. In patients who have undergone splenectomy, memory B cells, IgM memory B cells, and switched B cells have been found to be significantly reduced than in controls,⁹ which may account for why this subset of patients was unable to produce switched memory B cells.

In conclusion, given the increasing number of reports of hypogammaglobulinemia detected after rituximab therapy, we recommend evaluating immunoglobulin levels and flow cytometry before initiation of therapy. In hypogammaglobulinemia noted after rituximab therapy, there appear to be 2 subsets of patients, one of which recovers and one with persistent hypogammaglobulinemia with long-lasting low or absent memory B cells. To determine the treatment length in patients, it is potentially important to trend the B-cell subsets by flow cytometry in addition to IgA and IgM levels.

TABLE I. Clinical information of patients with hypogammaglobulinemia and rituximab therapy with most recent flow cytometry data

Patient	Age at first RTX exposure (y)	Sex	Indication for RTX	Cumulative amount of RTX (g)	Duration of IgG replacement therapy	Still receiving IVIG	IgG (mg/dL) before IgG replacement therapy	CD19 ⁺ (%) (13-27)	CD27 ⁺ IgD ⁺ IgM ⁺ (%)	CD27 ⁺ IgM ⁺ (%)
A	2	F	ITP	1.6	5 y	Yes	423	2	31.3	6
B	10	M	Humoral rejection (kidney transplant)	0.2	2 y 10 mo	Yes	528	0	—	—
C	20	F	MG	8	2 y 9 mo	Yes	399	5.6	8.5	1.9
D	24	M	GPA	14	1 y 2 mo	Yes	393	0	—	—
E*	32	F	ITP	3.2	10 y 10 mo	Yes	96	18.2	0	3
F	32	F	JRA	2	8 mo	No, clinically infection-free	595	0.8	—	—
G*	34	F	ITP	10	6 y	Yes	450	16.5	0	2.6
H	42	F	SS	6	2 y 6 mo	Never required	479	4.3	0	0.7
I*	44	M	HCL	4.8	12 y	Yes	Low	24.2	0.3	10
J*	45	F	ITP	2.8	3 y 9 mo	Yes	285	17.3	0	5.4
K	45	F	MZL	9.8	3 y 3 mo	Yes	334	3.1	1.5	0.8
L	48	M	WM	1.7	2 y 4 mo	Yes	755	1.9	15.3	37
M	49	F	Demyelinating CNS disease	2	11 mo	Yes	289	12.9	6	0.5
N	59	F	RA	1	10 mo	Yes	387	3.8	4.6	3
O*	62	M	ITP, AIHA	3.4	2 y	Yes	543	32.2	1.1	1.2
P	65	M	RA	20	5 m	Yes	324	0	0	0
Q	71	M	ITP	2.8	1 y 8 mo	No	336	5.7	12.7	1.7

AIHA, Autoimmune hemolytic anemia; CNS, central nervous system; F, female; GPA, granulomatosis with polyangiitis; HCL, hairy cell leukemia; ITP, idiopathic thrombocytopenic purpura; JRA, juvenile rheumatoid arthritis; M, male; MG, myasthenia gravis; MZL, marginal zone lymphoma; RA, rheumatoid arthritis; RTX, rituximab; SS, Sjögren syndrome; WM, Waldenström macroglobulinemia.

*These patients had recovery of B cells but had a sustained absence/decrease in memory B cells and will likely need long-term IgG replacement therapy.

Sara Barmettler, MD
Christina Price, MD

From ^athe Department of Internal Medicine and ^bthe Section of Allergy and Clinical Immunology, Yale School of Medicine, New Haven, Conn. E-mail: christina.price@yale.edu.

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