Original Article

Rituximab and Immune Deficiency: Case Series and Review of the Literature

Blanka Kaplan, MD[a,b,c,*], Yelena Kopyltsova, MD[a,*], Amrita Khokhar, MD[b,c], Fung Lam, BS[d], and Vincent Bonagura, MD[a,b,c,d] *Great Neck, NY*

What is already known about this topic? As the indications and use of rituximab continue to expand, the reports of long-term effects of anti-CD20–mediated B-cell depletion on immune function accumulate.

What does this article add to our knowledge? We report a group of patients with persistent immune dysfunction that required immunoglobulin replacement therapy after rituximab use. B-cell phenotype data were notable for a significant decrease in switched and memory B cells and a predominance of naive B cells.

How does this study impact current management guidelines? Routine baseline serum immunoglobulin levels and B-cell numbers are required to help distinguish preexistent primary immunodeficiency disease from secondary rituximab-induced immune suppression. Periodic monitoring of B-cell numbers and serum immunoglobulins is prudent to identify immune recovery of patients treated with rituximab.

BACKGROUND: As the indications and use of rituximab continue to expand, the reports of long-term effects of anti-CD20–mediated B-cell depletion on the immune system accumulate.

OBJECTIVE: We report a group of patients with immunodeficiency who were treated with rituximab and present their immunologic data.

METHODS: A retrospective chart review identified patients with immunodeficiency who received rituximab for treatment of their primary disease and required immunoglobulin replacement therapy (IGRT). Pre-IGRT immunoglobulins, specific antibodies, B-cells, and B-cell phenotype were recorded and analyzed.

RESULTS: We identified 11 patients with immunodeficiency who received rituximab and required IGRT. Two of these patients were diagnosed with common variable immunodeficiency before rituximab treatment. Nine other patients had hypogammaglobulinemia and did not achieve an adequate response to polysaccharide vaccine. There was a significant delay in B-cell recovery. B-cell phenotypes identified predominantly naive B cells in the blood of these patients with significant decrease in switched and memory B cells.

CONCLUSION: There are patients with persistent B-cell dysfunction long after rituximab treatment was discontinued. Some of these patients required IGRT. These patients should be distinguished from patients with primary immunodeficiency diseases. Routine baseline B-cell numbers and serum immunoglobulin levels before starting immunomodulatory therapy are required to help distinguish primary immunodeficiency diseases from secondary rituximab-induced, transient, and, at times, prolonged immune suppression. Periodic monitoring is prudent to identify immune recovery. Post-rituximab B-cell phenotyping may help identify the patients who will develop persistent immune dysfunction caused by an unidentified underlying disease or the prolonged effect of rituximab treatment. **© 2014 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2014;2:594-600)**

Key words: *Rituximab; Immunodeficiency; Hypogammaglobulinemia; Immunoglobulin replacement therapy; IGRT; B-cell phenotype; Persistent immunodeficiency after treatment with immunomodulatory drug; PITID*

Rituximab is an anti-CD20 chimeric antibody, one of the first of its kind to be used clinically. It has been used successfully to treat B-cell neoplasms and autoimmune diseases, including refractory rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, and anti-neutrophilic cytoplasmic antibodies-associated vasculitis. In addition, it also has been used to treat proliferative lymphadenopathy that can occur after bone

[a]Division of Allergy, Asthma and Immunology, North Shore-LIJ Health System, Great Neck, NY
[b]Hofstra-North Shore-LIJ School of Medicine, Hempstead, NY
[c]Long Island Jewish Medical Center, New Hyde Park, NY
[d]Feinstein Institute for Medical Research, Manhasset, NY
*These authors contributed equally to this work.
No funding was received for this work.
Conflicts of interest: Y. Kopyltsova is employed by New York Allergy and Sinus Centers. V. Bonagura is the editor in chief of the *Journal of Clinical Immunology;* has received consultancy fees from CSL Behring and Baxter; has received research support from the National Institute of Allergy and Infectious Diseases and National Institute of Dental and Craniofacial Research; has received lecture fees from Grand Rounds National Organizations. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication June 19, 2013; revised June 12, 2014; accepted for publication June 14, 2014.
Available online August 7, 2014.
Corresponding author: Blanka Kaplan, MD, Division of Allergy, Asthma and Immunology, North Shore-LIJ Health System, 865 Northern Blvd, Suite 101, Great Neck, NY 11385. E-mail: bkaplan@nshs.edu.
2213-2198/$36.00
© 2014 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaip.2014.06.003

Abbreviations used
AIHA- Autoimmune hemolytic anemia
CLL- Chronic lymphocytic leukemia
CVID- Common variable immunodeficiency
IGRT- Immunoglobulin replacement therapy
ITP- Idiopathic thrombocytopenic purpura
MRSA- Methicillin-resistant Staphylococcus aureus
NHL- Non-Hodgkin lymphoma
PNA- Pneumonia
PITID- Persistent immunodeficiency after treatment with immunomodulatory drug
PTLD- Posttransplantation lymphoproliferative disease
R-CHOP- Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
WG- Wegener granulomatosis
URI- Upper respiratory infections

marrow transplantation.[1-3] By targeting B cells, rituximab induces complete depletion of normal B lymphocytes in peripheral blood, with a reported average B-cell recovery time of 6 to 9 months.[4,5] In the pivotal rituximab clinical trials, hypogammaglobulinemia occurred in 14% of treated patients. Mild reduction in IgM levels at 6 months after treatment, with recovery to normal levels by 8 months, with normal IgG and IgA levels were noted.[6,7] Typically, B-cell numbers recover, and the majority of patients do not have residual immune dysfunction associated with an increased risk of developing severe or recurrent infection. However, there have been reports of patients who developed prolonged hypogammaglobulinemia after rituximab therapy. Prolonged hypogammaglobulinemia and severe B-cell deficiency that required IgG replacement was reported in a patient treated with rituximab for EBV-associated posttransplantation lymphoproliferative disease.[8] Panhypogammaglobulinemia was reported after treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy in a case of HIV-associated lymphoma.[9] Prolonged hypogammaglobulinemia also was reported 6 years after rituximab and combined immunotherapy for follicular lymphoma.[10] In a recent retrospective study of 211 patients treated with rituximab for non-Hodgkin lymphoma, a high frequency of hypogammaglobulinemia was observed, as well as an association of symptomatic hypogammaglobulinemia with multiple courses of rituximab.[11]

Selective, delayed recovery of memory B cells and impaired immunoglobulin isotype expression were observed when adjuvant rituximab was used after allogeneic stem cell transplantation for non-Hodgkin lymphoma.[12] There was a delay in the redistribution of $CD27^+$, $CD40^+$, and $CD80^+$ B cells, and an impairment of *in vitro* immunoglobulin production reported. There also are reports that describe rituximab-induced persistent hypogammaglobulinemia in patients with rheumatoid arthritis and other autoimmune disorders.[13,14] In a case series of 37 patients with rheumatoid arthritis who were treated with rituximab, a decrease in immunoglobulin levels below the normal range was noted; 12 patients developed low IgM, 7 developed low IgG, and 1 developed low IgA.[15] Two adults with idiopathic thrombocytopenic purpura developed recurrent infections after rituximab use. Both patients had low IgA and 1 had low IgG levels before rituximab use. Both patients progressed to panhypogammaglobulinemia and required IGRT. The investigators suggested that rituximab accelerated the presentation of immunodeficiency in these patients.[16]

As clinical immunologists, we have seen many patients with recurrent, severe, or unusual infections that present after treatment with immunomodulatory drugs. In recent years, we have seen patients with hypogammaglobulinemia after receiving rituximab. Here we present a case series of pediatric and adult patients treated with rituximab who developed persistent hypogammaglobulinemia that required IGRT.

METHODS

A retrospective chart review of immunodeficient patients referred to our tertiary clinical immunology care center was performed after obtaining approval from the North Shore-Long Island Jewish Health System's institutional review board and after written informed consent to participate and to have B-cell phenotyping performed were obtained from all patients. We

TABLE I. Clinical history and immunoglobulin levels on presentation

Patient no.	Age, y	Disease	IgG, mg/dL (normal for age)	IgM, mg/dL (normal for age)	IgA, mg/dL (normal for age)	Clinical presentation
1	2	AIHA	117 (424-1051)	40 (48-168)	<5 (14-123)	PNA, periorbital cellulitis, sinusitis
2	58	NHL	546 (694-1618)	18 (52-242)	20 (70-312)	Sinusitis, PNA, URIs
3	23	PTLD	791*/485 (694-1618)	75*/63 (52-242)	56*/47 (70-312)	Sinus infections, PNA
4	27	WG	334 (694-1618)	40 (52-242)	23 (70-312)	Skin infections, PNA
5	66	NHL	599*/353 (694-1618)	22*/31 (52-242)	67*/11 (70-312)	Recurrent *Clostridium difficile* colitis
6	69	ITP	524*/422 (694-1618)	71*/86 (52-242)	87*/51 (70-312)	Recurrent bronchitis, PNA
7	17	Evan syndrome/ITP	436 (528-2190)	31 (52-242)	<5 (70-312)	Endocarditis, sinusitis, bronchitis
8	72	NHL	458 (694-1618)	38 (52-242)	60 (70-312)	Recurrent PNA
9	57	WG	543 (694-1618)	<13 (52-242)	91 (70-312)	Sinusitis, MRSA bacteremia PNA
10†	19	Evan syndrome/ITP	1000*/1037 (694-1618)	23*/16 (52-242)	<7*/<7 (70-312)	Recurrent sinusitis, otitis media before IGRT
11†	74	CLL	1070 (694-1618)	<7 (52-242)	<5 (70-312)	Recurrent PNA, sinusitis before IGRT

AIHA, autoimmune hemolytic anemia; *CLL,* chronic lymphocytic leukemia; *ITP,* idiopathic thrombocytopenic purpura; *MRSA,* Methicillin-resistant *Staphylococcus aureus*; *NHL,* non-Hodgkin lymphoma; *PNA,* pneumonia; *PTLD,* posttransplantation lymphoproliferative disease; *URI,* upper respiratory infections; *WG,* Wegener granulomatosis.
*Prerituximab levels were available only for patients 3, 5, 6 and 10.
†These patients were diagnosed with CVID and started on IGRT before receiving rituximab.

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