Successful use of rituximab in the treatment of childhood and juvenile pemphigus

Keshavamurthy Vinay, MD,[a] Amrinder J. Kanwar, MD, FRCP,[a] Gitesh U. Sawatkar, MD,[a] Sunil Dogra, MD, FRCP,[a] Norito Ishii, MD,[b] and Takashi Hashimoto, MD[b]
Chandigarh, India, and Fukuoka, Japan

Background: There is a lack of data on outcomes of management of pemphigus in children.

Objective: We sought to evaluate rituximab treatment in childhood and juvenile pemphigus.

Method: All cases of pemphigus treated with rituximab in patients younger than 18 years were included. Clinical and epidemiologic data and details of rituximab administration were recorded. Response to treatment was assessed as control of disease activity, partial remission, complete remission, and relapse/flare.

Results: Ten patients aged 9 to 17 years received rituximab treatment. After therapy, they were followed up for a median period of 16 months (range 8-36 months). Complete remission without concomitant therapy was achieved in 7 patients by a mean of 21 weeks. One patient each achieved complete remission (on immunosuppressant therapy), control of disease activity, and partial remission (on immunosuppressant therapy) by 15, 8, and 14 weeks, respectively. Relapse/flare occurred in 6 patients by a mean period of 13 months. Two patients received a second cycle of rituximab infusions with good clinical response. Infusion reactions were the most common adverse event. There were no long-term complications.

Limitation: Small sample size and retrospective study design are limitations.

Conclusion: The current data suggest that rituximab is useful in treating childhood and juvenile pemphigus. (J Am Acad Dermatol 2014;71:669-75.)

Key words: autoimmune bullous diseases; childhood pemphigus vulgaris; juvenile pemphigus vulgaris; rituximab.

Pemphigus is rare in children and adolescents. In a study of pemphigus from North India, children younger than 15 years accounted for 3.7% of total cases.[1] Pemphigus in children younger than 12 years is known as childhood pemphigus, and in those aged 12 to 18 years as juvenile pemphigus.[2] A recent review of the English-language literature found 33 cases of childhood pemphigus vulgaris (PV) and 47 cases of juvenile PV.[3,4] Most reports are of sporadic cases and small series, and lack data on treatment outcomes. Treatment modalities include systemic corticosteroids, azathioprine, dapsone, mycophenolate mofetil, cyclophosphamide, and intravenous immunoglobulin.[3,4] Reported adverse events such

Abbreviations used:

CR:	complete remission
Dsg:	desmoglein
ELISA:	enzyme-linked immunosorbent assay
PF:	pemphigus foliaceus
PR:	partial remission
PV:	pemphigus vulgaris

From the Department of Dermatology, Venereology, and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh[a]; and Department of Dermatology, Kurume University School of Medicine, and Kurume University Institute of Cutaneous Cell Biology, Fukuoka.[b]

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Reprint requests: Amrinder J. Kanwar, MD, FRCP, Department of Dermatology, Venereology, and Leprology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. E-mail: ajkanwar1948@gmail.com.

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as infections, weight gain, Cushing disease, menstrual irregularity, hypertension, acne, cataract, growth retardation, osteopenia, conduct disorder, diabetes mellitus, and avascular necrosis may have profound effects on the physical growth, social interactions, and psychosocial health of children and adolescents.

Rituximab, a monoclonal antibody directed to CD20 antigen on the cell surface of B lymphocytes, has shown promising results in the treatment of pemphigus. It acts by inducing apoptosis of $CD20^+$ cells.[5,6] Data on rituximab use in childhood and juvenile PV are limited to individual case reports.[7] Our study presents data on 10 patients with childhood/juvenile pemphigus treated with rituximab.

CAPSULE SUMMARY

- Data on treatment outcomes of childhood and juvenile pemphigus are limited.
- We report a positive clinical and immunologic outcome in 10 cases of childhood/juvenile pemphigus treated with rituximab.
- Rituximab is a promising treatment option for severe/refractory pemphigus in children and adolescents.

METHODS

Patients

This was a retrospective analysis of clinical records of patients with pemphigus treated and followed up at the Postgraduate Institute of Medical Education and Research, Chandigarh, India, from October 2010 to June 2013. As this was a retrospective analysis of the patient treatment records, institutional review board approval was not required.

Ten patients younger than 18 years with pemphigus who received rituximab treatment with at least 6 months of posttreatment follow-up were identified. Clinical and epidemiologic data extracted included age at rituximab administration, gender, and disease duration. The clinical diagnosis and previous therapies were evaluated.

Rituximab treatment

All 10 patients were treated with either of 2 regimens: (1) a fixed-dose regimen, where rituximab (500 mg) was administered twice, 15 days apart; and (2) a body-weight regimen, where rituximab (375 mg/m^2 body surface area) was administered twice, 15 days apart. In every patient the pre-rituximab evaluation and treatment followed a protocol described previously.[8,9]

Indications for treatment were resistant disease, severe disease, or contraindications to conventional therapies. Resistant disease was defined as the continued extension of old lesions, continued development of new lesions, or failure of established lesions to begin to heal, despite 3 weeks of therapy with prednisolone (1.5 mg/kg/d) or its equivalent and concurrent use of cyclophosphamide (2 mg/kg/d) or azathioprine (2.5 mg/kg/d) for 12 weeks.[10] Patients were also considered to have resistant disease if new lesions continued to appear and/or old lesions failed to heal with 6 pulses of intravenous dexamethasone (100-mg dose), administered monthly.

At every visit, the disease was assessed according to the revised severity index for pemphigus described by Ikeda et al[11] (Ikeda severity score). Each item in the severity index was scored from a minimum of 0 to a maximum of 3. Thus: (I) the ratio of the affected area to the total skin surface as a percentage (0, none; 1, <5%; 2, 5%-15%; and 3, >15%); (II) the presence or absence of the Nikolsky phenomenon (0, none; 1, only focal; 2, positive; and 3, distinct); (III) the number of newly developed blisters per day (0, none; 1, occasional blisters; 2, 1-5 blisters; and 3, >5 blisters); and (IV) the presence or absence of oral lesions as a percentage (0, none; 1, <5%; 2, 5%-30%; and 3, >30%). The severity of each case was rated by the total sum of the scores. Disease was assessed to be mild, moderate, and severe, if the scores were less than 5, 5 to 7, or higher than 7, respectively.

Follow-up and response to treatment

After rituximab infusions, the patients were followed up for a variable time period. At each visit, response to treatment was assessed as per standard definitions, including control of disease activity, partial remission (PR), complete remission (CR), and relapse/flare, as defined by the consensus statement from the International Pemphigus Committee.[10] PR and CR were further defined depending on intake of concomitant immunosuppressant therapy: on therapy [CR (on) and PR (on)] or off therapy [CR (off) and PR (off)].[10]

Immunologic evaluation

At baseline, skin biopsy specimens were taken from all patients, and the specimens were submitted for histopathologic assessment using hematoxylin-eosin staining and for direct immunofluorescence for IgG, IgA, IgM, and C3. Enzyme-linked immunosorbent assay (ELISA) for IgG anti-desmoglein (Dsg)1 and Dsg3 antibodies was performed as described