Efficacy of rituximab in pediatric pemphigus: A literature review

To the Editor: Pemphigus encompasses a group of autoimmune blistering skin conditions caused by the loss of intraepidermal adhesions.[1] Although it is proposed that 1.4% to 2.9% of all pemphigus vulgaris cases present in pediatric patients, there is a lack of synthesized data regarding the use of rituximab in this population.[1] We performed a systematic review examining the safety and efficacy of rituximab in pediatric patients with pemphigus. We searched EMBASE, PubMed, Web of Science, and Google Scholar databases using the terms "pemphigus AND rituximab" from database inception to May 2, 2021. Two reviewers independently performed title and abstract screening followed by full-text review using the Covidence systematic review software. Original studies utilizing rituximab for the treatment of a pemphigus condition in a pediatric (≤17 years) patient were included.

Study and patient characteristics, as well as preceding and concomitant treatments are detailed in Table I.[1-16] Sixteen studies containing 43 patients (36 with pemphigus vulgaris and 7 with pemphigus foliaceous) were included. The patients were aged from 1.75 to 17 years, with a mean duration of disease of 2 years. Complete resolution was reported in 77% of patients, 21% experienced partial resolution, and 1 patient died of sepsis-related complications without response assessment. The most common adverse events were infusion reaction (fever, dyspnea, rigor, tachycardia, and chills; 18%), angioedema (7%), reduction in peripheral B-cell counts (5%), and the onset of sepsis (5%).

We found evidence to support the efficacy of rituximab for the treatment of pediatric pemphigus. All but 1 patient experienced disease improvement, and the majority achieved complete resolution. Most adverse events were mild and did not require treatment discontinuation. Two patients developed B-cell depletion. However, neither experienced subsequent infection or sepsis. There is limited evidence to suggest that the long-term absence of B cells in patients with rheumatoid arthritis treated with rituximab increases the risk of malignancy or infection.[17] Children also appear to be at increased risk of hypogammaglobulinemia with rituximab compared with adults.[18] Two patients developed sepsis, which is one of the most common causes of death in pemphigus patients. One patient on concomitant immunosuppressant therapy developed neutropenic sepsis but recovered following the administration of subcutaneous granulocyte-macrophage colony-stimulating factor.[10] Another patient died of *Staphylococcus aureus*–positive sepsis 1 week after drug initiation (concomitant immunosuppression was not reported).[6]

The management of pemphigus vulgaris with rituximab in adults typically follows either the rheumatoid arthritis protocol (two 1000-mg infusions at 2-week intervals) or the lymphoma protocol (4 weekly infusions of 375 mg/m^2). Our review demonstrates considerable heterogeneity in rituximab dosing regimens when prescribed for pediatric patients. This heterogeneity precluded our ability to perform a meta-analysis and to provide data in selecting the most effective dosing schedules for pediatric patients.

Limitations of this review include the small number of patients and incomplete data reporting in some studies, as well as the potential for bias. Through its targeting of autoreactive B cells in pemphigus, rituximab appears to be a promising new therapy for pediatric pemphigus. However, long-term clinical follow-up is needed to conclude the safety of rituximab in the pediatric population reasonably and to determine the optimal dosage and frequency of rituximab cycles and the length of maintenance therapy.

Meera H. Patel, BS,[a] *Caitlin M. Brumfiel, MS,*[b] *Nicholas Bohrer, MD,*[c] *and Amanda F. Marsch, MD*[c]

From the Creighton University School of Medicine Phoenix Regional Campus, Phoenix, Arizona[a]*; Georgetown University School of Medicine, Washington, District of Columbia*[b]*; and Department of Dermatology, University of California, San Diego, California.*[c]

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Correspondence to: Meera H. Patel, BS, Creighton University School of Medicine Phoenix Regional Campus, 600 N. 4th St. Unit 869, Phoenix, AZ 85004

E-mail: Meerapatel1@creighton.edu

Conflicts of interest

None disclosed.

Table I. Characteristics of the studies and patients

	Patient				Rituximab				Outcome			
Study type/No. of patients/Country	Age/sex	Duration (years)	Preceding systemic treatments	Concomitant systemic CCS	Dose	Frequency	No. of infusions	Cumulative dose	Adverse events	Treatment assessment	Time of treatment assessment (months)	Follow-up period (months)
Retrospective cohort study/5/Turkey[2]	16/M	1	MP, AZA	Yes	1000 mg	Every 15 days	2	2000 mg	None	CR	12	60
	14/M	3	MP, AZA, dapsone, MMF, IVIG	No	1000 mg	Every 15 days	2	2000 mg	None	PR	12	49
	13/M	4	MMF, MP, AZA, dapsone	No	1000 mg	Every 15 days	2	2000 mg	None	PR	12	60
	9/F	4	MP, AZA, IVIG, dapsone	Yes	500 mg	Every 15 days	2	1000 mg	None	CR	12	25
	10/F	1	MP, IVIG	Yes	375 mg/m^2	Weekly	NR	NR	None	CR	12	19
Case report/1*/United States[3]	1.75/F*	NR	MP, IVIG	Yes	375 mg/m^2	Weekly	12	4500 mg/m^2	None	CR	3	3
Case report/1/Italy[4]	11/M	0.8	PRED, IVIG	No	375 mg/m^2	18 days apart	2	750 mg/m^2	None	PR	10	10
Case report/1/Spain[1]	14M	9	MP, PRED, cyclosporine, AZA, dapsone, oral gold	Yes	375 mg/m^2	Weekly	4	1500 mg/m^2	None	CR	1	12
Case report/1/India and Japan[5]	11/M	0.3	DP, PSL, AZA	Yes	375 mg/m^2	Every 15 days	2	750 mg/m^2	None	CR	8	8
Prospective cohort study/2/India and Japan[6]	9/M	0.5	DP, AZA, PSL	Yes	375 mg/m^2	Every 15 days	2	750 mg/m^2	Angioedema during infusion	CR	2.25	11.5
	17/M	0.75	DCP, CP, PSL	Yes	1000 mg	Every 15 days	2	2000 mg	Sepsis	Died due to sepsis-related complications	NR	NR

Continued

Table I. Cont'd

	Patient				Rituximab				Outcome			
Study type/No. of patients/Country	Age/sex	Duration (years)	Preceding systemic treatments	Concomitant systemic CCS	Dose	Frequency	No. of infusions	Cumulative dose	Adverse events	Treatment assessment	Time of treatment assessment (months)	Follow-up period (months)
Case series/ 12/Iran[7]	14/M	3.08	PSL, AZA, MMF	No	500 mg	Every 15 days	4	2000 mg	None	CR	16	103
	14/F	2.5	PSL, AZA	No	500 mg	Every 15 days	4	2000 mg	Chills and fever	CR	15	18
	14/F	0	None	Yes	500 mg	Every 15 days	4	2000 mg	None	PR	15	28.5
	16/F	0	None	Yes	500 mg	Every 15 days	4	2000 mg	Fever	CR	15	58
	17/M	0.08	None	Yes	500 mg	Every 15 days	4	2000 mg	Dyspnea	CR	56	57
	16/F	1.3	PSL, AZA	No	500 mg	Every 15 days	4	2000 mg	Dyspnea, rigor, tachycardia	PR	33	51
	16/F	0.6	PSL, AZA, MMF	No	500 mg	Every 15 days	4	2000 mg	None	CR	27	102
	17/F	0.08	None	Yes	500 mg	Every 15 days	4	2000 mg	None	CR	29	51.5
	16/F	0.8	PSL	No	500 mg	Every 15 days	4	2000 mg	Dyspnea	CR	24	5
	11/M	0.3	PSL, AZA	Yes	500 mg	Every 15 days	2	1000 mg	Fever, infection	CR	3	97
	14/F*	0.08	None	Yes	500 mg	Every 15 days	4	2000 mg	None	PR	16	25
	16/M*	0.08	None	Yes	500 mg	Every 15 days	4	2000 mg	Headache	CR	5	55
Case report/ 1/Canada[8]	4/F	0.16	PRED, IVIG, AZA	Yes, and AZA	375 mg/m^2	Every 15 days	2	750 mg/m^2	Infusion reaction (urticaria and low-grade fever)	CR	2	12
Case report/1/ United States[9]	17/F	7	AZA, PRED, MP, MMF, IVIG, PP	Yes	375 mg/m^2	Every 15 days	4	1500 mg/m^2	Five days after the first infusion, CD20 B cells decreased from 3.2% to 0.2% and CD19 B cells decreased from 3.7% to undetectable. After 4 infusions, CD20 B cells remained at 0.2% and CD19 B cells were 0.1%	CR	17	17
Retrospective cohort study/1/ Singapore[10]	9/M	NR	MMF, AZA, PSL, MTX	NR	700 mg/m^2	Every 2 weeks	2	1400 mg/m^2	Neutropenic sepsis	CR	25	25

Case report/1/ United States[11]	17/M*	0.83	AZA, doxycycline, PRED	Yes	375 mg/m^2	Every 15 days	2	750 mg/m^2	None	PR	3	3
Case series/2/ United States[12]	16/F	NR	IMC, PRED, MMF, AZA, IVIG	No, and PP	375 mg/m^2	Weekly	8	3000 mg/m^2	None	CR	6	6
	16/F	2	PRED, MMF, PP	No, IVIG added after	375 mg/m^2	Weekly	4	1500 mg/m^2	None	PR	3	3
Retrospective cohort study/ 2/France[13]	14/F	NR	SCS, IVIG	Yes	375 mg/m^2	Weekly	2	750 mg/m^2	None	CR	62	62
	4/M*	NR	SCS, dapsone	Yes	375 mg/m^2	Weekly	1	375 mg/m^2	None	CR	23	23
Retrospective cohort study/ 1/India[14]	17/M	6	PRED, AZA	Yes	1000 mg	Every 15 days	3	3000 mg	Fatigue	CR	12	40
Case report/1/ Germany[15]	14/M	2.5	PSL, AZA, dapsone, SPAIP, MMF, CP, MP, IVIG	Yes, and MMF, IVIG	375 mg/m^2	Weekly	3	1125 mg/m^2	Circulating B cells became undetectable within 2 weeks after the first infusion	CR	9	24
Retrospective cohort study/ 10/India and Japan[16]	9/M	0.5	AZA, SCS, DP	Yes	375 mg/m^2	Weekly	2	750 mg/m^2	Angioedema	CR	4.5	36
	11/M	1	AZA, SCS, DP	Yes	375 mg/m^2	Weekly	2	750 mg/m^2	Infusion reaction	CR	4.5	8
	16/M	3	AZA, SCS, DP, MTX	Yes	500 mg	Weekly	2	1000 mg	None	CR	6	20
	17/M	1	AZA, SCS, DP, MMF	Yes	500 mg	Weekly	2	1000 mg	None	CR	4	19
	17/M	7	SCS	Yes	500 mg	Weekly	2	1000 mg	Infusion reaction	CR	4	18
	17/F	3	SCS	Yes	500 mg	Weekly	2	1000 mg	None	CR	5.5	17
	13/M*	3	AZA, SCS, DP	Yes	500 mg	Weekly	2	1000 mg	None	CR	7	15
	13/F	1	AZA, SCS	Yes	500 mg	Weekly	2	1000 mg	URTI	CR	5	14
	12/M	2.5	AZA, SCS	Yes	500 mg	Weekly	2	1000 mg	Angioedema	CR	2	12
	12/M*	3	SCS	Yes	500 mg	Weekly	2	1000 mg	None	PR	3.5	8

AZA, Azathioprine; *CCS*, corticosteroid; *CP*, cyclophosphamide; *CR*, complete resolution; *DCP*, dexamethasone cyclophosphamide pulse; *DP*, dexamethasone pulse; *IMC*, intramuscular corticosteroids; *IVIG*, intravenous immunoglobulin; *MMF*, mycophenolate mofetil; *MP*, methylprednisolone; *MTX*, methotrexate; *NR*, not reported; *PP*, plasmapheresis; *PR*, partial resolution; *PRED*, prednisone; *PSL*, prednisolone; *SCS*, systemic corticosteroids; *SPAIP*, Staphylococcal protein A immunoadsorptions in combination with prednisolone; *URTI*, upper respiratory tract infection.
*Diagnosed with pemphigus foliaceous.

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