Biologic treatment outcomes in refractory bullous pemphigoid: An evidence-based review

To the Editor: Bullous pemphigoid (BP) is an autoimmune disorder characterized by tense blisters and intense pruritus.[1] Initial treatment typically involves the use of topical and systemic corticosteroids, with refractory cases often requiring systemic immunosuppressives or biologics. This systematic review examines treatment outcomes of systemic biologics for BP refractory to other systemic therapies.

Following PRISMA criteria, a MEDLINE and Embase Ovid search was conducted, using specific keywords (Supplementary File 1, available via Mendeley at https://doi.org/10.17632/fcswf74g3x.2). Quality of evidence was assessed using Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. After independent screening of 765 articles by 2 reviewers, 68 studies (publication date: 2005-2022) involving 211 patients were included (Fig 1; Supplementary File 2, available via Mendeley at https://doi.org/10.17632/fcswf74g3x.2). The mean age was 64.6 years (range: 0.4-94 years), with 100 men (47.4%) and 100 women (47.4%); gender was not stated for 11 patients (5.2%). Drug-induced BP accounted for 10.9% of patients.

A total of 216 instances of systemic biologic use with outcomes were documented in the 211 patients; Rituximab (136 of 216, 63%) was the most reported one, followed by dupilumab (39 of 216, 18.1%) and omalizumab (38 of 216, 17.6%). (Table 1). Treatment duration was described in 192 instances (mean: 2.9 months; range: 0.25-14 months). Outcomes were reported as complete resolution (CR), partial resolution, or no resolution in 171 of 216 (79.2%), 35 of 216 (16.2%), and 10 of 216 (4.6%) of instances, respectively. Rituximab, dupilumab, and omalizumab led to CR in 101 of 136 (74.3%), 32 of 39 (82.1%), and 35 of 38 (92.1%) of instances, respectively. BP recurrence was reported in 9.9% of patients. All cases included were refractory nonbiologic systemic therapy (Supplementary File 2, available via Mendeley at https://doi.org/10.17632/fcswf74g3x.2). Biologic therapy with no concurrent systemic treatment was noted in 24.2% of cases. Treatment-related adverse events were reported in 20 cases (9.3%); none resulted in treatment discontinuation or death.

The incidence of BP continues to increase with an estimated 3.1-fold rise over the past 2 decades, possibly due to an aging population, iatrogenic cases, and improved diagnostics. It is evident that new and effective treatments are needed.[1,2] Rituximab was the most used systemic biologic for BP, showing CR in 74.3% of cases. Its efficacy is explained by the selective depletion of CD20-positive B cells that produce pathogenic autoantibodies against the hemidesmosomal proteins BP180 and/or BP230.[3] Dupilumab was the second most used systemic biologic for BP, showing CR in 82.1% of cases. As interleukin (IL) 4 and IL-13 inhibitors approved in many jurisdictions for atopic dermatitis, their efficacy may be explained by emerging evidence that type 2 cytokines, including IL-4 and IL-13, have been implicated in BP pathogenesis.[4] The European Dermatology Forum and European Academy of Dermatology and Venereology published consensus-based recommendations for BP management, with rituximab and omalizumab as third-line options.[5] Novel treatments showing clinical effectiveness such as dupilumab should also appear in newer guidelines.[5]

Study limitations included the novelty of systemic biologics for BP, lack of follow-up data, and potential selection bias for cases with improved outcomes. Given the lack of standardized outcome measures and small sample size, a meta-analysis could not be performed. Despite this, we highlight evidence for the effectiveness of systemic biologics, specifically rituximab and dupilumab, for the treatment of refractory BP. More rigorous and long-term studies are warranted.

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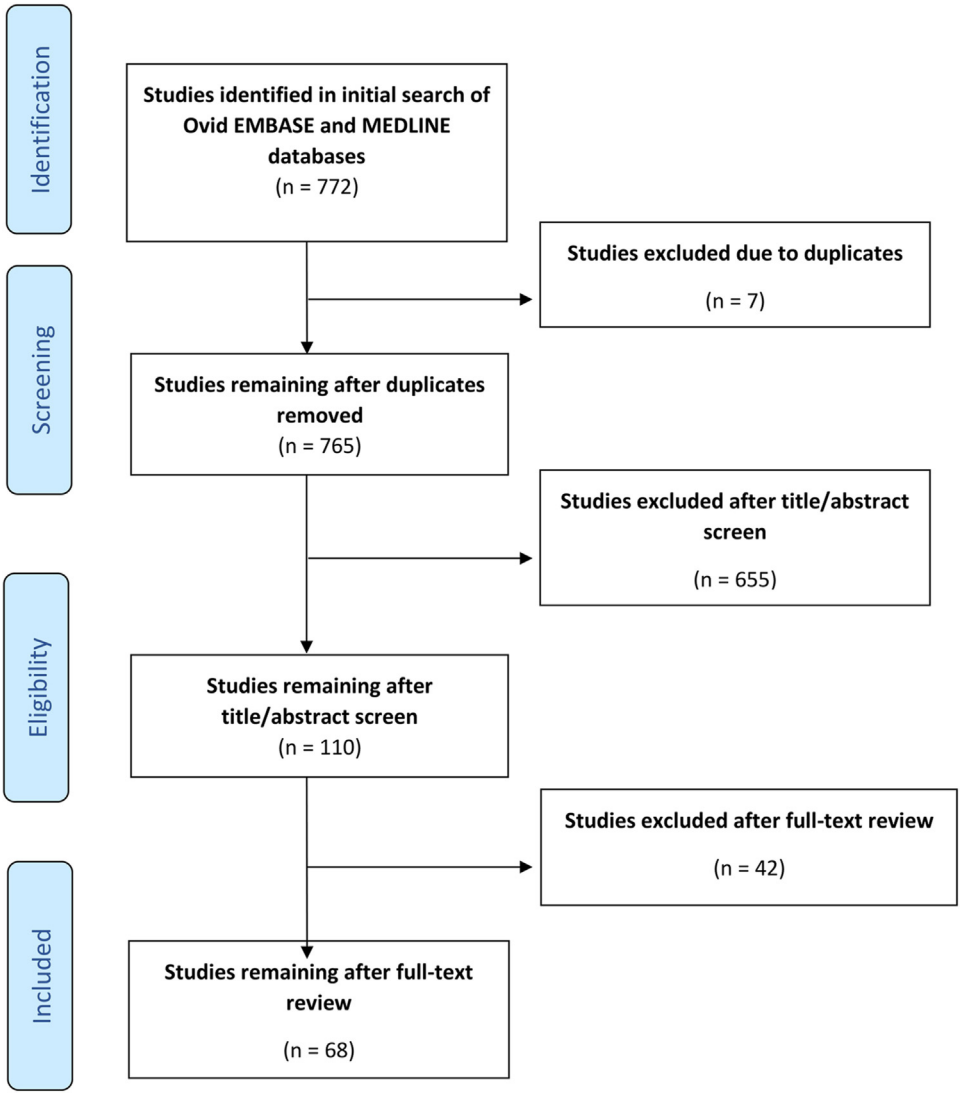

Fig 1. Flow diagram of literature screening using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Figure adapted from http://prisma-statement.org. The criteria for study inclusion were (1) patient(s) with a diagnosis of bullous pemphigoid, (2) patient(s) treated with systemic biology therapy, (3) studies that were observational or experimental in nature, including case reports, case series, retrospective and prospective cohort studies, as well as randomized controlled trials (RCTs), and (4) data in the English language.

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Table I. Outcomes of systemic biologic therapy use for BP

Systemic immunosuppressive therapy (%, *n/N*)	Study design (*n/N*)	Treatment outcome (%, *n/N*)	Refractory case (*n/N*)	Mean change in BPDAI measures from baseline (*n/N*)	Treatment duration, months (*n/N*)	Recurrence (*n/N*)	Adverse events (*n/N*)	Mean follow-up period, months (*n/N*)
Rituximab (63%, 136/216)	Case report (27/43) Retrospective study (10/43) Case series (3/43) Cohort study (2/43) Randomized controlled trial (1/43)	CR (74.3%, 101/136) PR (20.6%, 28/136)	Y (60/101) Y (27/28)	−27.1 (23/101) −60 (1/28)	10.6 (91/101) 8.7 (17/28)	N (8/101) Y (11/28) N (5/28)	NR Infection (8/28); herpes simplex infection (2/28); diarrhea (1/28); fever (1/28); polyarthritis (1/28); SIADH (1/28)	20.5 (9/101) 10.3 (15/28)
		NOR (5.1%, 7/136)	Y (7/7)	NR	NR	NR	Neutropenia (1/7)	7.8 (6/7)
Dupilumab (18.1%, 39/216)	Case report (8/12) Retrospective study (3/12)	CR (82.1%, 32/39)	Y (14/32)	−30.6 (8/32)	1.5 (30/32)	N (6/32) Y (1/32)	Injection-site reaction (1/32); osteoporosis (1/32)	8.9 (17/32)
	Case series (1/12)	PR (10.3%, 4/39)	Y (4/4)	NR	2 (4/4)	N (2/4) Y (1/4)	NR	4.6 (4/4)
		NOR (7.7%, 3/39)	Y (3/3)	NR	NR	NR	NR	NR
Omalizumab (17.6%, 38/216)	Case report (13/19) Case series (2/19) Cohort study (2/19) Retrospective study (2/19)	CR (92.1%, 35/38)	Y (34/35)	−32.5 (9/35)	3.1 (32/35)	N (17/35) Y (7/35)	Injection-site reaction (1/35); thrombocytopenia (1/35)	10.1 (25/35)
		PR (7.9%, 4/38)	Y (3/4)	NR	3.5 (2/4)	N (3/4) Y (1/4)	Tachycardia (1/4)	8.5 (4/4)
Belimumab (0.5%, 1/216)	Case report (1/1)	CR (100%, 1/1)	Y (1/1)	NR	5.6 (1/1)	NR	NR	NR
Daclizumab (0.5%, 1/216)	Case report (1/1)	CR (100%, 1/1)	Y (1/1)	NR	0.5 (1/1)	NR	NR	7 (1/1)
Infliximab (0.5%, 1/216)	Retrospective study (1/1)	CR (100%, 1/1)	Y (1/1)	NR	2.9 (1/1)	NR	NR	6 (1/1)

Additional details on systemic biologic therapy dosing, route of administration, concomitant therapy use, baseline BSA and BDPAI, and time to achieve BPDAI changes are listed in Supplementary File 2, available via Mendeley at https://doi.org/10.17632/fcswf74g3x.2.

BPDAI, Bullous Pemphigoid Disease Area Index; *BSA*, body surface area; *CR*, complete resolution; *N*, no, *NR*: none reported; *PR*, partial resolution; *NOR*, No resolution; *SIADH*, Syndrome of inappropriate antidiuretic hormone secretion; *Y*, yes.

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Conflicts of interest

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