Macrolides for the treatment of bullous pemphigoid

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To the Editor:

Bullous pemphigoid (BP) is an autoimmune bullous disorder that has traditionally been treated using topical and systemic corticosteroids [1]. Despite the increasing use of tetracycline as a steroid-sparing agent in treating mild BP due to its anti-inflammatory properties, there has been limited research and discussion on using macrolides as a treatment option despite similar anti-inflammatory mechanisms of action [1]. We present an updated review of macrolides in the treatment of BP.

Literature searches were conducted on PubMed and Google Scholar from 1982 (when the first reported cases of macrolide-treated BP were published) to the present (August, 2022). English-language articles were selected based on subject relevance and recency, and references within articles were also screened. This yielded four case reports and four case series, with all but one case employing erythromycin as the treatment agent [2–9].

The four case reports are described in **Table 1**; overall, three of the four patients (all infants) achieved remission via treatments involving macrolides [2–5]. However, none achieved remission via macrolide monotherapy; instead, macrolides were used in conjunction with topical corticosteroids, systemic corticosteroids, nicotinamide, and ranitidine [2–5]. In two patients, macrolides and topical/systemic corticosteroid combination therapy were used as initial treatment [2,5], whereas two others were given macrolides as corticosteroid-sparing agents following failure to control BP using initial corticosteroid therapy or corticosteroid with antibiotic combination therapy [3,4].

The four-case series are described in **Table 2**; overall, 20 of 31 patients achieved remission via treatments involving macrolides [6–9]. In total, there were 10 pediatric patients and 21 adults [6–9]. Only one patient was treated with erythromycin monotherapy, which displayed a good response but disease recurred after discontinuation [7]. The other 30 combined erythromycin with adjunct treatments including nicotinamide and topical corticosteroids [6–9]. All 31 cases had initiated erythromycin from the time of diagnosis [6–9]; there were 6 patients who failed initial treatments involving erythromycin and were switched to systemic corticosteroids [6,8].

Macrolides inhibit the production of multiple proinflammatory cytokines including interleukin-1 (IL1), IL6, IL8, and tumor necrosis factor (TNF); this is hypothesized to occur via the suppression of transcription regulators such as nuclear factor-κB and activator protein-1 [1,6]. Furthermore, macrolides inhibit neutrophil chemotaxis by blocking the production of leukotriene B4 and adhesion molecules, modulate monocyte and lymphocyte differentiation, and inhibit eosinophil recruitment [1,5,6]. These anti-inflammatory mechanisms of action are similar to those of tetracyclines, which downregulate TNF and IL1β, inhibit neutrophil activation and degranulation, and inhibit leukocyte chemotaxis [10].

Macrolide adverse effects include gastrointestinal disturbances and rare hepatotoxicity, as seen among

several patients treated with erythromycin [3,5,6]. Macrolides have lower side effect profiles than tetracyclines and corticosteroids and are safe for use in children and in pregnancy [6]. Though 14/35 of our BP patients treated with macrolides were infants and children, none of whom suffered adverse effects beyond gastrointestinal upset and diarrhea. However, one limitation is that no pregnant patients were identified in our review.

Overall, 23/35 BP patients (65.71%) in this review appeared to respond well to macrolide-based therapy with adverse effects of hepatotoxicity and gastrointestinal upset [2–9]. However, these promising results are limited by the clinical generalizability of case series and case report studies, the use of multiple adjunct therapies while taking macrolides, and the exclusion of relevant non-English-language studies [2–9]. Though macrolides represent another potential corticosteroid-sparing treatment option for BP, more rigorous studies involving randomized controlled trials comparing macrolides to tetracyclines, corticosteroids, and immunosuppressive therapies are warranted.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Case reports on bullous pemphigoid treated with macrolides.*

Patient age and sex	Location of lesions	Macrolide	Dose	Treatment duration	Adjunct treatment(s)	Clinical outcome	Adverse effects
14-week-old male	Hands, feet, trunk, limbs	Erythromycin	125mg four times daily	42 days	Topical mometasone furoate 0.1% ointment	Remission in 2 days without recurrence	Mild gastrointestinal upset after 6 weeks
3-month-old male	Soles of feet, trunk, back, limbs	Erythromycin	21mg per day	57 days	Prednisolone 20mg/day and dapsone 12.5mg/day	Flared after 65 days. Failed to respond to erythromycin and dapsone. Remission achieved after 2 courses of IVIG	None reported
5-month old female	Hands, feet, limbs	Clarithromycin	25mg twice daily, increased to 75mg twice daily at week 10	90 days	Oral prednisolone 4mg daily tapered, ranitidine 4mg three times daily, Topical fusidic acid 2% & betamethasone 0.1% twice daily	Remission with recurrence after 60 days	Diarrhea for 2 weeks on erythromycin 125mg twice daily, changed to clarithromycin 25mg twice daily
2.5-month-old male	Trunk	Erythromycin	26mg/kg/day	30 days	Prednisone 2mg/kg/day, dapsone 2mg/kg/day, nicotinamide 5mg/day	Remission after 4 months without recurrence at 10-month-follow-up.	None reported

Table 2. *Case series on bullous pemphigoid treated with macrolides.*

Number of patients	Male:female ratio	Age range and Mean (years)	Macrolide	Dose	Adjunct treatment(s)	Clinical outcome	Adverse effects
5	4:1	Range: 62-87 Mean: 76.8	Erythromycin	500mg three times daily	Nicotinamide 400mg three times daily	4: Complete remission after 1 month of therapy 1: hepatotoxicity after 9 days of therapy, switched to systemic corticosteroids	Hepatotoxicity (N=1)
2	0:2	Range: 4.5-87 Mean: 45.75	Erythromycin	4.5-years old: Unspecified 87-years old: 250mg four times daily	4.5-years old: None reported 87-years old: Intermittent topical steroids	Both: Significant improvement, but BP flared after erythromycin was discontinued	None reported
15	6:9	Range: 54-93 Mean: 78.7	Erythromycin stearate	1g three times daily x 10-15 days, then 1g twice daily after 15 days	None	10 patients experienced remission within 10-35 days. 3 patients required erythromycin & systemic steroids combination therapy and experienced remission within 30-60 days. 2 patients failed to achieve remission even with combination therapy involving steroids	None reported
9	Unspecified (39:38 with 4 unknowns in entire infantile cohort, N=81)	Unspecified, infantile cohort (Range: 1-12 months, Mean: 4.5 months in entire cohort, N=81)	Erythromycin	Unspecified	1: Topical corticosteroids 8: Nicotinamide	1: Good response 8: Good response in 3, partial to uncertain response in 5	None reported