

# Exploring methotrexate's efficacy in treating Bullous Pemphigoid induced by immune checkpoint inhibitors



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## BACKGROUND

Bullous pemphigoid is an autoimmune blistering disorder characterized by pruritus and urticarial or eczematous eruption typically followed by bullae formation due to autoantibody response to hemidesmosomal proteins BP180 and BP230 [1] (**Figure I**). Immune checkpoint inhibitor-induced bullous pemphigoid (ICI-BP) is a rare, antibody-mediated skin toxicity, reportedly affecting up to 1.0% of ICI-treated patients, with bullous dermatoses representing 1 to 8% of cutaneous immune-related adverse effects (irAEs) according to retrospective studies [1, 2]. ICI cessation is often necessary and existing algorithms for the management of ICI-BP typically recommend use of systemic corticosteroids or immunosuppressive treatments, which may blunt the anti-tumor response or cause immunosuppression [3, 4]. However, the clinical impact of immunosuppressive agents on the ICI-mediated antitumor response is unknown.

Methotrexate represents a steroid-sparing, cost-effective immunomodulator that has demonstrated benefit for ICI-induced psoriasis, BP unrelated to ICI use, and rheumatic irAEs; yet methotrexate use in ICI-BP remains infrequently described [5].

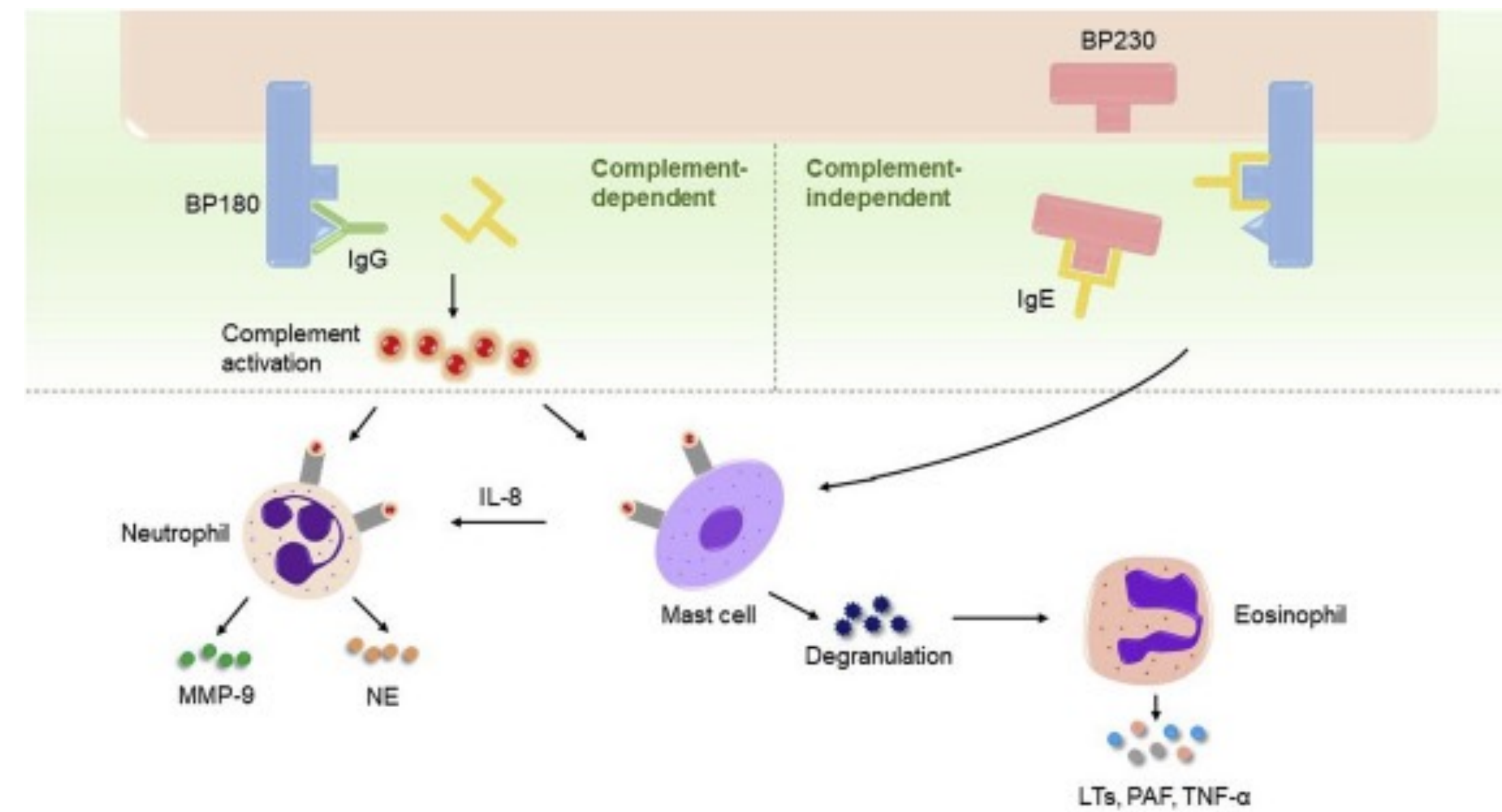
## OBJECTIVES

We aimed to assess the efficacy and tolerability of methotrexate in treating ICI-BP with focus on treatment outcomes, demographics, and cancer status of patients with ICI-BP treated with methotrexate.

## METHODS

We conducted a retrospective case review of four ICI-BP patients diagnosed by established criteria and seen at UNC Dermatology within the previous three years. Demographics, oncologic history, and ICI-BP features were collected through chart review. We examined tolerability and efficacy of methotrexate in ICI-BP cases induced by nivolumab (n=2) and pembrolizumab (n=2).

## PATHOGENESIS



**Figure I.** Pathogenesis of bullous pemphigoid [1].

## RESULTS

Average time from initiating ICI therapy to biopsy-proven BP onset was 16.0 months (11.9-22.0 month range). Methotrexate treatment duration ranged from 5.4-28.3 months, with all four patients receiving ongoing treatment at 5-15mg weekly.

Prior to receiving methotrexate, all patients trialed various ICI-BP treatments without resolution, including prednisone, IVIG, dapsone, niacinamide, doxycycline, and topical steroids. Following methotrexate initiation, all patients (n=4, 100%) achieved resolution of BP and discontinued systemic steroids (after 4.0 months on average, range 2.3-5.8 months). Only one patient required topical steroids to manage a subsequent localized BP flare. The onset of ICI-BP resulted in immunotherapy cessation in all cases. Cancer status following ICI discontinuation and BP treatment included complete remission (n=1), stable disease (n=2) and progression (n=1) (**Table I**).

## RESULTS (CONT.)

Literature review revealed six reported cases of ICI-BP treated with methotrexate. In a case series of five patients by Shi et al. most experienced complete disease resolution (n=4, 80%) [5]. Three patients (60%) discontinued systemic steroids while on methotrexate without disease exacerbation. One patient, already on chronic low-dose prednisone for non-cutaneous irAE, did not require dose adjustment for ICI-BP. Only one of five (20%) had adverse effects (mild diarrhea), not necessitating treatment discontinuation. A case report by Rofe et al. highlighted one patient with significant improvement and only occasional single blisters [6].

Age	Sex	Time to BP-onset <sup>1</sup> (mo.)	MTX Treatment Duration (mo.)	Max Dosage (mg weekly)	Disease Outcome on MTX	Months to Steroid Cessation <sup>**</sup>	Adverse Effects	Cancer Status following ICI Discontinuation
79	M	11.9	24.5	15	R	2.3	No	Stable
76	M	22	4.8	15	R	5.8	No	Complete Remission
79	M	12.8	2.6	7.5	R	2.9	No	Stable
76	F	17.3	5.6	10	R	4.9	GI upset, fatigue	Progression
-	-	10	(A) 6 <sup>2</sup> (B) 9	25	R	N/A	No	Progression
-	-	19	8	10	R	2	Diarrhea	Stable
-	-	14	48	15	R	18	No	Stable
-	-	7	10	10	R	-	No	Complete Remission
-	-	19	5	10	U	-	No	Stable
-	-	7	N/A	20	I	N/A	No	Complete Remission

<sup>1</sup>Time between ICI therapy initiation and biopsy-proven BP onset

<sup>2</sup>MTX initially given concurrently with prednisone for 2 mo., then stopped after 6 mo. due to complete improvement. Recurrence occurred 6 mo. later; MTX alone achieved complete improvement.

\*R=resolution; I = improvement; U = unchanged.

\*\*Time from MTX initiation to systemic steroid (prednisone) discontinuation.

UNC Dermatology: [redacted] Shi et al. (2021) [5]: [redacted] Rofe et al. (2017) [6]: [redacted]

**Table I.** ICI-BP treated with MTX at UNC and Summary of Literature

## DISCUSSION

Early recognition and management of ICI-BP is essential to patient safety, yet optimal treatment is not clearly defined. Indirect inhibition of antitumor-specific T cells is favorable to avoid hindering the ICI antitumor effect. Unlike mycophenolate mofetil and azathioprine, methotrexate does not directly inhibit T-cells targeting underlying cancer, theoretically reducing the likelihood of tumor progression [7].

We present four cases of ICI-BP treated with methotrexate, resulting in remission, except for one with a localized flare resolved with topical steroids. Methotrexate was well-tolerated, with one patient (25%) experiencing fatigue and gastrointestinal upset, not requiring treatment discontinuation. All previously tried various treatments with minimal improvement or disease exacerbation upon steroid tapering. Methotrexate allowed for successful taper off steroids.

Six prior cases treated with methotrexate showed similar positive responses, most achieving resolution without significant adverse effects. Half of those on concurrent prednisone discontinued systemic steroids while on methotrexate without worsening ICI-BP, suggesting reduced systemic steroid dependence with methotrexate.

Our findings indicate that methotrexate may be effective and safe in inducing clinical improvement in ICI-BP and minimizing prolonged high-dose systemic corticosteroid exposure, and therefore should be considered in ICI-BP treatment guidelines.

## LIMITATIONS

Our results are limited by the retrospective design and small sample size, due to the rarity of ICI-BP. More research is indicated to better understand the response to ICI-BP to methotrexate as well as the impact of treatment of ICI-BP with methotrexate on tumor progression.

## REFERENCES





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# Disclosures



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Authors have no financial disclosures or conflicts of interest to declare.