Title of Abstract:

IL-31 Signaling in Bullous Pemphigoid: Implications for Pruritus and Emerging Therapeutic Opportunities

Authors:

Jayalakshmi N. Alagar, M.Phil.[1] & Indrani M. Alagar, M.D.[2]

Affiliations:

[1]Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania, USA.

[2]University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

Keywords:

Bullous pemphigoid; IL-31; IL-31 receptor; pruritus; type 2 inflammation; biologic therapy

Main text:

Background: Bullous pemphigoid (BP) is a subepidermal blistering disease that primarily affects older adults. Pruritus is a prominent feature and may precede characteristic tense blisters in up to 20% of cases, potentially contributing to diagnostic delay [1]. An autoimmune response against hemidesmosomal proteins underlies BP pathophysiology. The presentation of BP180 and BP230 antigens activates T-helper 2 lymphocytes, which secrete cytokines including IL-4 and IL-13 that promote IgG and IgE autoantibody production and eosinophilic inflammation. This inflammatory pathway has been implicated in BP-associated pruritus, with most evidence highlighting IgG, IgE, and eosinophils [2]. While IL-31 has emerged as a potential pruritogenic mediator, its specific role in BP remains incompletely characterized. Therefore, we aimed to evaluate the evidence implicating IL-31 signaling in BP and its therapeutic potential.

Methods: We conducted a literature review of studies evaluating IL-31 and IL-31 receptor expression, cellular sources, associations with pruritus, and potential pathogenic roles in BP. This analysis was complemented by a search of ClinicalTrials.gov for ongoing interventional studies of biologic therapies in BP.

Results: IL-31 has been detected in BP blister fluid and lesional skin, with eosinophils identified as an important cellular source. Several clinical studies have found positive associations between IL-31 levels and itch severity. In 2025, IL-31 was, for the first time, identified as an independent factor associated with BP disease progression and positively correlated with disease severity as measured by body surface area; IL-31 levels were also found to decrease in patients with resolving lesions, suggesting potential utility as a marker of treatment response [3]. There is also

emerging evidence of the role of IL-31 in recruiting basophils to lesional tissue [4]. Comparatively less work has been done on characterizing contributions of the IL-31 receptor, despite multiple cases of BP development following treatment with the IL-31 receptor antagonist nemolizumab [5]. Augmented IL-31 receptor expression at peripheral nerves in BP lesions was first described in 2023 [6]. Our ClinicalTrials.gov search identified no trials specifically targeting IL-31 or IL-31RA in BP **(Table 1)**. We identified a trend in the literature toward repurposing biologics, including omalizumab (targets IgE), rituximab (targets CD20), bertilimumab (targets CCL11/eotaxin-1), mepolizumab and reslizumab (targets IL-5), benralizumab (targets the IL-5 receptor), nemolizumab, and dupilumab (targets IL-4 and IL-13), for BP [7]. Such awareness of the landscape presents an opportunity to explicitly evaluate the effects of biologic therapies on BP-associated pruritus, which remains an understudied outcome despite important implications for patient care and quality of life. Furthermore, no studies, to our knowledge, have focused on how these interleukin pathways interact to influence both pruritus and disease severity.

Conclusions: IL-31 signaling appears to be implicated in BP-associated pruritus but remains a largely untested therapeutic target in BP. Amid a growing interest in biologics for BP, prospective studies incorporating measures of itch, quality of life, and disease activity will be important to determine the therapeutic relevance of IL-31 pathway inhibition.

Table 1. Ongoing clinical trials evaluating biologic therapies in bullous pemphigoid.

NCT number	Interventions	Target	Allocation	Masking	Phase	Status
NCT07210554	stapokibart	IL-4Rα	Randomized	Quadruple	3	Not yet recruiting
NCT06371417	RAY121	C1s protein	N/A, single arm	None	1	Recruiting

References:

1. Lamberts A, Meijer JM, Jonkman MF. Nonbullous pemphigoid: A systematic review. J Am Acad Dermatol. 2018 May;78(5):989-995.e2. doi: 10.1016/j.jaad.2017.10.035. Epub 2017 Nov 1. PMID: 29102490.
2. Sun C, Feng S. Recent developments in the pathogenesis of pruritus in bullous pemphigoid. Int J Dermatol. 2021 Dec;60(12):1441-1448. doi: 10.1111/ijd.15589. Epub 2021 May 26. PMID: 34037252.
3. Zhang Y, Liu X, Hou L, Zhao Y, Hao J, Zhang N, Tian J, Li X, Liu Z, Zhou H, Xu C, Ren Y, Zhou H. IL-5, IL-31 and systemic immune-inflammation index as biomarkers predicting severity and progression in bullous pemphigoid. Front Med (Lausanne). 2025 Oct 15;12:1657952. doi: 10.3389/fmed.2025.1657952. PMID: 41169429; PMCID: PMC12568495.
4. Gibbs BF, Patsinakidis N, Raap U. Role of the Pruritic Cytokine IL-31 in Autoimmune Skin Diseases. Front Immunol. 2019 Jun 21;10:1383. doi: 10.3389/fimmu.2019.01383. PMID: 31281316; PMCID: PMC6598004.
5. Katsuta M, Kamide R, Ishiuji Y, Nobeyama Y, Asahina A. Bullous Pemphigoid that Developed During Nemolizumab Treatment for Atopic Dermatitis: Two Case Reports. Acta Derm Venereol. 2024 Sep 2;104:adv40634. doi: 10.2340/actadv.v104.40634. PMID: 39221836; PMCID: PMC11558856.
6. Ergun EZ, Aoki R, Horváth ON, Hartmann D, Satoh TK, Calabrese L, Aksu AEK, Gürel MS, Manav V, Flaig MJ, Sárdy M, Ruzicka T, French LE, Bağcı IS. Divergent in situ expression of IL-31 and IL-31RA between bullous pemphigoid and pemphigus vulgaris.

Exp Dermatol. 2023 Sep;32(9):1412-1419. doi: 10.1111/exd.14842. Epub 2023 Jun 1. PMID: 37260420.

7. Werth VP, Murrell DF, Joly P, Heck R, Orengo JM, Ardeleanu M, Hultsch V. Pathophysiology of Bullous Pemphigoid: Role of Type 2 Inflammation and Emerging Treatment Strategies (Narrative Review). Adv Ther. 2024 Dec;41(12):4418-4432. doi: 10.1007/s12325-024-02992-w. Epub 2024 Oct 19. PMID: 39425892; PMCID: PMC11550233.

Acknowledgments & Funding Sources:

There are no funding sources, acknowledgments, or other support.

Encore Disclosure:

This research has not been presented or published previously.

Medical Writing / Editorial Assistance:

No medical writing or editorial assistance was provided.