Drugs in Context

drugsincontext.com

CASE SERIES

Anti-IL-17 monoclonal antibodies and bullous pemphigoid: treatment or causal agents? A case series and review of the literature

Anna Paola Lugli[1,2], Giacomo Caldarola[1,2], Gennaro Marco Falco[1,2], Costanza Montedoro[3], Camilla Mulas[3], Clara De Simone[1,2]

[1]Dermatologia, Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; [2]UOC di Dermatologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli – IRCCS, Rome, Italy; [3]School of Medicine, Università Cattolica del Sacro Cuore, Rome, Italy

Abstract

Bullous pemphigoid (BP) is an autoimmune bullous disease, typically affecting the elderly, characterized by the production of autoantibodies directed against structural components of the dermal–epidermal junction. An association between BP and psoriasis has been described several times, but the mechanisms underlying this association have yet to be clearly defined. The pathophysiological mechanism underlying psoriasis may be implicated in the pathogenesis of BP, as psoriasis precedes BP in most cases; in particular, a promoting role has been hypothesized by biologic therapies, which may induce a switch from a T helper 1 (T_H1)/T_H17-dominant cytokine milieu, typical of patients with psoriasis, to a T_H2-dominant one, typical of patients with BP. IL-17 inhibitors, in particular, have also been successfully used to treat BP in patients with psoriasis. The use of these drugs in these patients has been based on *in vitro* studies. However, cases of new-onset BP or relapses of BP already diagnosed in patients with psoriasis treated with biologic drugs have also been reported, and they occurred mainly in patients on anti-TNF drugs, yet very few cases with anti-IL-17A drugs have been described. We hereby describe two cases of new-onset BP in two patients treated with anti-IL-17 drugs for psoriasis.

Keywords: bullous pemphigoid, psoriasis, paradoxical reaction.

Citation

Lugli AP, Caldarola G, Falco GM, Montedoro C, Mulas C, De Simone C. Anti-IL-17 monoclonal antibodies and bullous pemphigoid: treatment or causal agents? A case series and review of the literature. *Drugs Context*. 2024;13:2024-4-3. https://doi.org/10.7573/dic.2024-4-3

Introduction

Bullous pemphigoid (BP) is an autoimmune blistering disease, typically affecting the elderly, characterized by the production of autoantibodies directed against components of the hemidesmosomes at the dermal–epidermal junction. Clinically, the condition is characterized by intense pruritus and tense bullae appearing on erythematous or normal skin. An association between BP and psoriasis has been described several times[1] but the mechanisms underlying this association have yet to be clearly defined. The pathophysiological mechanism underlying psoriasis may be implicated in the pathogenesis of BP, as psoriasis precedes BP in most cases; in particular, a promoting role has been hypothesized by biologic therapies, which may induce a switch from a T helper 1 (T_H1)/T_H17-dominant cytokine milieu, typical of patients with psoriasis, to a T_H2-dominant one, typical of patients with BP.

The association between BP development and certain drugs, like dipeptidyl peptidase IV inhibitors and loop diuretics, is well known.[2] Moreover, cases of BP have been reported also in patients with psoriasis being treated with biologic drugs, mainly in patients receiving anti-TNF agents, whereas very few cases have been described with anti-IL-17 drugs.[3] IL-17 inhibitors have been successfully used to treat BP in patients with psoriasis. The use of these drugs in these patients has been based on *in vitro* studies; indeed, Chakievska et al.[4] found that peripheral blood of patients with BP had high numbers of $CD4^+$

IL-17A lymphocytes and identified $CD3^+$ cells as the main source of IL-17A in early BP skin lesions. However, cases of new-onset BP or relapses of BP already diagnosed in patients with psoriasis treated with biologic drugs have also been reported, occurring mainly in patients on anti-TNF drugs, yet very few cases with anti-IL-17A drugs have been described.

We herein report on two cases of bullous BP developing after the administration of bimekizumab and ixekizumab, which are an anti-IL-17A/F and anti-IL-17A agents, respectively.

Case reports

CARE guidelines were used in the production of this article. Informed consent for publication was obtained from the two included patients.

Case 1

A 68-year-old Cape Verdean woman was admitted to our dermatology ward presenting elevated body temperature, hypocalcaemia and pustules all over her body (Figure 1a). Suspecting generalized pustular psoriasis, we performed cultures of sterile pus and a skin biopsy, which confirmed the diagnosis. The patient's medical history was otherwise significant for chronic ischaemic heart disease, hypertension and dyslipidaemia on treatment with atorvastatin, acetylsalicylic acid, telmisartan and amlodipine. She was started on intravenous corticosteroids with fast resolution of the cutaneous lesions and fever, but she relapsed soon after methylprednisolone tapering. Subsequently, we decided to administer bimekizumab at the scheduled dosage (320 mg every 4 weeks for the first 16 weeks and then every 8 weeks) in association with 10 mg of daily acitretin. This treatment induced complete remission of generalized pustular psoriasis within 15 days. However, 9 weeks after the first administration of bimekizumab, whilst still on treatment with both, the biologic and acitretin, the patient came to a follow-up visit presenting bullous lesions on her wrists and thighs (Figure 1b). Based upon the different clinical appearance from the initial manifestations, a new skin specimen was collected from her left thigh, and the histopathological examination showed subepithelial bullae with neutrophilic infiltrate and fibrin deposits, compatible with BP (Naranjo Scale 7). We also performed direct immunofluorescence from perilesional skin, which showed linear deposits of IgG and C3 along the dermal–epidermal junction. High titres of anti-BP180 and anti-BP230 antibodies (232 UI/ml and 188 UI/ml, respectively) were found at ELISA testing. Bimekizumab administration was interrupted whilst keeping acitretin at a dosage of 10 mg per day. Intravenous methylprednisolone at a dosage of 40 mg was started with resolution of the cutaneous lesions within 22 days and remission of BP was observed after steroid tapering. Acitretin was suspended and methotrexate was started at a dosage of 10 mg weekly; after 7 weeks of therapy, she was still in clinical remission.

Case 2

A 64-year-old Italian man affected by chronic plaque psoriasis since childhood, without other comorbidities, came to our attention for the first time presenting with eczematous and bullous lesions on his trunk and upper limbs (Figure 2); these lesions first appeared 3 months earlier. At the time of the observation, he was also successfully on treatment for his psoriasis with ixekizumab, started 4 years before. Moreover, he referred he did not take any new drug or topical treatment in the months preceding the development of the cutaneous lesions.

A skin specimen was obtained, and histopathological examination reported the presence of suprabasal bullae with fibrin deposits and eosinophilic infiltrate. Direct immunofluorescence from perilesional skin showed linear deposits of C3 along the dermal–epidermal junction, confirming the suspicion of BP (Naranjo Scale 4). Furthermore, the ELISA test confirmed the presence of antibodies against BP180 (252 UI/ml). We decided to interrupt ixekizumab and start oral methylprednisolone at a dosage of 48 mg per day. Clinical remission of cutaneous bullous lesions was observed after 16 days of treatment. At 42 days after ixekizumab withdrawal, the patient was still taking 16 mg of methylprednisolone per day associated with subcutaneous methotrexate 10 mg weekly with complete remission of both BP and psoriasis. However, as for this case, it must be noted that BP may also have arisen independently of the drug because the patient was still on steroid therapy despite the discontinuation of ixekizumab.

Discussion

Psoriasis vulgaris is a common inflammatory skin disorder that may occasionally be associated with BP and other autoimmune blistering diseases, like antilaminin-γ1 pemphigoid, previously known as anti-p200 pemphigoid.[5] In detail, a cohort study by Ho et al. suggests that psoriasis is independently associated with an increased risk of developing BP.[5] They also found that patients with psoriasis affected by BP are younger than patients diagnosed with BP only, and that more than one-third of BP cases are diagnosed in the first year after incident psoriasis. The mechanisms underlying the association between BP and psoriasis have not yet been clearly defined. However, it seems that the pathophysiological mechanism of psoriasis may be implicated in BP pathogenesis as psoriasis precedes BP

Figure 1. A, B. Sterile pustules on erythematous skin. C. Tense bullae and eroded lesions on the forearms and thighs.

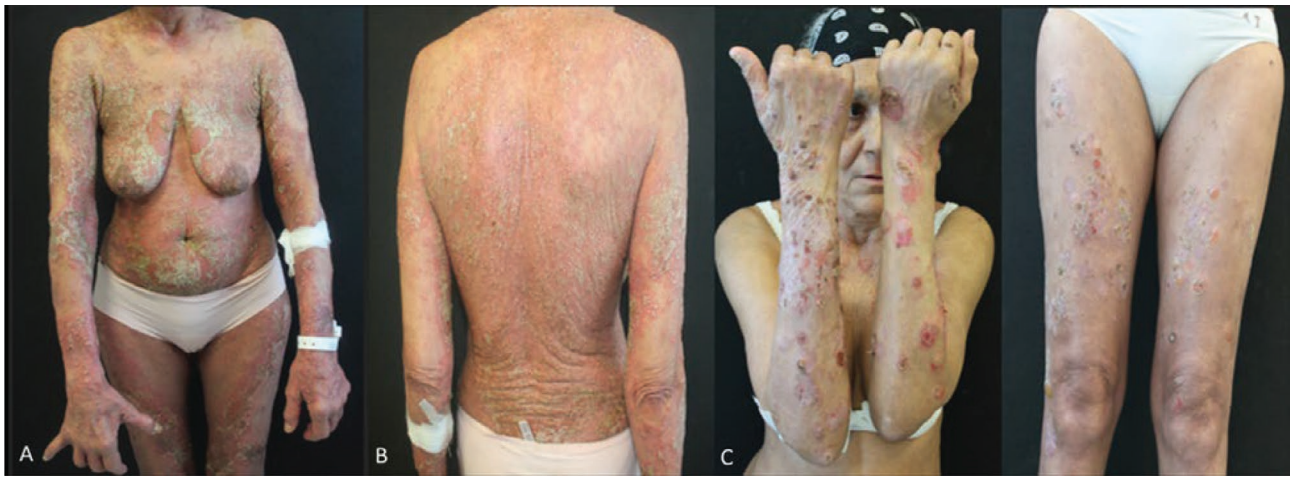
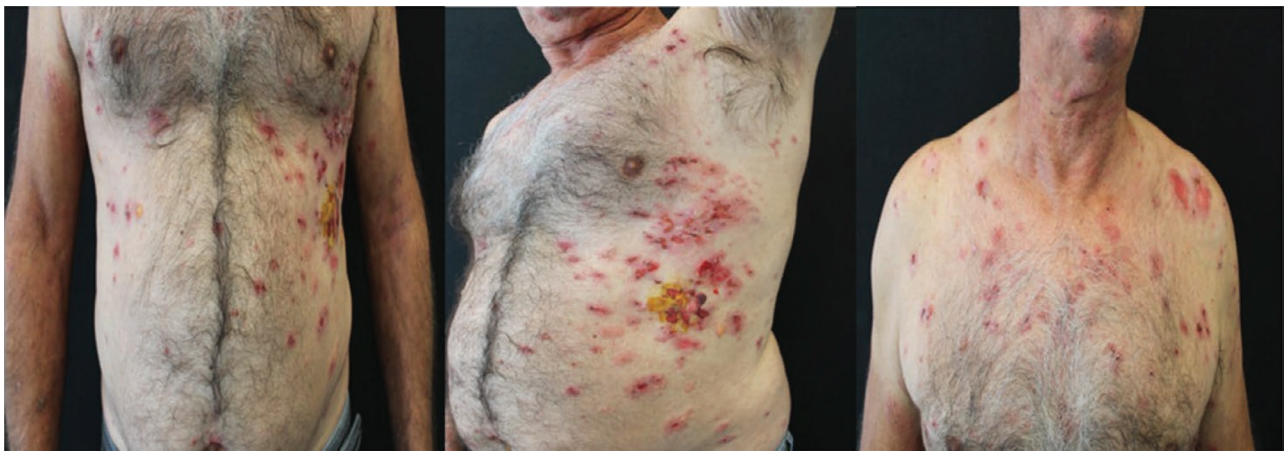


Figure 2. Crusted, eczematous and bullous lesions appeared on the man's trunk during remission of psoriasis.



in most cases. Amongst the different factors that have been proposed as possible triggers of the immunological reactions leading to BP, infections and epigenetic changes at the basement membrane zone of psoriatic skin could precipitate autoimmune blistering diseases in genetically predisposed individuals, probably by altering, unveiling or exposing new antigens.[5,6] Finally, in some cases, promoting a role for antipsoriatic biological therapies, that may induce a switch from a T_H1/T_H17-dominant cytokine milieu, typical of patients with psoriasis, to a T_H2-dominant one, typical of patients with BP[7] has been suggested.

We reported two cases of patients with psoriasis who developed BP during treatment with anti-IL-17 agents. Although the onset of BP in these patients may be coincidental, we hypothesized that IL-17 blockage may have favoured BP occurrence. This is in line with previous studies describing other cases of BP induced or relapsing after anti-IL-17 therapies (Table 1).

On the other hand, notably, IL-17 inhibitors have also been successfully used to treat BP in patients affected by concomitant psoriasis[8,9] (Table 1). The use of these drugs in these patients was based on *in vitro* studies. In fact, interestingly, Chakievska et al.[4] found high numbers of IL-17A$^+$CD4$^+$ lymphocytes in the peripheral blood of patients affected by BP and identified CD3$^+$ cells as a major source of IL-17A in early BP skin lesions. They also described the upregulation of *IL17A* and related genes in the skin of patients with BP, hence suggesting a relevant role of IL-17A in BP pathogenesis and the potential use of IL-17 inhibitors in the treatment of BP.

Table 1. Reported cases of BP developing *de novo*/relapsing or being treated with IL-17 inhibitors.

Study	Age	Sex	Race	Condition being treated	Type of IL-17 inhibitor used	*De novo*/ relapsing BP	Onset of bullous lesions after drug initiation (weeks)	BP remission after drug initiation (weeks)
Wang et al.[10]	71	Male	Asian	Chronic plaque psoriasis	Ixekizumab	Relapsing BP	4 weeks	Not available
Wang et al.[10]	66	Male	Asian	Chronic plaque psoriasis	Secukinumab	Relapsing BP	2 weeks	Not available
Sugihara et al.[11]	68	Male	Asian	Pityriasis rubra pilaris	Ixekizumab	*De novo* BP	38 weeks	Not available
Fatima et al.[12]	62	Male	White	Psoriatic arthritis	Secukinumab	*De novo* BP	52 weeks	Not available
Our case	77	Female	Creole	General pustular psoriasis	Bimekizumab	*De novo* BP	9 weeks	Not available
Our case	64	Male	White	Chronic plaque psoriasis	Ixekizumab	*De novo* BP	204 weeks	Not available
Lu et al.[6]	37	Female	Asian	Chronic plaque psoriasis + BP	Ixekizumab	Not available	Not available	2 weeks
Yun et al.[13]	68	Male	Asian	Refractory psoriasis + BP	Secukinumab	Not available	Not available	31 weeks
Holtsche et al.[14]	85	Female	White	BP	Secukinumab	Not available	Not available	12 weeks

Conclusion

Thus, it is not clear whether anti-IL-17 agents may cause the relapse or development of BP as an adverse event or rather ameliorate its clinical course, especially when co-morbid with psoriasis. Further experience and laboratory studies are needed to understand the complex mechanisms underlying these conditions and the role that anti-IL-17 monoclonal antibodies may play in this setting.

Contributions: All authors contributed equally to the preparation of this manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: GC has received consulting fees, honoraria and support for attending meetings from Abbvie, Lilly, Janssen, UCB, Novartis and Leopharma. CDS has received support for consulting fees, honoraria and support for attending meetings from Abbvie, Lilly, Janssen, UCB, Novartis, Leopharma, Sanofi and Almiral. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2024/07/dic.2024-4-3-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/anti-il-17-monoclonal-antibodies-and-bullous-pemphigoid-treatment-or-causal-agents-a-case-series-and-review-of-the-literature

Correspondence: Gennaro Marco Falco, Università Cattolica del Sacro Cuore, Dermatologia, Rome, Italy and Fondazione Policlinico Universitario A. Gemelli - IRCCS, Largo A. Gemelli 8, 00168 Rome, Italy. Email: gianmarcofalco@gmail.com

Provenance: Submitted; externally peer reviewed.

Submitted: 15 April 2024; **Accepted:** 28 June 2024; **Published:** 30 July 2024.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights, and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Maronese CA, Cassano N, Genovese G, Foti C, Vena GA, Marzano AV. The intriguing links between psoriasis and bullous pemphigoid. *J Clin Med*. 2022;12(1):328. https://doi.org/10.3390/jcm12010328
2. Verheyden MJ, Bilgic A, Murrell DF. A systematic review of drug-induced pemphigoid. *Acta Derm Venereol*. 2020;100(15):adv00224. https://doi.org/10.2340/00015555-3457
3. Husein-ElAhmed H, Steinhoff M. Bullous pemphigoid induced by biologic drugs in psoriasis: a systematic review. *J Dermatolog Treat*. 2022;33:2886–2893. https://doi.org/10.1080/09546634.2022.2089331
4. Chakievska L, Holtsche MM, Künstner A, et al. IL-17A is functionally relevant and a potential therapeutic target in bullous pemphigoid. *J Autoimmun*. 2019;96:104–112. https://doi.org/10.1016/j.jaut.2018.09.003
5. Ho YH, Hu HY, Chang YT, Li CP, Wu CY. Psoriasis is associated with increased risk of bullous pemphigoid: a nationwide population-based cohort study in Taiwan. *J Dermatol*. 2019;46(7):604–609. https://doi.org/10.1111/1346-8138.14902
6. Phan K, Goyal S, Murrell DF. Association between bullous pemphigoid and psoriasis: systematic review and meta-analysis of case-control studies. *Australas J Dermatol*. 2019;60:23–28. https://doi.org/10.1111/ajd.12899
7. Caldarola G, Pirro F, Di Stefani A, et al. Clinical and histopathological characterization of eczematous eruptions occurring in course of anti IL-17 treatment: a case series and review of the literature. *Expert Opin Biol Ther*. 2020;20(6):665–672. https://doi.org/10.1080/14712598.2020.1727439
8. Lu L, Yu Y, Zhang J, et al. Incidental amelioration of bullous pemphigoid during ixekizumab treatment for psoriasis. *J Dermatol*. 2022;49:e13–e15. https://doi.org/10.1111/1346-8138.16189
9. Zhang J, Wang SH, Zuo YG. Paradoxical phenomena of bullous pemphigoid induced and treated by identical biologics. *Front Immunol*. 2023;13:1050373. https://doi.org/10.3389/fimmu.2022.1050373
10. Wang R, Wang A, Wang M. Two cases with bullous pemphigoid relapsed after using interleukin-17A inhibitors for psoriasis: A paradoxical reaction. *J Dermatol*. 2023;50(7):956–959. https://doi.org/10.1111/1346-8138.16765
11. Sugihara N, Kamiya K, Nakano N, et al. A case of bullous pemphigoid developing after ixekizumab therapy for pityriasis rubra pilaris. *J Dermatol*. 2023;50(6):e185–e186. https://doi.org/10.1111/1346-8138.16711

12. Fatima R, Altorok N. Secukinumab-induced bullous pemphigoid in a patient with psoriatic arthritis. *Am J Ther*. 2024;31(4):e434–e435. https://doi.org/10.1097/MJT.0000000000001642
13. Yun JS, Scardamaglia L, Tan CG, McCormack CJ. Successful secukinumab treatment of active bullous pemphigoid and chronic severe psoriasis: a case report. *Australas J Dermatol*. 2022;63(2):e155–e158. https://doi.org/10.1111/ajd.13803
14. Holtsche MM, Hammers CM, Chakievska L, et al. Adjuvante therapie mit secukinumab induziert langzeitremission bei einer patientin mit schwerem bullösen pemphigoid. *J Dtsch Dermatol Ges*. 2020;18(12):1478–1480. https://doi.org/10.1111/ddg.14291_g