Bullous pemphigoid induced by ustekinumab: a case report

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SUMMARY

A possible case of bullous pemphigoid (BP) that developed during treatment with ustekinumab is reported. Ustekinumab is a human monoclonal antibody found in pathologies such as psoriasis, which works by inhibiting the activity of interleukin-12 and interleukin-23. We describe the case of a 75-year-old woman who presented with new onset of erythematous and bullous lesions 5 days after receiving a fifth dose of ustekinumab. The patient was treated with corticosteroids and dapsone, whereupon the lesions disappeared. Ustekinumab was withdrawn. Currently the patient remains asymptomatic. In addition, the histopathological and immunofluorescence findings confirmed the diagnosis of BP. Three causality algorithms were applied and revealed a probable causal relationship. There may be a causal relationship between the use of ustekinumab and BP. This association should be taken into account by physicians when prescribing and reviewing drug therapies.

BACKGROUND

Bullous pemphigoid (BP) is an autoimmune, subepithelial bullous disease characterised by skin blisters and erosive lesions of the mucosa.[1] In the development of BP, autoimmune reactions caused by exposure to infections or drugs may play an important role. Although the aetiology of this condition is unknown, several drugs could be associated with BP development, especially monoclonal antibodies.[1 2] Its appearance could be delayed after treatment commences (from months to years).

Ustekinumab is a humanised monoclonal IgG1 *k* antibody that binds the p40 protein subunit of interleukin 12 (IL-12) and IL-23. It is used in the treatment of immune-mediating diseases such as psoriasis, psoriatic arthritis or Crohn's disease.[3]

Herein, we present the case of a woman with chronic plaque psoriasis treated with ustekinumab, who presented with new onset of erythematous and bullous lesions. The erosions resolved after treatment with corticosteroids and dapsone, and the diagnosis of BP was confirmed by histopathological and immunofluorescence findings.

Consequently, we consider it relevant to describe this case to highlight that BP might be an unknown adverse event related to ustekinumab use that should be studied.

CASE PRESENTATION

A 75-year-old Spanish woman with a 20-year history of chronic plaque psoriasis was admitted because of new onset of pruritic, erythematous and bullous lesions, red-wine coloured on the trunk and extremities, 5 days after receiving a fifth dose of ustekinumab.

The patient had a history of asthma and osteoporosis, and had been prescribed ustekinumab 45 mg every 12 weeks since 2016. Her usual treatment included montelukast 10 mg/day, pantoprazole 40 mg/day, calcium 500 mg/day, denosumab 60 mg/6 months, and as topical treatment, methylprednisolone, calcipotriol/betamethasone and pimecrolimus.

Previous medication included methotrexate 20 mg, acitretin 25 mg and adalimumab 40 mg administered fortnightly for 2 years. Then, because of a flare-up after adalimumab treatment, ustekinumab was prescribed. After five ustekinumab doses, the patient developed erythematous and bullous lesions. Physical examination revealed the aforementioned erosions. Nikolsky sign was negative.

INVESTIGATIONS

The initial suspicion of BP was confirmed with complementary tests, both analytical and skin biopsies. Two skin biopsies from a blister on the patient's trunk showed an intraepidermal cleft, with marked eosinophils and lymphocytes in the dermis. Split-skin direct and indirect immunofluorescence demonstrated linear deposition of immunoglobulin G (IgG) and C3 at the basement membrane zone. Autoantibodies against BP180NC16 were negative and autoantibodies to anti-epidermis ASA were positive, IgE value was 1906 U/mL (0–120 U/mL). From these histopathological and immunofluorescence findings the diagnosis of BP was confirmed.

The clinical pharmacist was asked by the clinician to review the patient's medication to determine whether BP could be secondary to some of the drugs she was receiving. On suspicion that the causative drug of BP was ustekinumab, this drug was discontinued. In addition, this adverse event was evaluated. According to the Naranjo *et al*[4] (table 1) adverse reaction probability scale, Karch–Lasagna algorithm[5] (table 2) and WHO-UMC system[6] (table 3), the causal relationship between BP and ustekinumab was classified as '*probable*'.

TREATMENT

The clinical pharmacist helped doctors to review the patient's medication list to determine whether the symptoms could be secondary to some of the drugs she was using. Ustekinumab was the main suspicious drug for this adverse event, so the pharmacist proposed that it be discontinued. Intravenous methylprednisolone (1 mg/kg/day) and dexchlorpheniramine 15 mg/day were prescribed. As topical treatment, clobetasol and zinc sulfate 1/1000 were used. The patient continued with

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Table 1 Naranjo adverse reaction probability scale

Question	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	**1**
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	**2**
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	**1**
Did the adverse event reappear when the drug was re-administered?	+2	-1	0	**0**
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	**0**
Did the reaction reappear when a placebo was given?	-1	+1	0	**0**
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	**0**
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	**0**
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	**0**
Was the adverse event confirmed by any objective evidence?	+1	0	0	**1**
Total score				**5**

Scoring: Definite: >9; Probable: 5–8; Possible: 1–4; Doubtful: 0.

calcipotriol/beclomethasone and pimecrolimus on the plaques. In addition, in order to prevent secondary bacterial infections, linezolid 600 mg twice daily and clindamycin 300 mg twice daily were prescribed.

Although the patient was treated with corticosteroids, new pruritic skin erosions appeared within 11 days and so dapsone 50 mg/day was added to the treatment regimen.

OUTCOME AND FOLLOW-UP

Two weeks after the last dose of ustekinumab, the patient's skin erosions improved on account of the systemic and topical treatment she received. She continued with dapsone 50 mg/day, prednisone 40 mg/day (dose reduction regimen), zinc sulfate 1/1000 (topical) and clobetasol (topical).

Three months after stopping ustekinumab treatment the patient remained asymptomatic. However, clinicians decided not to try a re-challenge on account of the previous adverse event and instead commenced treatment with ixekizumab, another humanised monoclonal antibody which acts by inhibiting the activity of interleukin 17, with adequate tolerance.

This adverse event was reported to the regional pharmacovigilance centre.

DISCUSSION

Drug-induced BP represents a small proportion of the total reported cases of BP. Its development has been associated with a wide variety of drugs such as amoxicillin, losartan, lisinopril, sulfasalazine, spironolactone and monoclonal antibodies, including nivolumab and pembrolizumab among others.[1] In addition, the use of drugs that inhibit tumour necrosis factor (anti-TNF), such as adalimumab or etanercept, are related to BP development and are described in the literature.[7–9]

Table 2 Karch–Lasagna algorithm

Question	Definite	Probable	Possible	Conditional
Reasonable time sequence (+2)	Yes	Yes	Yes	Yes
Previous knowledge about the adverse reaction (+2)	Yes	Yes	Yes	No
Adverse reaction improved when the drug was discontinued (+2)	Yes	Yes	Yes/No	Yes/No
Adverse event reappeared when the drug was re-administered (0)	Yes	?	?	?
Another alternative explanation (–1)	No	No	Yes	No
Total score		**6**		

Scoring: Definite: ≥ 8; Probable: 6–7; Possible: 4–5; Conditional: 1–3; Doubtful: 0.
Author to add a footnote tah explains the significnace f the undrlines terms in Table 2

The ustekinumab datasheet[3] lists various adverse effects related to the immune system, such as rash, urticaria, anaphylaxis and angioedema, but BP is not described. However, in the EudraVigilance EMA database, 13 cases of pemphigoid associated with ustekinumab have been reported,[10] but only three have been published in the literature.[11–13]

Ustekinumab blocks the differentiation and clonal expression of Th1 and Th17 effector cells. This results in reduced production of pro-inflammatory cytokines, including TNF-α6 agents. Le Guern *et al*[12] suggested that modification of the immune response could cause the onset of BP, although the mechanism is not yet understood.

BP treatment depends on the location of the lesions. The published literature suggests different guidelines for clinicians to follow. Several authors have established that the risk of morbidity with the disease is low when lesions only appear in the oral mucosa or skin. Consequently the first-line therapy indicated is treatment with topical or systemic corticosteroids. However, if there is also skin involvement, or when patients do not improve

Table 3 WHO–UMC causality categories

Assessment criteria	Causality term
Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognised pharmacological phenomenon) Rechallenge satisfactory, if necessary	Certain
Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required	Probable/Likely
Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear	Possible
Event or laboratory test abnormality More data for proper assessment needed, or Additional data under examination	Conditional/Unclassified
Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations	Unlikely
Report suggesting an adverse reaction Cannot be judged because information is insufficient or contradictory Data cannot be supplemented or verified	Unassessable/Unclassifiable

with the usual treatments, dapsone (50–200 mg/day) is usually prescribed. Moreover, it is often necessary to prescribe inmunosuppressive agents such as cyclophosphamide or azathioprine.[14]

The relationship between biological agents and autoimmune blistering diseases is controversial because it is well known that psoriasis and bullous diseases occasionally coexist.[8] Although the exact relationship is uncertain, it is notable that all the reported BP cases, including this one, have a history of anti-TNF-α treatment.

In conclusion, based on available clinical data, the literature review and application of causality analyses, a causal relationship between the administration of ustekimumab and BP is probable. Knowledge of the possible appearance of BP associated with this treatment allows early recognition of the causality and subsequent management of patients. It is important to highlight the importance of knowing the adverse effects of widely used drugs. Special caution should be exercised in elderly patients, who are more sensitive to drug-related adverse events. Cooperation between physicians and pharmacists is useful in detecting and reporting adverse events, and promotes the safe use of medicines.

Learning points

- The possibility of autoimmune blistering diseases such as bullous penphigoid (BP) during usekinumab treatment must be taken in to account.
- The association between ustekinumab and BP was classified as *probable* by the Naranjo adverse drug reaction probability scale, Karch–Lasagna algorithm and WHO–UMC systems.
- Its appearance can be delayed after treatment commencement (from months to years), and there is a clear clinical improvement after drug withdrawal, and with systemic and topical corticosteroids and dapsone.
- Cooperation between clinicians and pharmacists is useful in detecting and reporting adverse events, and promotes the safe use of medicines.

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REFERENCES

1 Stavropoulos PG, Soura E, Antoniou C. Drug-induced pemphigoid: a review of the literature. *J Eur Acad Dermatol Venereol* 2014;28:1133–40.
2 Tan CWX, Pang Y, Sim B, *et al*. The association between drugs and bullous pemphigoid. *Br J Dermatol* 2017;176:549–51.
3 European Commission. Stelara data-sheet. Available: https://ec.europa.eu/health/documents/communityregister/2016/20160715135582/anx_135582_es.pdf [Accessed 8 Dec 2018].
4 Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
5 Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther* 1977;21:247–54.
6 World Health Organization. WHO-UMC. Available: http://www. who. int/ en/ [Accessed 8 Dec 2018].
7 Bordignon M, Belloni-Fortina A, Pigozzi B, *et al*. Bullous pemphigoid during long-term TNF-alpha blocker therapy. *Dermatology* 2009;219:357–8.
8 Kluk J, Goulding JMR, Bhat J, *et al*. Drug-induced bullous pemphigoid: cases triggered by intravenous iodine and etanercept. *Clin Exp Dermatol* 2011;36:871–3.
9 Toosi S, Bystryn J-C. Does adalimumab cause bullous pemphigoid? *Clin Exp Dermatol* 2010;35.
10 European Medicines Agency. EudraVIgilance. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5 [Accessed 8 Dec 2018].
11 Nakayama C, Fujita Y, Watanabe M, *et al*. Development of bullous pemphigoid during treatment of psoriatic onycho-pachydermo periostitis with ustekinumab. *J Dermatol* 2015;42:996–8.
12 Le Guern A, Alkeraye S, Vermersch-Langlin A, *et al*. Bullous pemphigoid during ustekinumab therapy. *JAAD Case Rep* 2015;1:359–60.
13 Onsun N, Sallahoglu K, Dizman D, *et al*. Bullous pemphigoid during ustekinumab therapy in a psoriatic patient. *Eur J Dermatol* 2017;27:81–2.
14 España A, del Olmo J, Marquina M, *et al*. [Mucous membrane pemphigoid: clinical manifestations and treatment with corticosteroids, dapsone and cyclophosphamide in 5 patients]. *Actas Dermosifiliogr* 2005;96:357–464.