

Dermatology 2009;219:357–358

DOI: [10.1159/000243805](https://doi.org/10.1159/000243805)**Bullous Pemphigoid during Long-Term TNF- $\alpha$  Blocker Therapy**Matteo Bordignon<sup>a</sup>, Anna Belloni-Fortina<sup>a</sup>, Barbara Pigozzi<sup>b</sup>, Marco Tarantello<sup>a</sup>, Mauro Alaibac<sup>a</sup><sup>a</sup>Unit of Dermatology, University of Padua, and<sup>b</sup>Veneto Institute of Oncology, IRCCS, Padua, Italy*Key Words*

Adverse drug reaction • Bullous pemphigoid • Etanercept • Tumor necrosis factor

Anti-TNF- $\alpha$  therapy has been reported to be effective in treating various inflammatory diseases, notably rheumatoid arthritis, psoriasis, and psoriatic arthritis. Three different agents have been developed to neutralize TNF- $\alpha$  activity: two are neutralizing antibodies (infliximab and adalimumab) and one is a fusion protein of TNF- $\alpha$  receptor (etanercept) [1].

With increasing use and longer follow-up periods of treatment, a new spectrum of adverse events are emerging, including infections, an increased risk of cancer and lymphoma, demyelinating disorders and cardiovascular diseases [1, 2]. There have also been several reports of autoimmune processes related to TNF- $\alpha$ -targeted therapies, ranging from asymptomatic immunologic alterations to life-threatening systemic autoimmune diseases [3].

Bullous pemphigoid (BP) is a blistering skin disease characterized by an autoimmune response to 2 hemidesmosomal proteins within the dermal-epidermal junction, designated BP180 and BP230. Recently, anti-TNF- $\alpha$  agents have been proposed for the treatment of autoimmune blistering disorders including pemphigus and pemphigoid [4–13]. Here, we report a case of BP during long-term treatment of rheumatoid arthritis with the TNF- $\alpha$  blocker etanercept.

In 2007, a 65-year-old Caucasian woman with a 30-year history of rheumatoid arthritis was referred to our Dermatology Unit for evaluation of a blistering disease involving the trunk, upper and lower limbs and oral mucosa. The patient had been under treatment with etanercept, 25 mg twice weekly for more than 2 years with good control of disease activity without taking any other drugs. She had no clinical or laboratory evidence of other autoimmune disorders. Using an ELISA approach we detected the presence of circulating autoantibodies against BP180 antigen (index value 37.28; normal range <9). The diagnosis of BP was confirmed by direct immunofluorescence. We stopped therapy with etanercept and excluded the presence of an associated systemic

disease by hemochemical and instrumental (computed tomography scan) evaluations. The patient was treated with oral steroid and methotrexate and after 2 months of therapy she was in complete remission. After 1.5 years of follow-up the patient is still in clinical and serological remission (ELISA index value 4.85).

In this article we have shown that long-term treatment with etanercept for rheumatoid arthritis can be associated with the development of BP. BP has been reported in association with rheumatoid arthritis [14], and, although rare, this association may be more than coincidental. Nevertheless, the development in our patient of BP during long-term treatment with etanercept and, moreover, the clinical and serological remission observed after suspension of the biological therapy support a possible etiologic relationship between BP and etanercept treatment. In this regard, Daulat et al. [15] have recently described a case of pemphigus vulgaris during treatment of psoriasis with etanercept. The condition disappeared when treatment with etanercept was discontinued and reappeared when the treatment was repeated using the same biological agent, which clearly indicates an etiologic relationship between pemphigus vulgaris and the biological drug.

Although the triggering role of etanercept remains unclear, we cannot exclude the possibility that etanercept could be an immunological trigger for autoimmune disorders, perhaps in constitutionally predisposed individuals. Thus, down-regulation of TNF- $\alpha$  by etanercept may indeed have led to development of BP in our patient. The possibility of an autoimmune cutaneous bullous disease should also be considered when managing patients under treatment with other biological agents, as triggering of BP has been described in association with efalizumab, a humanized monoclonal antibody against CD11a [16].

In conclusion, we report a case of BP observed during long-term treatment with the TNF- $\alpha$  blocker etanercept. The onset of BP in our patient may have been coincidental, nonetheless this case should alert clinicians prescribing etanercept to the possibility of the emergence of new autoimmune diseases during this therapy. Moreover, our observation indicates that caution should be exercised when considering the use of TNF- $\alpha$  blockers for treatment of autoimmune blistering disorders.

*References*

- 1 Lin J, Ziring D, Desai S, Kim S, Wong M, Korin Y, et al: TNF $\alpha$  blockade in human diseases: an overview of efficacy and safety. *Clin Immunol* 2008;126:13–30.
- 2 Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V: Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275–2285.
- 3 Ramos-Casals M, Brito-Zeron P, Muñoz S, Soria N, Galiana D, et al: Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)* 2007;86:242–251.

- 4 Sacher C, Rubbert A, König C, Scharffetter-Kochanek K, Krieg T, Hunzelmann N: Treatment of recalcitrant cicatricial pemphigoid with the tumor necrosis factor alpha antagonist etanercept. *J Am Acad Dermatol* 2002;46:113–115.
- 5 Berookhim B, Fischer HD, Weinberg JM: Treatment of recalcitrant pemphigus vulgaris with the tumor necrosis factor alpha antagonist etanercept. *Cutis* 2004;74:245–247.
- 6 Lin MH, Hsu CK, Lee JY: Successful treatment of recalcitrant pemphigus vulgaris and pemphigus vegetans with etanercept and carbon dioxide laser. *Arch Dermatol* 2005;141:680–682.
- 7 Jacobi A, Shuler G, Hertl M: Rapid control of therapy-refractory pemphigus vulgaris by treatment with the tumour necrosis factor-alpha inhibitor infliximab. *Br J Dermatol* 2005;153:448–449.
- 8 Pardo J, Mercader P, Mahiques L, Sanchez-Carazo JL, Oliver V, Fortea JM: Infliximab in the management of severe pemphigus vulgaris. *Br J Dermatol* 2005;153:222–223.
- 9 Yamauchi PS, Lowe NJ, Gindi V: Treatment of coexisting bullous pemphigoid and psoriasis with the tumor necrosis factor antagonist etanercept. *J Am Acad Dermatol* 2006;54:S121–S122.
- 10 Canizares MJ, Smith DI, Connors MS, Maverick KJ, Heffernan MP: Successful treatment of mucous membrane pemphigoid with etanercept in 3 patients. *Arch Dermatol* 2006;142:1457–1461.
- 11 John H, Whallett A, Quinlan M: Successful biologic treatment of ocular mucous membrane pemphigoid with anti-TNF-alpha. *Eye* 2007;21:1434–1435.
- 12 Prey S, Robert PY, Drouet M, Sparsa A, Roux C, Bonnetblanc JM, Bédane C: Treatment of ocular cicatricial pemphigoid with the tumour necrosis factor alpha antagonist etanercept. *Acta Derm Venereol* 2007;87:74–75.
- 13 Saraceno R, Citarella L, Spallone G, Chimenti S: A biological approach in a patient with psoriasis and bullous pemphigoid associated with losartan therapy. *Clin Exp Dermatol* 2008;33:154–155.
- 14 Hsu VM, Krey PR, Schwartz RA: Bullous pemphigoid and rheumatoid arthritis. *Cutis* 1989;43:30–32.
- 15 Daulat S, Detweiler JG, Pandya AG: Development of pemphigus vulgaris in a patient with psoriasis treated with etanercept. *J Eur Acad Dermatol Venereol* 2009;23:483–484.
- 16 Monnier-Murina K, Du Thanh A, Merlet-Albran S, Guillot B, Dereure O: Bullous pemphigoid occurring during efalizumab treatment for psoriasis: a paradoxical auto-immune reaction? *Dermatology* 2009;219:89–90.

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