



ACTAS Derma-Sifiliográficas

Full English text available at
www.actasdermo.org



RESIDENT'S FORUM

Doxycycline, a Well-Tolerated, Economic, and Effective Alternative for the First-Line Treatment of Bullous Pemphigoid[☆]



Doxiciclina, una alternativa efectiva, bien tolerada y de bajo coste como tratamiento de primera línea del penfigoide ampuloso

D. Morgado-Carrasco, C. Riquelme-Mc Loughlin, X. Fustà-Novell, P. Iranzo*

Dermatology Department, Hospital Clínic de Barcelona, Barcelona, España

KEYWORDS

Bullous pemphigoid;
Blistering diseases;
Tetracyclines;
Doxycycline;
Therapy

PALABRAS CLAVE

Penfigoide ampuloso;
Enfermedades ampulosas;
Tetraciclinas;
Doxiciclina;
Tratamiento

Bullous pemphigoid is the most common autoimmune blistering disease and one that is associated with high morbidity and mortality. Treatment can be complicated by advanced age, comorbidities, and cognitive and/or physical limitations of the patients. Traditionally, oral

corticosteroids have been used at doses of 0.5-1.5 mg/kg, but it has been shown that high-potency topical corticosteroids (HPTCs) applied over the entire body have a similar effectiveness with fewer side effects,¹ and so these are recommended as first-line treatment of bullous pemphigoid.² However, use of these agents can be difficult due to lack of therapeutic adherence given the patient characteristics, logistic constraints, and adverse effects associated with systemic absorption. Among other treatment alternatives, tetracyclines have been widely used for treatment of bullous pemphigoid, thanks to their anti-inflammatory effect (Table 1), low cost, and good tolerability; however, robust evidence of their efficacy has not been available.

Recently, Williams et al.⁴ published the results of a randomized noninferiority clinical trial (defining an effectiveness margin of 37% as acceptable) comparing doxycycline (200 mg/day, 132 patients) with prednisolone (0.5 mg/kg/day, 121 patients). Both groups were allowed to apply HPTCs to cutaneous lesions only, without exceeding 30 g/week, for the first 3 weeks. The mean age of the patients was 77 years and 68% had moderate or severe bullous pemphigoid. The main outcome measures were effectiveness at 6 weeks, where effectiveness was defined as having ≤ 3 blisters, and safety, determined by severe adverse effects at 52 weeks. In the doxycycline group, 74% achieved total control of bullous pemphigoid at 6 weeks compared with 91% in the prednisolone group (adjusted difference of 18.6% [90% CI: 11.1%-26.1%]), enabling the conclusion to be drawn that doxycycline was not inferior to prednisolone. Severe adverse effects were reported in 18%

[☆] Please cite this article as: Morgado-Carrasco D, Riquelme-Mc Loughlin C, Fustà-Novell X, Iranzo P. Doxiciclina, una alternativa efectiva, bien tolerada y de bajo coste como tratamiento de primera línea del penfigoide ampuloso. Actas Dermosifiliogr. 2018;109:549–550.

* Corresponding author.

E-mail address: piranzo@clinic.cat (P. Iranzo).

Table 1 Tetracyclines in the Treatment of Bullous Pemphigoid.

<i>Possible mechanism of action</i>	Inhibition of chemotaxis and neutrophil migration, and indirect inhibition of neutrophil elastase Decrease in T-cell, mast cell, and eosinophil activation and proliferation Inhibition of phospholipase A ₂ and proinflammatory cytokines Inhibition of metalloproteinases Increased collagen production (proanabolic effect)
<i>Precautions</i>	
Cutaneous adverse effects	Dose-dependent phototoxicity, onycholysis
Special populations	Not recommended in pregnancy (FDA category D) Do not use in children under 8 years of age, it can cause permanent tooth decoloration

Source: Monk et al.³

of the doxycycline group and 36% of the prednisolone group, including 3 and 11 treatment-related deaths, respectively. The recurrence rate was similar in both groups, as well as the decrease in Dermatology Quality of Life Index. Both treatments were less effective in patients with severe disease, and the use of topical corticosteroids was greater in the doxycycline group.

Despite doubts about whether the 37% limit for noninferiority of doxycycline treatment is acceptable (this limit was based on a survey of dermatologists in the United Kingdom, in which the specialists responded that they would accept up to a 25% reduction in the effectiveness of treatment provided it was accompanied by a reduction in adverse effects⁴), the study shows that doxycycline is highly effective, and allows adequate disease control with fewer side effects and deaths than with oral corticosteroids. Moreover, in the cost-effectiveness analysis of this study, no significant differences were found between the cost of treatment with doxycycline and with prednisolone.⁵

In view of the above results, we consider a reasonable therapeutic alternative is to initiate treatment for bullous pemphigoid with doxycycline and HPTC limited to cutaneous lesions, and initiate oral corticosteroids in the event of therapeutic failure.

References

1. Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med.* 2002;346:321–7.
2. Feliciani C, Joly P, Jonkman MF, Zambruno G, Zillikens D, Ioannides D, et al. Management of bullous pemphigoid: The European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. *Br J Dermatol.* 2015;172:867–77.
3. Monk E, Shalita A, Siegel DM. Clinical applications of non-antimicrobial tetracyclines in dermatology. *Pharmacol Res.* 2011;63:130–45.
4. Williams HC, Wojnarowska F, Kirtschig G, Mason J, Godec TR, Schmidt E, et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: A pragmatic, non-inferiority, randomised controlled trial. *Lancet Lond Engl.* 2017;389(10079):1630–8.
5. Chalmers JR, Wojnarowska F, Kirtschig G, Mason J, Childs M, Whitham D, et al. A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200mg/day) with that of oral prednisolone (0.5mg/kg/day) for initial treatment of bullous pemphigoid: the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial. *Health Technol Assess.* 2017;21:1–90.