



Allergologia et immunopathologia

www.elsevier.es/ai



ORIGINAL ARTICLE

Efficacy and safety of azathioprine and dapsone as an adjuvant in the treatment of bullous pemphigoid

A. Tirado-Sánchez*, V. Díaz-Molina, R.M. Ponce-Olivera

Servicio de Dermatología, Hospital General de México, Mexico City, Mexico

Received 12 October 2010; accepted 23 December 2010

Available online 14 April 2011

KEYWORDS

Adjuvant;
Azathioprine;
Bullous pemphigoid;
Dapsone;
Treatment

Summary

Background: Bullous pemphigoid is a chronic, blistering and autoimmune disease, common in old age. The treatment usually includes systemic steroids, however, these cause high morbidity rates, and then different products that function as adjuvants have been tried. At present, there are no studies to determine which adjuvant offers a better efficacy and safety profile.

Methods: We performed a retrospective study which included the records of patients with bullous pemphigoid, treated either with azathioprine or dapsone. We evaluated the time to achieve complete remission, the time to inhibit disease progression, and the control of pruritus.

Results: Fifteen records of patients were selected, eight (53%) treated with azathioprine and seven (47%) with dapsone. Complete remission was achieved at week six in both groups. We found no difference in the inhibition of disease progression ($p=0.083$). Pruritus was controlled at four weeks of treatment in both treatments.

Conclusions: Both products are effective as adjuvant in the treatment of bullous pemphigoid, with an acceptable safety profile.

© 2010 SEICAP. Published by Elsevier España, S.L. All rights reserved.

Introduction

Bullous pemphigoid (BP) is an autoimmune disease, characterised by subepidermal blistering. The disease usually presents in elderly patients. Bullous pemphigoid rarely affects the mucous membranes and is associated with substantial morbidity. The disease express autoantibodies directed against cutaneous autoantigens, BP230 and BP180,

called antigen 1 and 2 of BP respectively, both located in the hemidesmosome and anchoring filaments.¹

The treatment of choice are systemic steroids, like prednisone, at the dose of 0.5–0.75 mg/kg/day,^{1,2} however, class I topical steroids are preferred in localised forms.³ Systemic steroids improve patients' survival in BP, but also increase the risk of death and life-threatening adverse events.⁴ Other immunosupresant drugs, called adjuvants, have been widely used to treat autoimmune diseases (e.g. Pemphigus vulgaris) to achieve a corticosteroid-sparing effect.^{3,4} The most frequently used agent is azathioprine, while dapsone is another effective option. Therefore we decided to conduct a retrospective study to evaluate

* Corresponding author.

E-mail address: atsdermahgm@gmail.com (A. Tirado-Sánchez).

Table 1 Demographic and clinical data of the sample.

Variable	Group (n = 15)	
	Azathioprine (n = 8)	Dapsone (n = 7)
Age (years) \pm SD	65.36 \pm 6.69	
Gender (Male) (%)	66.4 \pm 7.83 5 (62)	64.2 \pm 5.38 4 (57)
BSA \pm SD	26.2 \pm 4.85	
Duration of the disease (months) \pm SD	24.65 \pm 6.13 5 \pm 2.38	28.22 \pm 2.64 5.86 \pm 1.35

BSA = Body surface affected.

the effectiveness and safety of azathioprine and dapsone in BP.

Material and methods

We selected the records of the patients with BP, diagnosed by clinical (lesions suggestive of BP), histological (subepidermal blister) and/or immunological criteria (linear deposition of IgG and/or C3 at the dermoepidermal junction), admitted at the Department of Dermatology, General Hospital of Mexico, in the period from January 2006 to January 2010. All patients had received prednisone 0.5–0.75 mg/kg/day in combination with either azathioprine (group 1, 2–3 mg/kg/day) or dapsone (group 2, 100 mg/day).

The primary outcome measure was the complete remission, defined as the complete reepithelialisation of all lesions. The secondary outcome measure was the inhibition of disease progression, defined as the time where no new lesions appear, and the control of pruritus.

Results from routine laboratory tests performed each week were obtained (complete blood count, liver function tests), as well as the daily records of blood pressure, heart and respiratory rates. The extent and location of the blisters were recorded. Drugs adverse events were classified as mild, moderate or severe and those that could endanger life.

Statistical analysis

We perform a Wilcoxon test to evaluate the primary outcome measure. Dichotomous and ordered categorical data were analysed with the Fisher exact and the Mann Whitney test respectively. The analysis was conducted using the statistical program SPSS (version 12 for Windows, Chicago, Ill., USA).

Results

Baseline

We selected 15 records of patients with BP, eight (53%) with azathioprine and seven (47%) with dapsone (demographic and clinical data of the sample are presented in Table 1). All patients represented newly diagnosis BP cases. The mean age was 65.36 \pm 6.69 years. The approximate body surface affected (BSA) was 26.2 \pm 4.85% (the calculation was made

based on the rule of nine). In group 1 (azathioprine), the mean age was 66.4 \pm 7.83 years, with BSA of 24.65 \pm 6.13%, while in the dapsone group, the average age was 64.2 \pm 5.38 years and 28.22 \pm 2.64% of BSA.

Monitoring

The complete remission (reepithelialisation of all lesions) was achieved by six weeks of both treatment groups (Fig. 1). However, disease progression was inhibited firstly in azathioprine group by around week two, and week three in dapsone group ($p=0.083$). Pruritus was controlled at week four in both treatments. No deaths were reported in the eight weeks of follow up.

Adverse events reported were: for azathioprine, vertigo (2/5, 40%), gastric intolerance (1/5, 20%), while for the group with dapsone, they were abnormal liver function tests (3/5, 60%). In one patient (dapsone group), it was necessary to discontinue the immunosuppressant medication dose and begin treatment with systemic steroid as monotherapy. Adverse events did not require additional treatment.

Discussion

Bullous pemphigoid is a chronic, autoimmune, bullous disease, most commonly seen in the elderly.^{5,6} The incidence

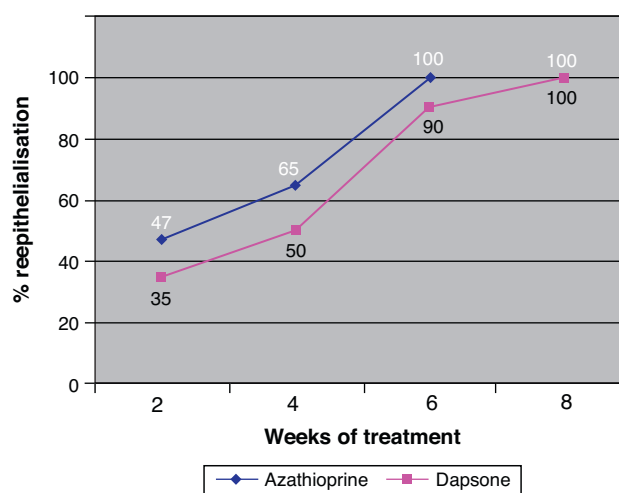


Figure 1 Percentage of reepithelialisation of the lesions in the patients studied.

does not vary among male and female.⁷ Bullous pemphigoid represents one of the most common subepidermal autoimmune blistering diseases. Patients generally exhibit disseminated lesions consisting in tense blisters, variable in number and size, accompanied by moderate to severe pruritus, often with erythematous or urticarial lesions that may precede the blister, and subsequently accompanied by erosions and pigmented lesions. It rarely affects the mucous membranes.⁸ The disease results from autoantibodies directed against cutaneous autoantigens at the dermoepidermal junction (BP180 and BP230). The antigen-antibody complex activates the complement cascade, resulting in the recruitment of eosinophils and neutrophils.⁵ Thus, on histology, there is a subepidermal blister with mixed inflammatory infiltrate rich in eosinophils. Direct immunofluorescence shows linear deposits of IgG and C3 along the basement membrane, while indirect immunofluorescence showed circulating antibodies (salt-split pattern). Bullous pemphigoid is potentially associated with substantial morbidity and even mortality. The mortality ranges from 25 to 40% during the first year. Risk factors of mortality identified are: elderly, female gender, concomitant diseases (cardiovascular disease, liver disorders, chronic lung disease, neuropsychiatric disorders, and diabetes mellitus, and malignancy, urological and endocrine disorders) and low Karnofsky (≤ 40).⁶

The selection of treatment options is based more on clinical experience than in controlled studies,⁸ and includes many drugs. The treatments of choice are topical/systemic corticosteroids; however, systemic antibiotics (like tetracycline) and systemic immunosuppressant are needed. Systemic corticosteroids have been considered the standard and the best-validated treatment,^{6,8} and have been used alone or combined. The recommended dose of systemic corticosteroid (prednisone) is 0.75 mg/kg/day (with ranges 0.3–1.25 mg/kg/day)⁸ until disease control and then reduce and keeping the adjuvant. Since complications related to the use of oral corticosteroids may contribute to the prognosis of patients with BP, more studies, which evaluate other treatment options are needed. Topical high-potency steroid like clobetasol propionate has also been studied, and is found to be useful in the control of localised and disseminated BP without increasing mortality, but it should be noted that the use of topical corticosteroids over large areas of body surface area (≥ 40 g/dia) can lead to epidermal atrophy and also determines drug absorption, and inducing systemic effects of the drug.⁸

Numerous studies suggest that the adjuvant use of immunosuppressant shows some steroid-sparing effect, thereby helping to reduce the total dose of systemic corticosteroid that the patient needs in order to control the disease. These drugs are azathioprine and dapsone, commonly used in our practice for this purpose. Azathioprine is an antimetabolite, a synthetic analogue of purine derivative of 6-mercaptopurine, used in the treatment of several skin diseases.^{9,10} It is the most frequently used adjuvant in the treatment of BP, at doses ranging from 1 to 3 mg/kg.^{8,9,11} The steroid-sparing effect of azathioprine has been reported.⁹ It is generally well tolerated; the most common side effect is myelosuppression, other adverse effects are gastrointestinal disturbances (nausea, diarrhoea), dizziness, alopecia, hepatotoxicity, increased incidence of malignancy in patients after kidney trans-

plantation, and opportunistic infections.^{9–11} The optimal therapeutic response occurs between 6 and 8 weeks; if no response were observed by week 12–16, the drug should be changed for another immunosuppressant.¹¹

Dapsone is a drug used primarily in the treatment of leprosy, pneumonia by *Pneumocystis jiroveci* and malaria, but has also been used in autoimmune bullous diseases for its steroid-sparing effect. In BP, it is reported an efficacy rate close to 84%, either alone or in combined therapy with systemic corticosteroids or another immunosuppressant. The most common adverse events of dapsone are haemolysis and secondary anaemia.¹² Other adverse events reported are methaemoglobinemia, nausea, vomiting, peripheral neuropathy, elevated transaminases, and cutaneous drug reactions.¹⁰

In our study, we found no difference in the effectiveness in the inhibition of disease progression ($p=0.083$), and in achieve disease control.

In accordance with the literature reviewed, the disease was more common in older adults. The most frequently observed adverse event was dizziness for azathioprine (40%) and impaired liver function test for dapsone (60%), whereas in the literature, haematological disorders are the most frequently reported for both drugs. Our patients responded well to treatment in both groups and no deaths were reported up to eight weeks.

Azathioprine is the most studied adjuvant and is used successfully in the treatment of autoimmune blistering diseases, being particularly important in the treatment of bullous pemphigoid. In addition, dapsone is a promising agent, useful in treating patients with bullous diseases of autoimmune aetiology, including BP. Adverse events of dapsone are dose dependent and usually reversible.

We recommend the use of an immunosuppressive agent at the beginning of the treatment. Both immunosuppressants are equally effective to inhibit disease progression and to induce reepithelialisation of all lesions at eight weeks of follow up. Both have an acceptable safety profile at eight weeks of treatment. More studies to evaluate these two drugs at longer term treatments are needed.

Conflicts of interest

The authors have no conflict of interest to declare.

References

1. Patrício P, Ferreira C, Gomes MM, Filipe P. Autoimmune bullous dermatoses: a review. *Ann N Y Acad Sci.* 2009;1173:203–10.
2. Cunha PR, Barraviera SR. Autoimmune bullous dermatoses. *An Bras Dermatol.* 2009;84:111–24.
3. Joly P, Roujeau JC, Benichou J, Delaporte E, D'Incan M, Dreno B, et al. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. *J Invest Dermatol.* 2009;129:1681–7.
4. Suárez-Fernández R, España-Alonso A, Herrero-González JE, Mascaró-Galy JM. Practical management of the most common autoimmune bullous diseases. *Actas Dermosifiliogr.* 2008;99:441–55.
5. Mutasim DF, Bilic M, Hawayek LH, Pipitone MA, Sluzevich JC. Immunobullous diseases. *J Am Acad Dermatol.* 2005;52:1029–43.

6. Joly P, Benichou J, Lok C, Hellot MF, Saiag P, Tancrede-Bohin E, et al. Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol*. 2005;141:691–8.
7. Khumalo NP, Murrell DF, Wojnarowska F, Kirtschig G. A systematic review of treatments for bullous pemphigoid. *Arch Dermatol*. 2002;138:385–9.
8. Beissert S, Werfel T, Frieling U, Böhm M, Sticherling M, Stadler R, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol*. 2007;143:1536–42.
9. Patel AA, Swerlick RA, McCall CO. Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol*. 2006;55:369–89.
10. Mutasim DF. Management of autoimmune bullous diseases: pharmacology and therapeutics. *J Am Acad Dermatol*. 2004;51:859–77.
11. Kazlow Stern D, Tripp JM, Ho VC, Lebwohl M. The use of systemic immune moderators in dermatology: an update. *Dermatol Clin*. 2005;23:259–300.
12. Gürcan HM, Ahmed AR. Efficacy of dapsone in the treatment of pemphigus and pemphigoid: analysis of current data. *Am J Clin Dermatol*. 2009;10:383–96.