

Successful full clinical remission of bullous pemphigoid with intravenous pulse methylprednisolone and cyclophosphamide: a case report.

Dimitrios Varytimiadis¹, Elena Sotiriou¹, Anastasia Trigoni², Dimitrios Ioannides¹

¹First Department of Dermatology-Venereology, 124 Delfon str., Aristotle University Medical School, Thessaloniki, Greece

²State Hospital for Skin and Venereal Diseases, Thessaloniki, Greece

ABSTRACT: We report a case of a 73 year old man with generalized bullous pemphigoid (BP). Oral steroid therapy was contr-indicated due to his personal medical history. The patient was treated with intravenous methylprednisolone pulse therapy (I.M.P.T.) followed by oral cyclophosphamide with satisfactory results. The therapeutic challenges of BP are being discussed with emphasis given on intravenous methylprednisolone pulse therapy.

Key Words: Bullous pemphigoid, Treatment, Methylprednisolone, Cyclophosphamide.

INTRODUCTION

Bullus pemphigoid (BP) represents the most frequent autoimmune blistering disease in Europe. It typically affects the elderly and is associated with a significant morbidity and mortality. The disorder is characterized by autoantibodies directed against BP180 (collagen type XVII, BPAg2) and less often BP230 (BPAg1). Recent studies have revealed that eventual blister formation is the result of multiple complex interactions involving autoantibody binding and complement activation leading to activation of cells such as neutrophils, eosinophils, and mast cells. Disease presentation may be limited to a localized form or may present with a widespread, generalized blistering eruption. As a result, treatment of BP depends greatly on the extent of disease as well as patient comorbidities. First-line treatments are typically general immunosuppressives¹⁻⁷. More extensive disease is usually treated with oral prednisone, which is the mainstay of therapy. Although the optimal dosing and formulation of systemic corticosteroid therapy remains unclear,

the complications of such therapy (including osteoporosis, diabetes, hypertension, cataracts, glaucoma, and systemic infection) are well documented and may be severe, particularly in the elderly with co-morbidities. Therefore, it is important to minimize the total dose and duration of therapy with oral glucocorticoids.⁸⁻⁹ The addition of steroid-sparing agents may facilitate tapering of systemic corticosteroids and help to minimize corticosteroid-associated adverse events.

CASE REPORT

A 73-year-old man was referred to our clinic with a generalized pruritic bullus eruption. The eruption, that had first presented 2 months ago, was multiforme and consisted of tense, bullae, 3-5 cm in diameter, on erythematous skin as well as of eroded and crusted lesions localized on the trunk, abdomen, chest, upper and lower extremities, thighs and scalp.

According to his medical history the patient was also suffering from glaucoma, cataract, diabetes mellitus and duodenal ulcer.

Diagnosis of BP was based on clinical and histopathologic criteria as well as on findings from direct and indirect immunofluorescence.

Histological examination revealed subepidermal blister with a dermal inflammatory infiltrate composed predominantly of eosinophils and neutrophils.

Direct immunofluorescence (DIF) examination characteristically showed continuous linear deposits of IgG along the epidermal basement membrane. The indirect immunofluorescence (IIF) study revealed circulating IgG autoantibodies typically binding to the epidermal side of salt-split normal human skin.

Clinical and laboratory investigation was unremarkable and revealed no further abnormalities.

Due to his medical history and in order to minimize the possibility of adverse events as well as to increase patients tolerability methylprednisolone pulse therapy was initiated.

Treatment cycle consisted of administration of methylprednisolone intravenously (15 mg/kg in 16 mL of bacteriostatic water over a period of 30-60 min/day)- for two consecutive days, followed by a five days rest period. Clinical examination, revealed eruption of a few new lesions localized on the trunk.

Sustained remission without eruption of new lesions was achieved after two treatment cycles. During the whole treatment period laboratory investigations was normal.

Complete remission and re-epithelialization with healing of all lesions was observed after four cycles of I.M.P.T.

Pulse intravenous methylprednisolone therapy was discontinued and treatment with cyclophosphamide, at the dose of 50 mg twice daily was initiated.

At a three weeks follow-up, his general condition was excellent with a total resolution of the pemphigoid lesions. Re-epithelialization and healing of all lesions was achieved, while no new lesions appeared.

Today, four months after discontinuation of intravenous methylprednisolone pulse therapy (I.M.P.T.) the patient remains free of new lesions, receiving only per os cyclophosphamide at a dosage of 50mg twice daily.

DISCUSSION

Bullous pemphigoid (BP), is the most common autoimmune blistering disease in Western countries.

The mortality rate in patients with BP is high, ranging from 10% to 40% after 1 year, possibly related to the advanced age of most patients, many of whom have multiple co-morbidities and/or an already altered general condition. The high doses of systemic steroids often used to treat this condition is also another factor contributing to the forementioned observed rate. Systemic corticosteroids are widely used in daily clinical practice, and their efficacy has been confirmed in uncontrolled and controlled studies. However, their use can be associated with significant side effects.

For patients with extensive disease, oral prednisone, at the dosage of 0.5 to 1 mg/kg/d, usually achieve control of the disease within 3 weeks. This dose is then progressively tapered over a period of 6 to 9 months¹⁰⁻¹³.

To minimize the iatrogenic effects of systemic corticosteroids, alternative therapies have been introduced such as immunosuppressive drugs (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil), gold, tetracyclines, dapsone, and intravenous immunoglobulins. The use of immunosuppressive drugs, such as azathioprine^{mycophenolate mofetil}, methotrexate, and, less frequently, chlorambucil and cyclophosphamide, is a matter of debate. Some clinicians introduce them only when corticosteroids alone fail to control the disease or if the latter are contraindicated. The choice of an immunosuppressive drug depends on the profile of its side effects, the patient's overall condition, the experience of the physician with the pharmaceutical agent, and finally, cost issues. Although mycophenolate mofetil, for example, is likely to have less hepatic side effects compared with azathioprine, the latter is much cheaper and may show a more rapid onset of action with a better corticosteroid-sparing effect. Dapsone, as well as the association of nicotinamide and minocycline or tetracycline, have also been tried alone or as adjuvant therapy with some success and may be helpful in mild disease. The experience with biological agents in BP, such as rituximab, is still anecdotal, but in certain situations, they likely represent the last therapeutic option available to try¹⁴⁻²¹.

Pulse therapy with steroids is reported to reduce the morbidity and mortality in pemphigus vulgaris. This treatment regimen was first described by Paricha et al²². Pulse therapy, *the big shot*, refers to the dis-

continuous intravenous infusion of very high doses of corticosteroids over a short time. Doses of each pulse are not standardized but are usually 500-1000 mg methylprednisolone or 100-200 mg dexamethasone. The number of pulses required to induce remission varies between patients. The aim of pulse therapy is to achieve a faster response and stronger efficacy and to decrease the need for long-term use of systemic corticosteroids. The reduction in daily steroid requirement following pulse therapy is a major advantage of this therapy. Although large doses of steroid are used in the pulse regime, it is clear that the route of administration of steroids is important in determining steroid related adverse effects, with intermittent intravenous methylprednisolone pulse therapy having a distinct pharmacological profile compared with moderate,

daily oral corticosteroids²³. There are only a few reports on the efficacy and safety of pulse therapy in BP treatment²⁴.

Based on these reports there seems to be no difference in efficacy in newly diagnosed and previously treated cases. It appears to be a good alternative to the standard continuous corticosteroid treatment.

In conclusion, pulse therapy with methylprednisolone for BP treatment is a cost-effective option although appropriate patient selection and rigid monitoring is essential in view of its toxicity profile. The optimum dosing regimen remains to be determined in a well conducted randomized controlled clinical trial, preferably in comparison to the mainstay treatment schema and with short and medium term safety outcomes included in the protocol analysis.

Επιτυχής αντιμετώπιση πομφολυγώδους πεμφιγοειδούς με συνδυασμό ενδοφλέβιας έγχυσης κατά ώσεις μεθυλπρεδνιζολόνης και από του στόματος χορήγηση κυκλοφωσφαμίδης. Παρουσίαση περιστατικού.

Δημήτριος Βαρυτιμιάδης¹, Έλενα Σωτηρίου¹, Αναστασία Τριγώνη², Δημήτριος Ιωαννίδης¹

¹Α' Πανεπιστημιακή Κλινική Δερματολογίας - Αφροδισιολογίας Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
²Νοσοκομείο Αφροδισίων και Δερματικών Νόσων Θεσσαλονίκης

ΠΕΡΙΛΗΨΗ: Παρουσιάζεται περίπτωση εκτεταμένου πομφολυγώδους πεμφιγοειδούς σε άντρα ηλικίας 73 ετών, που λόγω του ιατρικού του ιστορικού (καταρράκτης, γλαύκωμα, σακχαρώδης διαβήτης και έλκος δωδεκαδακτύλου), δεν μπορούσε να λάβει από του στόματος αγωγή με υψηλή δόσης στεροειδών. Η νόσος αντιμετωπίστηκε επιτυχώς με συνδυασμό ενδοφλέβιας έγχυσης κατά ώσεις μεθυλπρεδνιζολόνης και από του στόματος χορήγηση κυκλοφωσφαμίδης. Με την ευκαιρία του περιστατικού αναφέρονται συνοπτικά οι θεραπευτικές επιλογές για την αντιμετώπιση του πομφολυγώδους πεμφιγοειδούς και δίνεται ιδιαίτερη έμφαση στη μέθοδο έγχυσης μεθυλπρεδνιζολόνης κατά ώσεις.

Λέξεις Κλειδιά: Πομφολυγώδες πεμφιγοειδές, Θεραπεία, Μεθυλπρεδνιζολόνη, Κυκλοφωσφαμίδη.

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