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The Management of Oral Pemphigus Vulgaris with Systemic Corticosteroid and Dapsone

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Abstract

Background and aims. Oral pemphigus vulgaris is a chronic autoimmune mucocutaneous intraepithelial disease that primarily affects patients over the age of fifty, resulting in mucosal ulceration and is a potentially life-threatening disease. The purpose of this study was to investigate the efficacy of dapsone in combination with systemic corticosteroids to treat the oral lesions of oral pemphigus.

Materials and methods. Twenty patients diagnosed with oral pemphigus were selected. Oral manifestations were graded according to the severity of disease from 1 to 3. All patients were treated initially with systemic corticosteroids. Each was assigned to one of 4 groups according to their response to therapy. Patients who responded less than 50% healing of lesions began a trial of dapsone. After 4 weeks, signs and symptoms were recorded, and if a patient was lesion-free, the dapsone dosage was gradually tapered.

Results. Five patients with mild to moderate disease were treated with systemic corticosteroids alone. 15 patients with moderate to severe disease were treated with systemic corticosteroid and dapsone therapy. Of these, 10 patients had significant benefits, while 5 patients did not respond to dapsone adjuvant.

Conclusions. The use of dapsone in combination with systemic corticosteroids is a useful method for treatment of oral pemphigus.

***Key words*: Corticosteroid, dapsone, oral pemphigus.**

Introduction

Pemphigus vulgaris is a potentially life-threatening disease that causes blisters and erosions of the skin and mucous membranes. These epithelial lesions are the result of autoantibodies. The immune reaction against these autoantibodies primarily affects the mucous membranes of patients over the age of 50 years, resulting in the formation of intraepithelial bullae and mucosal ulceration.[1] These autoantibodies, usually of the IgG class, are directed against desmosal glycoproteins present on the cell surface of the keratinocyte. The specific protein target has been identified as desmoglein 3, one of the several proteins in the desmosomal cadherine family.[2]

Lesions of pemphigus present as painful ulcers preceded by bullae. The first sign of the disease appears in the oral mucosa in approximately 60% of cases and eighty to ninety percent of patients with pemphigus vulgaris

develop oral lesions sometime during the course of the disease. Bullae rapidly rupture, leaving a red painful ulcerated base. It is common for the oral lesions to be present up to 4 months before the skin lesions appear. If treatment is instituted during this time, the disease is easier to control, and the chance for an early remission of the disorder is enhanced.[1] The lesions of pemphigus vulgaris may involve any mucosal surface, but they most frequently involve the oral mucosa. Most commonly the lesions start on the buccal mucosa, often in areas of trauma along the occlusal plane. The palate and gingival are other common sites of involvemet.[1] The management of a patient with pemphigus is complicated by the chronic nature of the disease and the fact that affected individuals tend to be elderly and have multiple medical problems. In addition, there is the potential for patients with pemphigus vulgaris to develop severe complications. Several forms of therapy have been advocated for the management of oral lesions of pemphigus vulgaris. When the lesions are confined to the oral mucosa, systemic corticosteroids will suppress their formation, but the clinician must weigh the benefits against the hazard from side effects of the durg. Pemphigus is a fatal disease, and long-term use of steroids for this purpose must be carefully evaluated, particularly because most cases are chronic, most patients are elderly, and treatment is required for a long period of time. When steroids must be used for long periods of time, adjuvants such as immunosuppressive drugs, antimetabolites and dapsone are added to the regimen to reduce the complications of long-term corticosteroid therapy. Prednisone is used initially to bring the disease under control, so the clinicians should weigh the potential benefits of adding adjuvant therapy against the risks of additional complications such as blood dyscrasia and hepatitis. Dapsone has been in clinical use for almost 50 years. It is effective in a variety of infectious diseases, including malaria and leprosy.[3]

Dapsone also has anti-inflammatory properties. In this capacity, it has been used as a corticosteroid sparing drug to treat a number of diseases, including bullous pemphigoid, rheumatoid arthritis, and dermatitis herpetiformis.[4] In the previous studies, dapsone has shown promise in treating conjunctival, oral, and laryngeal lesions of mucous membrane pemphigoid and pemphigus.[5-9]

The purpose of this study was to investigate the efficacy of dapsone, when used in combination with systemic corticosteroids, to treat the oral lesions of pemphigus vulgaris.

Materials and Methods

Twenty patients referring to the Department of Oral Medicine, University of Jundishapur Ahwaz, Iran, from 2002 to 2005, subsequently diagnosed with pemphigus vulgaris were selected. Each patient included in this study fulfilled the following criteria: (1) the patient had oral mucosal ulcers, vesicles, or bulla; (2) a biopsy specimen was obtained for routine histologic analysis and demonstrated intraepithelial cleavage characteristic of pemphigus vulgaris observed by oral pathologist. Exclusion criteria included having any systemic or medical problems. These patients had only oral lesions and did not show any skin lesions. The clinical oral features and site involvement at the time of initial presentation were recorded. These features were then graded according to severity of the disease based on the classification used by Rogers & Mehregan in 1988.[6] Severity of each lesion was assigned a grade from 1 to 3; 1 representing mild, localized disease; 2 representing generalized desquamative gingivitis only; and 3 representing generalized severe disease (involvement of multiple sites). All patients were treated initially with systemic corticosteroids (prednisone 40 mg/day) according to Ciarrocca & Greenberg.[8] Prednisone was used for 4 weeks. When a patient had more than 50% healing of lesions, systemic therapy was reduced and tapered for another 4 weeks, after which the patient was re-evaluated. Those who responded minimally less than 50% healing of lesions to corticosteroid treatment began a trial of dapsone after glucose 6-phosphate dehydrogenase (G6PD) screen and baseline hemoglobin were taken. Patients continued to use corticosteroids after dapsone therapy was initiated. We began dapsone therapy at a low dosage gradually increasing it at 3-day intervals as outlined by Rogers & Mehregan.[6] Treatment lasted for 4 weeks: 25 mg daily for 7 days, 25 mg twice daily for 7 days, 25 mg 3 times daily for 7 days, and 50 mg twice daily for 7 days. Each patient, regardless of treatment modality, was assigned

to one of the following 4 groups according to his or her response to therapy: Complete resolution, substantial resolution (more than 75% improvement), partial resolution (more than 50% improvement), and no noticeable change. Resolution was defined as complete clearance of lesions and absence of clinical disease in oral cavity. At least two investigators determined the response to therapy at each visit.[6,7]

A complete blood count as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) tests were obtained at each visit preceding the initiation of dapsone therapy and then repeated at each of subsequent follow-ups. After 4 weeks of treatment, symptoms of patients were recorded. If a patient was lesion- free, the dapsone dosage was gradually tapered. The dosage was decreased by 25 mg/day for 1 week. If no new lesions developed, the taper was continued; however, if the patient developed new ulcerations, the dosage was increased by 25 mg/day at weekly intervals until the patient was once again lesion-free. After tapering the dose of dapsone for 4 weeks and the 3-month follow-up, no new lesion was seen; therefore, addition of dapsone to the treatment regime was not continued.

Results

A total of 20 patients including 15 women and 5 men (34 to 68 years old, mean age 52.6 years) were studied. 15 patients showed desquamative gingivitis, 18 had buccal mucosal lesions, 9 had palatal lesions, 14 had lip lesions, and 13 had tongue and floor of mouth lesions. Initial therapy for each of the 20 patients consisted of the use of systemic corticosteroids. Five patients with mild to moderate disease were treated with systemic corticosteroids alone (prednisone 40 mg/day) for the duration of the study; 1 of these 5 patients had complete resolution, 1 had more than 75% improvement, and 3 had more than 50% improvement. 15 patients with moderate to severe disease were treated initially with systemic corticosteroids, and since they had less than 50% improvement, dapsone therapy was then added to the regimen. 10 patients had significant benefits: 7 of 15 patients had complete resolution and 3 had more than 75% improvement. The remaining 5 patients who had less than 50% improvement continued with conventional treatment and were referred to a hospital center.

Discussion

Systemic corticosteroids have been the mainstay of treatment for pemphigus vulgaris. An immunosuppressive agent has also been used in some patients as a primary agent or as a supplement to systemic corticosteroids.[10] Dapsone, originally an anti-leprosy agent, has become a valuable therapeutic agent in many inflammatory diseases and is currently being used as the first line therapy for the treatment of dermatitis herpetiform (DH) and ocular pemphigoid.[11] It has also been found to be an effective adjunct to topical or systemic corticosteroid therapy in treatment of some vesiculobullous conditions, including mucous membrane pemphigoid (MMP) and pemphigus.[4]

The results of our study was in agreement with some of the previous studies.[5,12,13] López-Jornet & Bermejo-Fenoll[5] found that dapsone could decrease the signs and symptoms of pemphigus patients. Heaphy et al[12] reported that pemphigus lesions improved following corticosteroid and dapsone therapy. Yeh et al[13] showed that dapsone is a good treatment for oral pemphigus. However, it can induce hemolytic anemia.

Stoopler et al[14] stated that corticosteroid therapy is the best method for treatment of MMP and pemphigus and that immunosuppressive agents and dapsone can not be effective in resolving ulcerative lesions of pemphigoid and pemphigus. Our findings showed the contrary. The reason of this difference could be intolerance of patients in that research to dapsone. Dapsone has been used for nearly 50 years to treat infectious diseases such as leprosy and malaria, and its antimicrobial effects involves the inhibition of the conversion of para-aminobenzoic acid to folic acid. More recently, however, dapsone has been used to treat noninfectious inflammatory diseases characterized by neutrophil-rich infiltrates, though the mechanism of its anti-inflammatory action remains unclear. Dapsone appears to inhibit the migration of polymorphonuclear leukocytes (PMNs) by inhibiting lysosomal enzyme activity, interfering with the leukocyte cytotoxic system, or preventing the cells from responding to chemotactic stimuli. Clues to the mechanism of the anti-inflammatory action of dapsone are

available from studies of DH, a skin disease caused by sensitivity to the protein gluten. The skin lesions are characterized by patches of small, itchy blisters, usually found on the arms and back.[14,15] Dapsone as also been shown to suppress neutrophil migration by blocking integrin-mediated adherence function.[4] For neutrophils to be directed to an extravascular lesion, they must first adhere to vascular endothelial and then penetrate the vessel wall. On the basis of these theories, the effectiveness of dapsone in the treatment of MMP and pemphigus is better understood by reviewing the pathogenesis of the disease. The pathogenesis of the intraepithelial lesion of pemphigus is believed to be an intricate cascade of events characterized initially by antigen/antibody complexes at the intraepithelial zone.[16] This Complexity is followed by complement activation and elaboration of chemotactic factors, which attract PMNs to the area.[17] Dapsone blocks PMN migration, thereby preventing inflammation or new vesicle formation.[18] Dapsone toxicity can be categorized as either idiosyncratic or dose-dependent.[19] Long-term administration in normal patients may result in significant methemoglobinemia. Clinicians using dapsone must be familiar with its potential side effects.

Conclusion

Our study showed that systemic corticosteroid and dapsone can decrease signs and symptoms of pemphigus vulgaris.

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