Ocular autoimmune pemphigoid and cyclosporin A

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ABSTRACT

Background: Ocular pemphigoid is a chronic autoimmune disease that leads to vision lost. In its etiology participate autoantibodies against the connective tissue of the conjunctiva of different isotypes (IgM, IgG and IgA) as well as the complement system (C3). Lymphocytes of the CD4 + and CD8 + phenotypes and monocytes were detected in the infiltrates of the biopsies of the conjunctiva.

Material and methods. We treated and studied 82 patients who had several topical and systemic treatments during years to alleviate this condition but whose side effects limited their usefulness. We started the administration of cyclosporin-A (Cy-A) 100 mg/day per os and diminishing gradually the intake of steroids. The relief of ocular pain and headache were the first symptoms that changed the patients' quality of life. Ophtalmological controls revealed improvement of the lesions of the conjunctiva and cornea and subsequent biopsies showed a marked decrease in the cellular infiltrates and in antibody deposits.

Conclusions. Thus, Cy-A is an useful treatment for ocular chronic autoimmune pemphigoid and eventually azathioprine (50 mg/day) can cheaply replace it although its well-known toxicity.

Key words: Ocular pemphigoid. Autoantibodies. Cytotoxic cells. Cyclosporin A.

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INTRODUCTION

Ocular inflammatory diseases are well known since the paramount description of Charles Blackley (1820-1900) who suffered his catarrhus aestivus or rhinoconjunctivitis in the presence of pollen grains; in 1872 Morrill Wyman at Harvard defined this condition as hay fever and although sustained Blackley's findings considered that his description was preceding in time. The classical ocular allergic diseases are classified into four categories: atopic keratoconjunctivitis (AKC), acute allergic conjunctivitis (AAC), vernal keratoconjunctivitis (VKC) and giant papillary conjunctivitis (GPC). Bacterial, viral, fungal and parasitic infections of the conjunctiva as well as dry eye disorders can also present with a sign and symptom profile that could be confused with ocular allergy. Thus, the "red-eye" comprises 4 major aetiologies:allergic, infectious (both mentioned above), autoimmune (episcleritis, pemphigoid, uveitis and vasculitis) and non-specific (dry-eye syndrome, foreign body, acne rosacea and chemical induced). It is interesting to note that some patients who underwent a "chronic conjunctivitis" during several years without a clinical relapse and a successful treatment could be really subjected to an ocular pemphigoid that was not taken into account until the first corneal ulcer and the severe pain that exhausted the patient.[1-5].

PATHOGENESIS. IMMUNOLOGY AND HISTOPATHOLOGY

Although the AKC and the AAC are typical mast-cell mediated hypersensitivity reactions in which the allergen or allergens react with specific IgE bound to the RFcε-I of the conjunctival mast cells it also involves eosinophils and several chemical mediators and cytokines detected in tear samples. The histopathological findings of AKC are specific and include a mixture

of mast-cells, eosinophils and lymphocytes infiltrating the conjunctival epithelium. Flow cytometry revealed increased naive Th (CD4/45RO+RA–) and memory Th (CD4/29+) cells in the blood and tear samples. In situ hybridization studies of AKC ocular tissue that expressed increased levels of mRNA for IL-2, IL-3, IL-4 and IL-5 when compared with normal tissue[6-9]. Langerhans'cells (CD1a+) bearing IgE on their surfaces have also been shown to be involved in ocular inflammatory responses. In VKC and GPC up to 50 % of CD4+T-cells coexpress CD45RO and CD45RA. The late phase reaction manifested itself in several forms including a classic biphasic response, a multiphasic response and a single prolonged response. The histologic evaluation of the conjunctiva revealed the influx of inflammatory cells such as neutrophils, basophils and eosinophils during the first 6 hours after allergen challenge and monocytes and lymphocytes as well as endothelial cell swelling, capillary dilatation and edema later on. The roles of IL-4, IFN-γ and IL-12 in the early and late phases of ragweed ocular allergy have been assessed. It would appear that the presence of IL-12 although better known as a TH1-inducing cytokine is important for the development and regulation of the late-phase pathologic features in ocular allergy and autoimmunity. Impairment of the ocular epithelium over the conjunctiva and cornea appears to be caused by a variety of factors that include the direct effects of eosinophil-based mediators, mononuclear derived cytokines as well as antibodies that reacted against T8 + and T4 + lymphocytes and the deposits of anti-IgM, anti-IgA, anti-IgG and anti-C3 in the conjunctiva and decreased IgAs, presence of Staphylococcus aureus'toxins (superantigens) and pseudotubule formation. The increase prevalence of HLA-B12 and DR4 in ocular pemphigoid patients is notorious. It is curious that lymphocytes develop similar activities in VKC and in ocular pemphigoid although in the last case predominate those cells exhibiting a γδ-RcT instead of αβ-RcT that predominates in the former. On the other hand, the antibodies detected specifically a 45 kDa conjunctival antigen in ocular pemphigoid meanwhile other allergic ocular pathologies showed positive immunoblots at 97, 180 and 230 kDa antigens. Apparently it has nothing to do with the adhesion molecule E-cadherine (130 kDa) related with pemphigous vulgaris in skin lesions[10-15].

PERSONAL EXPERIENCE

In the last 20 years we studied 82 patients aged 44-67 years (64 women and 18 men) with ophtalmological and histopathological diagnosis of ocular autoimmune pemphigoid. Twenty of them had lost the vision of one eye and during years they received local and systemic steroids, decongestionants, antiinflammatory and analgesic drugs for their illness suffering different adverse reactions to them. This was the main fact that decided us to use immunosuppressive drugs such as cyclosporin-A (Cy-A) per os 100 mg/day to replace the former treatment and to "cool-down" the conjunctival inflammation. All these patients were subjected to clinical, infectological and immunological evaluations previously to be exposed to Cy-A. Those who suffered cushingoid untoward signs were carefully diminished in their daily steroids intake meanwhile they started with Cy-A. All the patients signed the informed consent according to the Helsinki's regulations for clinical investigations[16-19].

The Cy-A – a fungal antimetabolite – was shown to decrease the signs and symptoms of VKC. Topical Cy-A inhibits various mediators and the development of mast-cell mediated allergic conjunctivitis. Because it is lipophilic, Cy-A must be dissolved in an alcohol-oil base which directly causes ocular irritation (i.e., burning, tearing, erythema, itching and headache). Acts primarily on T lymphocytes by inhibiting the production of lymphokines, particularly, IL-2, as well as, IL-3, IL-5, TNF-α and IFN-γ. Considering the untoward effects of the topical pharmaceutical form we decided to use the oral administration of Cy-A. Once the patient was accepted as suitable to receive the Cy-A treatment (clinical, infectological and immunologically within acceptable normal parameters) the drug was daily administered at 100 mgs per os with a careful clinical follow-up and routine laboratory tests each 90 days. The first sign of success with Cy-A (after 7-12 days) was the disappearance of the headache and the ocular pain changing dramatically the patients' quality of life. The ophtalmological follow-up with a meticulous exam revealed a positive change in the conjunctiva and the corneal limb. Diminished vascularization was evident and slow but sustained repair of corneal damage was observed. When conjunctival biopsies were performed the cellular infiltrate appeared reduced in intensity although mononuclear cells predominated (LTCD8 + > LTCD4+ and macrophages). Autoantibodies remained unmodified by immunofluorescence but the original image (lineal or continuous) was replaced by frequent and repeated patches. When a period of six months was reached and the patients'improvement was stable the administration of Cy-A was diminished to five capsules a week instead of seven as before ("week-end relief"). This improvement was associated with a blood level of Cy-A between 90-110 mcg/ml which is lesser than that useful in organ transplantation. No side effects were recorded in blood samples, nitrogen metabolism and liver function. Fifteen patients

were submitted to cataracts surgery to improve their vision meanwhile all of them were taking 7 capsules a week of Cy-A before and after the surgery until the ophtalmologist informed about the success of the surgery. Then the previous scheme of 5 capsules/ week was reestablished up to the end of the treatment (2 or 3 years) when the conjunctiva was "cool", there was no pain and the biopsies showed marked diminution in the infiltrate[20-21].

As our country suffered a socioeconomical bankrupt in 2002 for some patients became very difficult to continue their Cy-A intake so we tried to replace it with another cheaper immunomodulator. We chose azathioprine 50 mg/day and we strictly controlled their routine laboratory analysis each month at the beginning of the replacement. If the drug was tolerated these controls were performed each 90 days. Although Cy-A treatment is the ideal the results with azathioprine were acceptable and nowadays is a new alternative for the treatment of ocular pemphigoid in those patients without social welfare and very low economical status.

Notwithstanding, we never consider the fact of a complete recover from sickness because of the poor knowledge about the etiological triggers of the illness.

Another change in the horizon of ocular pemphigoid is the dependence on the present form of delivery of topical agents (i.e., solutions, suspensions and ointments). Liposomal drug delivery has been shown to increase therapeutic activity with decreased toxicity. Compounds encased in liposomal microscopic capsules have been shown to have a more penetrating effect into the cornea, aqueous, vitreous and conjunctiva. A new carrier, α-cyclodextrin (an azolic oligosaccharide) has been developed and has shown increased penetration and low toxicity. Topical application of blocking antibodies to ICAM-1, LFA-1, IL-1Ra and the soluble form of P-selectin glycoprotein ligand-1 have a profound inhibitory effect on the development of conjunctivitis in an animal model. As the inhibition of experimental autoimmune uveitis in animals by the administration of specific antigens (retinal-S and intestinal retinol binding protein) was successful we hope that new immunotherapeutic strategies will be develop in the future to solve this annoying condition.

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