Auranofin Is Ineffective in Atopic Dermatitis

SIR,

Gold compounds have been extensively used as therapeutic agents in the treatment of rheumatoid arthritis. Their mechanism of action in vivo remains, however, unclear. The pharmacokinetic properties of the recently available oral compound auranofin (Ridaura®) differ greatly from parenteral gold formulations. Auranofin appears to have anti-inflammatory activity due to (a) reduction of the release of inflammatory mediators such as lysosomal enzymes (1, 2), histamine (3), prostaglandins (4) and interleukin 8 (5); (b) inhibitory effect on the first component of the complement (6); and (c) inhibitory effect on the chemotactic and phagocytic response of macrophage and PMN (7). In addition, it has specific immunomodulatory properties such as inhibition of antibody-dependent cell-mediated toxicity, complement lysis (8) and stimulation of suppressor T cells (9). Furthermore, it has anti-inflammatory activity.

Since auranofin may act at several levels of the inflammatory and immune response with fewer and milder side-effects than classical gold salts (10), it might be useful in the treatment of atopic dermatitis (AD), a disease with immunologic abnormalities including abnormal regulation of IgE synthesis, disturbed T cell function and altered pharmacological reactivity and releasability of vasoactive mediators. We have used it in several patients with AD during the past years. As some positive effects were noticed (subjective lesional and topographical improvement described by 4 patients after 2 months’ therapy), we decided to prospectively study the effect of this compound in 4 patients with severe AD during a 6-month period.

Four patients (all male, mean age 32 years (range 26–35 years)) entered this prospective study after informed consent. All patients had severe AD fulfilling the criteria of Hanifin & Rajka (11). Patients with abnormal renal, hepatic or hematological function were excluded. The range of serum IgE value at start was 2,920–16,910 IU/ml.

Each patient was treated with a triple combination consisting of auranofin (Ridaura®) 6 mg/d, aminzestil (Hismanal®) 10 mg/d and ramikinem (Zantac®) 300 mg/d (taken for a period of 6 months (September 1992 to March 1993). Patients were allowed to continue using topical corticosteroids as necessary. An opthalmologic examination was performed at the beginning and at the end of the treatment period. Standard biochemical parameters of renal and hepatic function were monitored monthly.

The response to treatment was evaluated by a monthly clinical scoring system (12). Itching sensation was reported by the patient on a classical visual analog scale, and requirements for topical steroids were recorded.

Three patients showed little or no change after 6 months of treatment and one patient had an exacerbation of the AD leading to discontinuation of the trial after 4 months. The reduction of the overall lesional score was only 10%, due to a 50% improvement of itch without significant change of other parameters such as surface involvement, erythema, scaling and excoriations. The reduction of the topical steroid consumption was insignificant (2.5 g/week).

Important fluctuation in the disease activity occurred during treatment in 3 out of the 4 patients. There was no major adverse effect including hepatic, renal, ocular or hematological function. Serum IgE levels and eosinophil blood count were unchanged.

A clinical effect of auranofin (reduction of the lesional and topographical scoring) was not detectable in this study. No patients described an improvement of their AD; none could omit or reduce significantly his topical corticosteroid treatment. The main benefit of the triple combination was the important reduction of the pruritus, which may have been due to the association of the H1 and H2 receptor antagonists given during the trial, although recent studies showed that H1 blockers had no effect regarding itch in AD.

The hypothesis of a possible benefit of auranofin in AD was based on the fact that AD, like rheumatoid arthritis and pemphigus, is a chronic disease associated with humoral and cellular immune abnormalities (13). This hypothesis was not confirmed in the present study.

REFERENCES

Early or Late Expression of Ia Antigen on Mouse Keratinocytes in Allergic Contact Dermatitis?

Sir,
Recent progress has been made in our understanding of the pathogenesis of allergic contact dermatitis (ACD). However, the cells able to present hapten during the elicitation of ACD are not clearly defined. The role of HLA-DR* keratinocytes as antigen-presenting cells in the effector limb of hapten immune response is still debated. Kinetic studies have reported either early or late induction of MHC class II molecule expression by keratinocytes after hapten elicitation (1-3). We would like here to report on personal observations in oxazolone-induced ACD in Balb/c mice, showing that Ia antigen expression on keratinocytes represents an early event in the course of ACD.

Mice were sensitized on the abdomen with 50 µl of a solution containing 2% oxazolone (4-ethoxymethylene-2-phenylazo-5-one) in acetone/olive oil. Five days later, animals were painted once on both faces of the left ear with 25 µl of 0.4% oxazolone. The right ear received the vehicle alone. Control mice received vehicle alone for the sensitization and 25 µl of 0.4% oxazolone for the elicitation. The delayed-type hypersensitivity response was assessed on days 1, 2, 3 and 7 by the mouse ear swelling test (4) (Fig. 1). Some mice were killed 12 h, 24 h, 48 h, 72 h and 7 days after the elicitation, and their ears were immediately frozen in liquid nitrogen. Ia expression was assessed on cryostat sections of the various skin samples using a rat monoclonal antibody (CD311), specific for mouse Ia antigen, kindly provided by Dr. A. L. Glasebrook (Eli Lilly, Indianapolis), and an immunoperoxidase technique. CD311, a monomorphic anti-Ia monoclonal antibody (MoAb), recognizes a determinant present on MHC class II molecules of a large number of H-2 haplotypes including d, k and b (5, 6). Foci of Ia* keratinocytes could be observed as early as 12 h after elicitation of contact sensitivity to oxazolone (Fig. 2). Maximum expression was seen at 48 h with a continuous staining of the basal cell layer, and basal keratinocytes were still Ia* on day 7. Only weak and focal labelling of keratinocytes was noted at 48 h in oxazolone-challenged skin in the non-sensitized animals.

Our results, demonstrating that Ia antigen expression by keratinocytes is an early event in ACD, are in accordance with the study of Roberts et al., in which oxazolene-sensitized mice expressed at 24 h a diffuse or focal Ia* staining of the basal keratinocytes (1). In humans, Ia* keratinocytes were found in ACD as early as 6 h after elicitation (2). However, early Ia molecule expression on keratinocytes was not found by Stringer et al. (3), who reported that Ia* keratinocytes could only be detected 3 days after elicitation of contact sensitivity using oxazolone in Balb/c mice.

One possibility, which might explain these discrepancies,