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Anaphylactic reaction after aceclofenac intake

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Keywords: aceclofenac; anaphylactic reaction; cross-reaction; diclofenac.

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the main aetiologies of severe anaphylaxis. The prevalence of severe anaphylaxis because of NSAIDs registered by the Allergy Vigilance Network over 2003–2004 (1) was 13%.

A 75-year-old man with a previous history of osteoarthritis, sporadically treated with various NSAIDs, took aceclofenac (100 mg/day). Clinical symptoms appeared 2 h after the second dose intake. Symptoms included itching in legs without cutaneous lesions, palpebral and labial edema, and dyspnea. The patient was treated with methylprednisolone and dexchlorpheniramine immediately. After

After this episode, therapeutic doses of diclofenac were tolerated.

this episode, therapeutic doses of diclofenac as well as other anti-inflammatory drugs, such as Ibuprofen and Metamizol, were tolerated.

Cutaneous tests with aceclofenac, both prick and intradermal tests (30 mg/ml and 3 g/ml, respectively), were performed. The result was positive for the intradermal test. Five controls were tested, with negative results.

Aceclofenac, [o-(2,6-dichloroanilino) phenylacetate glycolic acid ester, is a NSAIDs of the phenylacetic acid group (2). After its absorption, the drug is hydrolyzed to diclofenac (3), also from the phenylacetic acid group (Fig. 1). Alclofenac and fenclofenac, two NSAIDs with similar chemical structure to aceclofenac, were withdrawn in the late 1970s and 1980s because of the high incidence of rash (4).

The most common hypersensitivity reaction described with aceclofenac is hypersensitivity vasculitis (4). A case of photoallergic contact dermatitis (5) and another one of exudative erythema multiforme (6), both related to aceclofenac, have been reported.

Two of these cases, showed no cross-reaction between aceclofenac and diclofenac, as occurred in the case reported above. It suggests that cross-reactions among phenylacetic-derived NSAIDs are not so frequent.

To our knowledge, this is the first report of an anaphylactic reaction after the intake of aceclofenac. Clinical features and cutaneous test with aceclofenac suggest an immunoglobulin E (IgE)-mediated mechanism.

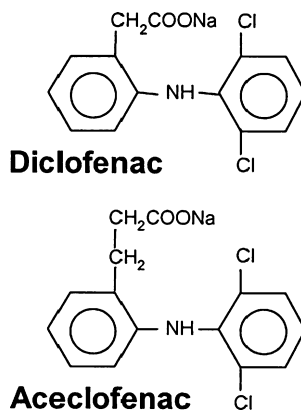


Figure 1. Chemical structure of diclofenac and aceclofenac.

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Sublingual immunotherapy and regulatory T cells

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Key words: bronchial hyperreactivity; IL-10 production; nasal eosinophils; regulatory T cells; sublingual immunotherapy.

Recently, a role for regulatory T cells (Tregs) has been evidenced in patients undergoing specific immunotherapy (SIT) for grasses and mites (1). Thus, it has been pointed out that SIT generates Tregs, secreting both interleukin(IL)-10 and tumour growth factor (TGFβ) and

specifically suppresses allergen-induced responses (1). This issue appears crucial as a evidenced by a recent experi-

SLIT-induced functional and immunological effects are associated with IL-10 production in a pilot study.

mental study of the defects of the Tregs in allergic patients (2). As the traditional subcutaneous route of administration had a risk of serious adverse reactions, the sublingual route of immunotherapy has been investigated and developed. The efficacy of sublingual immunotherapy (SLIT) for rhinitis has been recently confirmed by a meta-analysis [Cochrane review (3)].

The immunological changes induced by SLIT have been recently demonstrated in two studies, concerning a group of mite allergic patients successfully treated. The changes include reduction of T-cell proliferation (4) and induction of a Tregs response as evidenced by *in vitro* IL-10 production (5).

Thus, this study aimed at comparing functional and immunological effects (including spirometry, methacholine bronchial challenge and nasal cytology) with IL-10 production in allergic patients.

Nine subjects suffering from allergic rhinitis undergoing SLIT had received mite allergen extract (Staloral 100 IR; Stallergenes, Milan, Italy) for 3 years; 10 allergic patients nontreated with SIT were considered as control. The demographic and clinical characteristics of the subjects have been previously reported (4, 5). Patients were clinically evaluated at baseline, i.e. before SLIT, and after 3 years.

Nasal scrap tests, spirometry and methacholine bronchial challenge were performed as previously reported (6). IL-10 production was stimulated by *Dermatophagoides farinae* or *Candida albicans* extracts (4, 5). The quantitative determination of *in vitro* production of IL-10 was performed by a commercial enzyme linked immunosorbent assay (ELISA) (Pantec s.r.l., Turin, Italy). Statistical analysis was performed using the nonparametric Mann-Whitney *U*-test, the Spearman test and the ANOVA test.

Nasal symptoms significantly improved after SLIT ($P < 0.01$). IL-10 production was detectable only in

SLIT-treated patients in comparison with allergic nontreated patients: *Candida*-induced IL-10 158 pg/ml (141–453) vs 0 (0–0) ($P = 0.002$); *D. farinae*-induced IL-10 80 pg/ml (0–113) vs 0 (0–0) ($P = 0.04$).

Nasal eosinophils significantly decreased after SLIT: from 7 (6–9.2) to 2 (1–3.2) ($P = 0.0002$). Moreover, PD20 level significantly increased after SLIT: from $856 \pm 665 \mu\text{g}$ to $1476 \pm 173 \mu\text{g}$ ($P = 0.03$). The decrease of eosinophils was associated with the improvement of bronchial hyper-reactivity (BHR) (Fig. 1). In addition, the decrease of eosinophils was inversely related with IL-10 production ($\text{Rho} = -0.78$) (Fig. 2).

Allergic rhinitis is characterized by a T-helper -2 cell (Th2)-polarized inflammation and nasal eosinophils may be considered the best predictor of allergic

inflammation as they relate with clinical, functional (including nasal airflow, spirometric parameters, and BHR) and immunological events (including Th1- and Th2-derived cytokines) in patients with allergic rhinitis (6).

Specific immunotherapy has been demonstrated capable of inducing IL-10 production by Tregs (1, 2). IL-10 exerts a number of activities that are relevant for understanding the mechanisms of action of SIT: the modulation of allergen-specific immunoglobulin E (Ig) production in favour of IgG4, the inhibition of allergen-dependent mast cell activation, the suppression of activation and survival of eosinophils, the reduction of pro-allergic cytokines and the hyporeactivity to allergens (1).

Sublingual immunotherapy is a safe and effective route of administration of

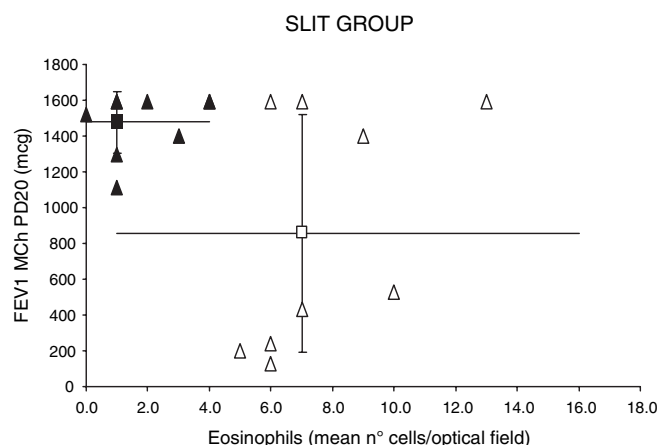


Figure 1. Single values (triangles), median eosinophils (upper-lower quartiles) and mean $\pm$ SD PD20 (squares) before (closed) and after 3-year SLIT treatment (open).

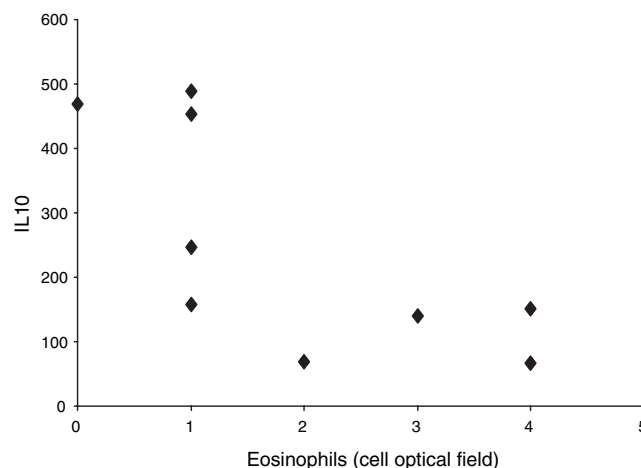


Figure 2. Single values of eosinophils and IL-10 levels after 3-year SLIT treatment.

allergen extracts in allergic patients. However, its mechanism of action is still poorly understood, as there are few data concerning the induced immunological changes. This study provides evidence that SLIT is able to induce immunological and functional effects that are associated with the induction of a Tregs response. Moreover, the assessment of nasal eosinophils is a simple way to detect anti-inflammatory activity exerted by SLIT.

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