

LETTERS TO THE EDITOR

Epidermolysis Bullosa Acquisita: Correlation of IgE Levels with Disease Activity under Successful Betamethasone/Dapsone Combination Therapy

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Sir,

We report on a possible association between epidermolysis bullosa acquisita (EBA) and elevated levels of circulating IgE. A 23-year-old man with a 3-month history of intensely itchy blisters fulfilled the diagnostic criteria for EBA (subepidermal blisters, linear IgG deposits in basement membrane zone, circulating IgG antibodies to dermal part of the basement membrane zone in split skin test, circulating antibodies reacting with a 290 kD component in dermal extracts by immunoblotting) (1, 2). The patient was successfully treated with a combination of betamethasone and dapsone. After 10 months of treatment, direct immunofluorescence had become negative, and circulating antibodies to basement membrane zone components could no longer be detected. Treatment was discontinued after 15 months, and the patient has been in remission during the 2 months that have elapsed since the treatment was stopped.

Interestingly, the patient had elevated serum levels of IgE (3,480 IU/ml vs. normally <250 IU/ml) at the first visit. Radio-allergosorbent tests showed polyclonal IgE against a wide variety of common environmental allergens such as dust and house mites, and *Candida albicans*. The serum IgE levels remained high as long as the patient had skin symptoms, but

then gradually decreased to normal levels as the disease activity decreased.

This appears to be the first reported case of EBA in which IgE has been evaluated. Although the potential pathophysiological relevance of our findings is not clear as yet, we suggest that it may be useful to evaluate total immunoglobulin levels in new patients with EBA and possibly also in other blistering diseases (3, 4).

REFERENCES

1. Woodley DT, Briggaman RA, O'Keefe EJ, Inman AO, Queen LL, Gammon WR. Identification of the skin basement-membrane autoantigen in epidermolysis bullosa acquisita. *N Engl J Med* 1984; 310: 1007–1013.
2. Shimizu H, McDonald JN, Gunner DB, Black MM, Bhogal B, Leigh IM, et al. Epidermolysis bullosa acquisita antigen and the carboxy terminus of type VII collagen have a common immunolocalization to anchoring fibrils and lamina densa of basement membrane. *Br J Dermatol* 1990; 122: 577–585.
3. Maekawa N, Hosokawa H, Soh H, Kasahara M, Izumi H, Yodoi J, et al. Serum levels of soluble CD23 in patients with bullous pemphigoid. *J Dermatol* 1995; 22: 310–315.
4. Soh H, Hosokawa H, Asada Y. IgE and its related phenomena in bullous pemphigoid. *Br J Dermatol* 1993; 128: 371–377.

Addition of Pentoxifylline Could Reduce the Side Effects of Fumaric Acid Esters in the Treatment of Psoriasis

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Sir,

Fumaric acid ester (FAE) therapy has proved to be effective in several multicentre trials, but while there are beneficial clinical effects, there are also some negative side effects (1). In a recent prospective multicentre trial including 101 patients, 69% reported adverse effects, mainly gastrointestinal complaints (50%; cramps, diarrhoea) and flushing (31%), in the first weeks after FAE treatment. These complaints led to cessation of the treatment in 4 patients (2). Other reports suggest a similar high incidence of side effects (1).

One explanation for the adverse effects could be a FAE-induced release of tumour necrosis factor- α (TNF- α) during the initial phase of therapy. This hypothesis is supported

by our observation that monocytes secrete TNF- α after FAE stimulation *in vitro* (3). TNF- α is a potent proinflammatory mediator and a likely candidate for gastrointestinal complaints (4) and flushing. In speculating that a reduction of FAE-induced TNF- α secretion would improve tolerability of the compound, in a clinical survey we compared FAE therapy and the combination of FAE plus pentoxifylline (PTX), a potent suppressor of TNF- α release.

MATERIAL AND METHODS

Forty-four adult patients (18 women and 26 men; mean age 52.9) with moderate to severe psoriasis vulgaris were included

in this open-label prospective trial. Patients were randomly assigned to one of the two study groups (A and B). All patients received a daily oral-systemic treatment of psoriasis with FAE (Fumaderm®) in accordance with standard ascending doses as recommended by the German consensus conference (1). The dose of FAE given in each group was therefore identical. In group B, patients additionally received PTX (2×400mg/day, Trental® 400; first application simultaneously with FAE). Patients were also treated topically and observed over an 8-week period. They were asked for adverse effects after weeks 3, 6 and 8. Severity of the side effects was recorded using a scoring system (0=no side effects, 1=mild, 2=moderate, 3=severe, 4=very severe for each of the side effects). The chi-squared test and the Mann-Whitney U test were used for comparing the groups.

RESULTS

In group A (FAE monotherapy), 16 out of 21 patients showed adverse effects; 4 patients ceased the FAE treatment, which is in line with earlier reports (2). The incidence was slightly lower in group B (combination therapy FAE plus PTX), where 12 patients out of 23 reported adverse effects leading to withdrawal from the study in 4 cases. The most frequent side effects in both groups were gastrointestinal complaints (diarrhoea, intestinal cramps) and flushing. Adverse effects were less frequently reported in the patients receiving PTX co-application. A significant reduction in severity of all side effects was found in the patients with combination therapy (Table I). There was no evidence of a different response to the antipsoriatic treatment between the two groups.

DISCUSSION

Our data provide first evidence that an addition of PTX to the standard FAE therapy regime may be a way to reduce the adverse effects of FAE. We found a reduction of diarrhoea by 31%, of intestinal cramps by 48%, and of flush symptoms by 63% in the patients who received PTX additional to the FAE therapy. It might be speculated that even more pronounced (and statistically significant) effects could be achieved when using higher concentrations of PTX. In fact, it is likely that the PTX plasma levels were not sufficient to completely block TNF- α release. Peak plasma levels of 2.25 µg/ml were found after oral administration of 400mg PTX (5), whereas 100 µg/ml PTX is necessary to achieve sufficient TNF- α inhibition *in vitro* (own results, not shown). In concurrence with this, Falanga et al. (6) have shown that higher doses of PTX (800mg three times a day) are more effective than lower doses (400mg three times a day) in treating venous leg ulcers. Further studies, including placebo-controlled trials, should be performed to analyse the reduction of side effects and the

Table I. *Side effects during therapy with fumaric acid ester (FAE) alone and in combination with pentoxifylline (PTX)*

	FAE (n = 21)	FAE + PTX (n = 23)
Occurrence of side effects	76.2%	52.2%
Cessation of therapy due to side effects	19.0%	17.4%
Mean severity score ($\pm$ SEM) for side effects	3.48 $\pm$ 0.6	1.91 $\pm$ 0.58*

* $p < 0.05$ significantly lower than in patients with FAE monotherapy.
SEM = standard error of the mean.

potential additive antipsoriatic effects of combining TNF inhibitors (e.g. higher dosages of PTX and neutralizing anti-TNF antibodies) with FAE. Such combinations seem suitable, since PTX and anti-TNF (7) have also been shown to be effective in treating psoriasis, due to the reduction of TNF- α (8), and in reducing keratinocyte proliferation (9), suggesting a potential additive antipsoriatic effect.

REFERENCES

- Mrowietz U, Christophers E, Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric Acid Ester Consensus Conference. *Br J Dermatol* 1999; 141: 424–429.
- Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study (German Multicentre Study). *Br J Dermatol* 1998; 138: 456–460.
- Asadullah K, Schmid H, Friedrich M, Rando F, Volk HD, Sterry W, et al. Influence of monomethylfumarate on monocytic cytokine formation – explanation for adverse and therapeutic effects in psoriasis? *Arch Dermatol Res* 1997; 289: 623–630.
- Neurath MF, Fuss I, Pasparakis M, Alexopoulou L, Haralambous S, Meyer zum Buschenfelde KH, et al. Predominant pathogenic role of tumor necrosis factor in experimental colitis in mice. *Eur J Immunol* 1997; 27: 1743–1750.
- Beermann B, Ings R, Mansby J, Chamberlain J, McDonald A. Kinetics of intravenous and oral pentoxifylline in healthy subjects. *Clin Pharmacol Ther* 1985; 37: 25–28.
- Falanga V, Fujitani RM, Diaz C, Hunter G, Jorizzo J, Lawrence PF, et al. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. *Wound Repair Regen* 1999; 7: 208–213.
- Oh CJ, Das KM, Gottlieb AB. Treatment with anti-tumor necrosis factor alpha (TNF-alpha) monoclonal antibody dramatically decreases the clinical activity of psoriasis lesions. *J Am Acad Dermatol* 2000; 42: 829–830.
- Omulecki A, Broniarczyk-Dyla G, Zak-Prelich M, Choczaj-Kukula A. Is pentoxifylline effective in the treatment of psoriasis? *J Am Acad Dermatol* 1996; 34: 714–715.
- Gilhar A, Grossmann N, Kahanovicz S, Reuven H, Cohen S, Eitan A. Antiproliferative effect of pentoxifylline on psoriatic and normal epidermis. *Acta Derm Venereol* 1996; 76: 437–441.