

Original article

Systemic ketoconazole is an effective treatment of atopic dermatitis with IgE-mediated hypersensitivity to yeasts

Background: IgE-mediated hypersensitivity to yeasts is often seen in atopic dermatitis (AD) patients, especially when dermatitis is located in the head, neck, and shoulder regions. Two studies have shown the efficacy of ketoconazole in the treatment of this type of AD, in contrast to results of topical treatment. The objective was to assess the clinical efficacy of antifungal treatment in AD in a randomized, double-blind, placebo-controlled study with oral ketoconazole and yeast-specific IgE levels and saprophytic yeast growth monitored simultaneously. **Methods:** Eighty patients with AD and positive *P. ovale* and/or *C. albicans* RAST/skin prick test results were randomized to receive ketoconazole or placebo for 30 days. The yeast growth of skin and pharynx; *P. ovale*, *C. albicans*, and *S. cerevisiae* RAST; serum total IgE; and the severity of the eczema (SCORAD) were assessed at day 0 and thereafter at 1 and 3 months.

Results: A significant improvement was seen in the SCORAD scale in the ketoconazole group at the second visit in comparison to the first visit ($P < 0.0005$; $n = 36$), but not in the placebo group ($n = 39$). Of the individual determinants of the SCORAD, itching ($P < 0.005$), the extent of dermatitis (area percentage), excoriation, lichenification ($P < 0.01$), erythema, papulation, and dryness ($P < 0.05$) improved significantly in the ketoconazole group. In the placebo group, only the extent of dermatitis (area percentage) decreased significantly ($P < 0.05$). In the ketoconazole group, the number of positive *P. ovale* cultures decreased from 60% to 31% ($n = 35$) compared to the placebo group (64% to 56%; $n = 39$). The clinical response was most significant in female patients with positive yeast cultures.

Conclusions: Saprophytic yeasts may be a source of allergens in AD. Thus, patients with AD, yeast growth, and elevated IgE levels to yeasts should be offered antifungal treatment.

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The *Malassezia* genus comprises seven species (1). One of them, *M. furfur*, seems to be linked to atopic dermatitis (AD). It has two morphologically different forms: an oval form, *Pityrosporum ovale*, and a round yeast form, *P. orbiculare* (1). It is a lipophilic yeast belonging to the normal microflora of the human skin (2). The significance of *M. furfur* in the pathogenesis of AD is disputed, although evidence exists that it can act as an allergen and trigger elevated IgE antibody production and positive skin prick test reactions, especially in patients with head, neck, and shoulder distributions of AD (3–7). Nordvall et al. reported that high levels of *M. furfur* IgE antibodies in RAST were associated with current eczema, especially when it was the only atopic manifestation, and required specialist care (8). Positive patch test reactions to *M. furfur* have also been found (9, 10) in AD patients. Recently, the cDNA encoding of some allergenic proteins of *M. furfur* has been sequenced (11–13).

Studies of the effect of systemic antifungal treatment in AD are rare. In 1983, in a double-blind, placebo-controlled study of 14 patients with head and neck dermatitis and positive skin prick test to *P. orbiculare*, Clemmensen & Hjorth (14) showed that oral ketoconazole therapy for 4 weeks reduced the intensity of the dermatitis. They recommended this therapy to women younger than 30 years of age with dermatitis in the face, scalp, neck, and upper back regions. In 1995, Bäck et al. (15) treated patients with ketoconazole daily for 2 months and twice weekly for a further 3 months. Among 20 AD patients, the clinical scores improved with a reduction in total serum IgE and *P. orbiculare*-specific IgE levels. The study was not placebo-controlled.

In our present randomized, double-blind, placebo-controlled study, we aimed to evaluate the efficiency of systemic ketoconazole in the treatment of AD. The specific serum IgE antibodies and skin prick test

reactions to *P. ovale*, *Candida albicans*, and *Saccharomyces cerevisiae*; total IgE level; and saprophytic yeast cultures from skin and pharynx were analyzed simultaneously in order to assess the predictive value of these parameters for the outcome of the treatment.

Material and methods

Patients

The study was carried out at the Department of Dermatology, University Central Hospital of Turku (Finland). It was officially approved by the local ethics committee and Finnish medical authorities. A total of 80 patients (≥ 18 years of age) with previous positive skin prick test or positive RAST to *P. ovale*, *C. albicans*, or *S. cerevisiae* and current atopic eczema were selected for the trial. Fifty-four out of 80 patients were sensitized to all three yeasts. All patients were voluntary outpatients who gave written informed consent. The diagnosis of AD had been established by the criteria of Hanifin & Rajka (16). All patients suffered from AD affecting the head, neck, and shoulder regions. Patients with known dysfunction of any organ or need for continuous, daily oral medication for any disease were excluded. Patients treated with UV light therapy or oral antibiotics had to wait at least 2 weeks before they were admitted to the trial.

Thirty-six of 40 patients in the ketoconazole group and 39/40 patients in the placebo group were accepted for final evaluations (Table 1). Before the second visit, one exclusion occurred in the placebo group due to heart palpitation and four exclusions in the ketoconazole group due to a worsening of eczema, gastrointestinal, and musculoskeletal symptoms, mental problems, and the use of antibiotics and pregnancy. By the third visit, five exclusions had occurred in both groups because of extensive need for extra therapy for eczema or noncompliance with the study.

Experimental design

Patients were randomized to receive either ketoconazole tablets 200 mg (Nizoral[®]) or placebo once daily for 30 days. Topical treatment with emollients or 1% hydrocortisone was allowed, provided that the same brand was used during the 30-day period of treatment. If other medications were needed, the patients were obligated to report it to the doctor.

The patients were followed for 3 months, and they were examined for screening at day 1 to start the trial (visit 1), after 30 days when finishing the medication (visit 2), and after 3 months (2 months without drug [visit 3]). At each visit, the activity of dermatitis was evaluated on a modified SCORAD scale (17); yeast cultures were taken from the neck, shoulder, and upper back areas and from the pharynx; and specific RAST for yeast and serum total IgE were examined. Liver enzyme alanine-amino-transferase (ALAT) was controlled at visits 1 and 2. Skin prick tests were performed at visits 1 and 3. After the treatment period at visit 2, the patients were allowed to use stronger topical treatment if needed, and visit 3 was arranged to monitor possible later changes in serum total IgE levels, specific RAST levels, and skin prick tests.

Clinical evaluation (SCORAD)

The extent of dermatitis was estimated as percentage of the body surface with adult measures (A). Six clinical features (erythema, papulation, excoriation, dryness, crusts, and lichenification) were each assessed on a scale of 0–3 (i.e., none, mild, moderate, and severe) (B). Pruritus and sleep disturbances were assessed on a scale of 0 (none) to 10 (severe) (C). The total score was counted as follows: $A/5 + 7B/2 + C$, the maximum score being 103.

In vitro IgE tests

Specific IgE levels against *P. orbiculare*, *C. albicans*, and *S. cerevisiae* were examined by RAST (Pharmacia CAP-RAST, Uppsala, Sweden). Serum total IgE was analyzed by a commercial radioimmunoassay (RIA) (Pharmacia IgE RIA, Uppsala, Sweden).

Yeast cultures

Yeast cultures were taken from the neck, shoulder, and upper back areas without disinfecting, and the samples were grown on medium containing reduced-fat cream, according to Leeming & Notman (18) and Dixon (19). Yeast cultures from the pharynx were cultured with Emmons' modification of Sabouraud's agar.

Skin prick test extracts

Skin prick test allergens for *P. ovale*, *C. albicans*, and *S. cerevisiae* crude extracts were prepared as described earlier. *P. ovale* (CBS 7854) was grown on agar plates on a medium containing reduced-fat cream supplementum (18), and *C. albicans* (CBS 5982) on agar plates on synthetic medium (20). *S. cerevisiae* was obtained from Oy Alko Ab (Helsinki, Finland). It was a commercial product for household use (21). The crude cytoplasmic extracts were prepared with disruption of the cells in an X-press Chamber (AB Bio, Göteborg, Sweden), as previously reported (20–22). The lyophilized antigens were stored at -20°C . The final extracts were prepared by reconstituting the antigens with ALK diluent (ALK, Hørsholm, Denmark) and 50% glycerol (Sigma, St Louis, MO, USA), and they were then sterile-filtered. A yeast antigen concentration of 1 mg/ml was used for the skin prick testing. A positive reaction was regarded as at least 50% of the diameter of the histamine wheal, which had to be at least 3 mm.

Statistical analysis

The paired comparisons were performed with the Wilcoxon signed rank test and the unpaired comparisons with the Mann-Whitney U-test.

Results

The study was conducted during the winters of 1996–8, and it was randomized, double-blind, and placebo-controlled. Eighty patients were admitted to the trial

Table 1. Patients included in final evaluation

	Ketoconazole ($n=36$)	Placebo ($n=39$)
Sex		
M	10	16
F	26	23
Age (years)	31.4 (7.8) ^a	29.4 (10.4)
S-IgE (kU/l)	3227 (3883)	3359 (3901)
RAST (kU/l)		
<i>P. ovale</i>	17.7 (16.4)	21.4 (21.9)
<i>C. albicans</i>	15.5 (19.9)	14.7 (18.4)
<i>S. cerevisiae</i>	8.7 (11.8)	6.9 (10.3)
SPT (index) ^b		
<i>P. ovale</i>	0.92 (0.22) $n=34$	1.00 (0.40) $n=38$
<i>C. albicans</i>	0.36 (0.35) $n=31$	0.42 (0.34) $n=37$
<i>S. cerevisiae</i>	0.38 (0.32) $n=34$	0.29 (0.29) $n=38$
SCORAD (score)	43.8 (13.1)	42.6 (14.0)

^a Mean (SD).

^b Mean wheal diameter/mean histamine wheal.

Table 2. SCORAD and its individual parameters at pre- and post-treatment visits

	Ketoconazole (<i>n</i> =36)			Placebo (<i>n</i> =39)		
	Visit 1	Visit 2	WSR ^a	Visit 1	Visit 2	WSR ^a
SCORAD	43.8 (13.1) ^b	35.9 (15.3) ^b	<i>P</i> <0.0005	42.6 (14.0) ^b	39.7 (14.3) ^b	NS
Area (%)	23.1 (14.7)	20.2 (13.5)	<i>P</i> <0.01	25.2 (11.9)	22.8 (12.8)	<i>P</i> <0.05
Activity (0–18)	8.3 (2.4)	6.7 (2.9)	<i>P</i> <0.0001	8.2 (2.6)	7.5 (2.6)	<i>P</i> <0.05
– Excoriation	1.2 (0.6)	0.9 (0.7)	<i>P</i> <0.01	1.4 (0.7)	1.2 (0.5)	NS
– Lichenification	1.0 (1.0)	0.7 (0.6)	<i>P</i> <0.01	0.8 (0.8)	0.7 (0.6)	NS
– Erythema	1.6 (0.6)	1.3 (0.7)	<i>P</i> <0.05	1.5 (0.6)	1.5 (0.7)	NS
– Papulation	1.6 (0.5)	1.3 (0.7)	<i>P</i> <0.05	1.6 (0.5)	1.6 (0.6)	NS
– Dryness	1.6 (0.6)	1.4 (0.6)	<i>P</i> <0.05	1.6 (0.7)	1.5 (0.6)	NS
– Crusts	1.3 (0.7)	1.1 (0.7)	NS	1.2 (0.6)	1.2 (0.7)	NS
Itching (0–10)	6.3 (2.2)	5.0 (2.6)	<i>P</i> <0.005	5.8 (2.3)	5.5 (2.5)	NS
Insomnia (0–10)	3.8 (3.5)	3.3 (3.1)	<i>P</i> =0.056	3.4 (2.7)	3.3 (2.9)	NS

^a Wilcoxon signed-rank test.^b Mean (SD).

and started medication. The number of evaluated patients, to complete the trial was 75, as shown in Table 1; 74/75 patients had AD in the head, neck, and shoulder areas, 25/75 in the body area, and 64/75 in the extremities.

Therapeutic outcome and the effect of ketoconazole therapy

A statistically significant improvement was seen in the clinical SCORAD scale in patients in the ketoconazole group (*P*<0.0005, *n*=36) at visit 2 in comparison to visit 1 (visit 1, 43.8; visit 2, 35.9). In the placebo group, no significant changes (visit 1, 42.6; visit 2, 39.7) were seen (*n*=39) (Table 2).

When the separate parameters of SCORAD were evaluated in more detail in the ketoconazole group activity (including erythema, papulation, excoriation, dryness, crusts, and lichenification) (*P*<0.0001), itching (*P*<0.005) and the extent of dermatitis (area percentage) (*P*<0.01) changed significantly, and there was a clear trend in insomnia (*P*=0.056) (Table 2). Of the individual determinants of the activity, excoriation (*P*<0.01), lichenification (*P*<0.01), erythema (*P*<0.05), papulation (*P*<0.05), and dryness (*P*<0.05) changed significantly. No changes in the severity of

crusts were seen. In the placebo group, the extent of dermatitis (area percentage) (*P*<0.05) changed significantly, but there were no significant changes in other parameters.

At the third visit, the SCORAD values (*n*=65) improved in both the ketoconazole (mean 31.4, SD 13.3; *P*<0.0001) and placebo (mean 33.5, SD 13.3; *P*<0.01) groups. However, these results were not regarded as reliable for the therapeutic effect of ketoconazole, as many patients had used extra topical treatment after visit 2, as was allowed in the protocol, and the most difficult cases were excluded, because of the need for other therapies (e.g., UV).

The predictive parameters for therapeutic outcome are shown in Table 3. A difference was seen in the ketoconazole group between male and female patients in the therapeutic outcome. Women benefited from the therapy significantly (*P*<0.05), but men did not. When *P. ovale* growth was compared with the therapeutic outcome of AD, it appeared that patients who had *P. ovale* growth in skin culture at the beginning and received ketoconazole therapy improved significantly (*P*<0.05). When the growth of *C. albicans* was compared in the same way, a similar trend was seen, but the association was not significant (*P*=0.086).

Table 3. Predictive parameters for therapeutic outcome and change in SCORAD score from pre- to post-treatment visits compared between ketoconazole and placebo groups

	Ketoconazole			Placebo			MWU ^a
	<i>n</i>	Visit 1	Visit 2	<i>n</i>	Visit 1	Visit 2	
Sex							
F	26	43.0 (12.3) ^b	33.5 (14.3) ^b	23	42.4 (14.5) ^b	41.2 (14.9) ^b	<i>P</i> <0.05
M	10	45.8 (15.7)	42.4 (16.8)	16	42.9 (13.6)	37.5 (13.6)	NS
<i>P. ovale</i> culture							
Positive	21	45.4 (14.4)	36.9 (17.8)	25	40.3 (13.2)	38.2 (14.0)	<i>P</i> <0.05
Negative	14	40.6 (11.1)	35.0 (11.8)	14	46.8 (14.9)	42.4 (14.9)	NS
Serum total IgE							
<5000 kU/l	29	44.1 (13.4)	35.3 (16.3)	28	39.8 (14.3)	38.3 (14.3)	<i>P</i> <0.05
>5000 kU/l	7	42.6 (12.9)	38.6 (10.5)	11	49.6 (10.8)	43.1 (14.7)	NS

^a Mann-Whitney U-test.^b Mean (SD).

Table 4. Yeast cultures from skin (*P. ovale*) and pharynx (*C. albicans*) at pre- and post-treatment visits

	Visit 1	Visit 2
Ketoconazole (n=35)		
<i>P. ovale</i>		
+++	3 (9%)	1 (3%)
++	4 (11%)	2 (6%)
+	14 (40%)	8 (22%)
—	14 (40%)	24 (69%)
<i>C. albicans</i>		
+++	4 (11%)	1 (3%)
++	2 (6%)	0 (0%)
+	5 (14%)	3 (9%)
—	24 (69%)	31 (89%)
Placebo (n=39)		
<i>P. ovale</i>		
+++	2 (5%)	2 (5%)
++	9 (23%)	7 (18%)
+	14 (36%)	13 (33%)
—	14 (36%)	17 (44%)
<i>C. albicans</i>		
+++	0 (0%)	0 (0%)
++	4 (10%)	3 (8%)
+	8 (21%)	8 (21%)
—	27 (69%)	28 (71%)

There was significant improvement of eczema in the ketoconazole group in comparison to the placebo group in patients who had a total IgE level of <5000 kU/l ($P<0.05$). If the total IgE level was higher than 5000 kU/l, no significant changes were seen in clinical parameters.

Saprophytic growth and the effect of ketoconazole therapy

After ketoconazole treatment, the positive *P. ovale* cultures were significantly reduced from 60% to 31% ($n=35$), but there was only a minor change in the placebo group (64% to 56%; $n=39$), as shown in Table 4. In the ketoconazole-treated group, the percentage of *C. albicans*-positive cultures decreased from 31% to 11% during medication. In the placebo group, there was no change (31% to 29%). At visit 3, 2 months after medication, the percentage of positive cultures of both *P. ovale* (64%; $n=28$) and *C. albicans* (21%; $n=28$) had returned almost to their pretreatment levels.

Serum total IgE, RAST, and skin prick tests

The sensitization pattern to the three yeasts (*P. orbiculare*, *C. albicans*, or *S. cerevisiae*) had no impact on the therapeutic outcome. There were no significant changes in the yeast-RAST levels during the 3-month treatment period (Table 5). In the ketoconazole-treated group, there was a slight fall in serum total IgE level ($P=0.063$) compared to the placebo group. When skin prick test results from visits 1 and 3 were compared, no significant changes were seen. The ALAT level was elevated during the ketoconazole treatment in one female patient (from 12 to 59 U/l), but during the follow-up period, it returned to baseline. ALAT levels were normal throughout the study in all other patients.

Discussion

According to our study, ketoconazole had a therapeutic effect in AD patients with serum IgE antibodies to *P. ovale*, *C. albicans*, and *S. cerevisiae*. However, not all patients benefited from the ketoconazole therapy. The growth of *P. ovale* from the skin cultures before the therapy had a significant role, and only the patients with *P. ovale* growth found before therapy clearly benefited from antifungal treatment. It appeared also that especially women with growth of *P. ovale* from the skin and with serum total IgE of <5000 kU/l benefited from the therapy. In patients with a total IgE of >5000 kU/l, the therapeutic outcome was rather poor. Those patients had the most severe forms of AD, and oral antifungal treatment alone was not sufficient.

Patients with AD have an increased tendency to develop viral, fungal, and bacterial skin infections (23–24). *P. ovale* has been considered to act as a pathogen or allergen in AD patients, especially in those with head, neck, and shoulder dermatitis. *P. ovale* growth generally favors skin areas with sebum production, such as the head, neck, and shoulder areas. Sensitization to *C. albicans* and *S. cerevisiae* has also been demonstrated in patients with head, neck, and shoulder dermatitis (25–26). Bäck et al. found that ketoconazole improved dermatitis and therapeutic response correlated with decrease in serum IgE level (15). Clemmensen & Hjorth found ketoconazole to

Table 5. Serum total and yeast-specific IgE levels at pre- and post-treatment visits

	Ketoconazole (n=34)			Placebo (n=38)		
	Visit 1	Visit 2	WSR ^a	Visit 1	Visit 2	WSR ^a
Total IgE (kU/l)	3152 (3956) ^b	2973 (3859) ^b	$P=0.063$	3447 (3915) ^b	3445 (3953) ^b	NS
RAST (kU/l) (n=39)						
<i>P. ovale</i>	18.7 (16.3)	18.9 (17.6)	NS	21.4 (21.9)	21.6 (21.9)	NS
<i>C. albicans</i>	16.4 (20.2)	17.8 (26.0)	NS	14.7 (18.4)	15.3 (19.5)	NS
<i>S. cerevisiae</i>	9.2 (11.9)	8.8 (12.4)	NS	6.9 (10.3)	6.3 (8.2)	NS

^a Wilcoxon signed-rank test.

^b Mean (SD).

improve the dermatitis of women younger than 30 years with dermatitis of the face, scalp, neck, and upper back (14). Thus, our results were in line with the two earlier studies described above, and we obtained new information of the clinical effect on ketoconazole therapy in AD and its effect on *P. ovale* and *C. albicans* cultures and serum IgE. There is also a report of topical antifungal treatment in AD with a less favorable result (27). This might indicate an association with *C. albicans* growth in the pharynx simultaneously or the lack of penetration of topical drugs into the hair follicles.

One question needing further study is the length of antifungal treatment. In our study, 30-day medication was chosen for practical reasons. Longer periods of treatment, such as 2 months, and then for 3 months twice weekly treatment, as in Bäck et al.'s study, seemed to maintain the low degree of disease activity (15). In our study, cultures showed regrowth of yeasts at visit 3, suggesting that there is a direct need to continue medication on a weekly or monthly basis with oral and/or topical antifungal medication.

In the two earlier studies and in our study, adverse events were insignificant. However, oral antifungal therapy in AD should, at least for the first time, be prescribed by a specialist according to yeast culture and IgE determinations. The mechanism of ketoconazole has been investigated earlier, since in addition to antifungal properties, it seems to have also anti-inflammatory properties. The decrease of yeasts cultured from the skin or pharynx after ketoconazole therapy was very clear in our study, but a clinical difference in *P. ovale* growth in culture was seen only in patients who had pretreatment. This supports the role

of *P. ovale* as a trigger of inflammation in AD and the importance of the antifungal effect of ketoconazole, instead of its supposed anti-inflammatory properties. This should be confirmed in further studies using newer antimycotic drugs, such as itraconazole or fluconazole.

All patients, except one, had at least some dermatitis in the head, neck, and shoulder regions. Some had almost generalized erythrodermic AD. The line between the pure form of head, neck, and shoulder dermatitis and other forms is very difficult to draw. In our study, it seemed that patients who had elevated IgE levels for yeast also had dermatitis in either the head, neck, or shoulder regions, but also possibly in other regions of the body. As described earlier, women benefited from ketoconazole therapy more than men, although the group of men was quite small. Thus, *P. ovale* seem to be a source of allergens in AD, leading to worsening of dermatitis. Antifungal treatment should be offered to patients with AD in the head, neck, or shoulder region; *P. ovale* growth found in skin cultures; and elevated IgE levels to *P. ovale* and/or *C. albicans*. Further studies are needed to assess the length of treatment time.

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