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Systemic ketoconazole for yeast allergic patients with atopic dermatitis

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Abstract

Background

Adult patients with atopic dermatitis (AD), especially with the head–neck distribution, are often sensitized to the lipophilic yeast *Malassezia furfur/Pityrosporum orbiculare*, which is considered to contribute to the pathogenesis of the dermatitis.

Objective

Evaluation of the efficacy of oral ketoconazole on immunological and clinical parameters in yeast allergic adult patients with AD.

Study design

Randomized double-blind placebo-controlled study.

Subjects

Twenty-nine patients with specific IgE antibodies to *M. furfur/P. orbiculare* and with elevated serum IgE participated in the investigation. Fifteen subjects were treated with 200 mg ketoconazole daily and 14 received placebo for 3 months. Betamethasone cream was allowed as supplementary therapy and the consumption was registered. The clinical score (SCORAD), total serum IgE and specific IgE antibodies to *M. furfur/P. orbiculare*, *Candida albicans* and *Dermatophagoides pteronyssinus* were monitored at the starting point and by the end of the first and third month.

Results

In the actively treated group the levels of specific IgE to *M. furfur/P. orbiculare* and *C. albicans* as well as total serum IgE decreased significantly. Sensitization to *D. pteronyssinus* was not influenced. The clinical score decreased in both groups, and the improvement was correlated to the consumption of topical steroids in the control group but not in the ketoconazole group.

Introduction Go to: Choose Go

The lipophilic yeast *Malassezia furfur/Pityrosporum orbiculare/ovale* will colonize the human skin in early infancy, and in adults the yeast is commonly present in the seborrhoeic areas. [1–3] The yeast is usually non-pathogenic, but excessive growth and/or inappropriate host immunoreactivity may cause skin disorders such as pityriasis versicolor, *Pityrosporum* folliculitis and seborrhoeic dermatitis. [4]

It has also been suggested that *M. furfur/P. orbiculare* is involved in atopic dermatitis (AD), particularly in the head–neck type. [5,6] The discovery that patients with AD may be skin prick test positive and have IgE antibodies against *M. furfur/P. orbiculare* has strengthened the idea that IgE-mediated allergy to the yeast could be important in AD. [6–10] The role of *M. furfur/P. orbiculare* in the pathogenesis of AD is, however, still a matter of dispute. It has been argued that specific IgE antibodies to *M. furfur/P. orbiculare* could be a secondary phenomenon and an effect of sensitization to the normal microflora through the damaged skin rather than being primarily involved in the pathogenesis of the dermatitis. [11] However, the first attempt to treat AD with antimycotic drugs [5] gave positive clinical results. Later Bäck *et al*. [10] demonstrated an improvement in the clinical score and a reduction of specific IgE to *M. furfur/P. orbiculare* and total serum IgE in AD patients treated with oral ketoconazole for 5 months in an open study. Topical antimycotic therapy was shown to reduce the colonization of *M. furfur/P. orbiculare*, but failed to improve the eczema score during a 4-week

☐ *Malassezia furfur/Pityrosporum orbiculare*
☐ specific IgE
☐
Search

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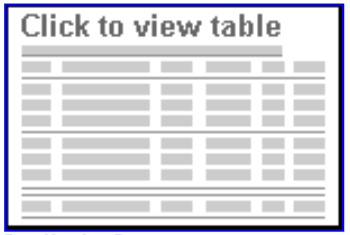

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Table 1 The ratios between values obtained at baseline (0), 1 and 3 months after start for total serum...

treatment period. [9] Although there is clinical experience showing beneficial effects of antimycotic treatment in head–neck AD, controlled studies are needed to confirm previous results and to establish some treatment standards, before antimycotics can be more widely approved for appropriate types of AD. Our objectives in this clinical trial were to evaluate the impact of oral antimycotic treatment in AD patients sensitized to *M. furfur/P. orbiculare* in a randomized, double-blind, placebo-controlled study with respect to immunological and clinical parameters.

Materials and methods Go to: Choose Go

Patients

Sixty-two adult patients with AD, diagnosed according to the criteria of Hanifin and Rajka, [12] having specific serum IgE antibodies to *M. furfur/P. orbiculare* (> 3.5 kU/L, Pharmacia CAP System RAST FEIA, Pharmacia Diagnostics AB, Uppsala, Sweden) and elevated serum IgE (> 400 kU/L) in previous screenings, were invited to participate in the study. Besides the sensitization to *M. furfur/P. orbiculare* the patients were also found to be sensitized to *Candida albicans* and *Dermatophagoides pteronyssinus*, except for one patient without specific IgE antibodies to *C. albicans* and *D. pteronyssinus* and four other patients negative to *D. pteronyssinus*. Individuals under treatment with peroral steroids, cyclosporin A, topical ketoconazole shampoo or with ultraviolet (UV) light during the last 2 months were excluded. After having given their informed consent 32 of the 62 patients entered the study. Three patients discontinued before the end due to personal reasons. The analysis of the results was based on the remaining 29 individuals, 13 men and 16 women, mean age 33 years, range 20–57; 14 patients were randomized to treatment with placebo, 15 with and ketoconazole. All the 29 patients had been under continuous treatment for their AD during the past 1–2 years. In addition to topical steroids and emollients, 18 patients had used ketoconazole shampoo, one patient selenium sulphide shampoo, eight cyclosporin A and one intermittent oral itraconazole. Of those with ketoconazole shampoo 16 had used it for more than 3 months. Before entry into the study there was a wash-out period for 2 months for the ketoconazole shampoo and other treatment modalities. In order to prevent flare-ups and secure enrolment in the study, the patients were allowed to use betamethasone cream and emollients as the only supplementary treatment and the use of the topical steroid was monitored. Thus, treatment with ketoconazole shampoo and other topical antimycotic preparations or UV light was not allowed during the study.

Experimental design

The investigation was performed as a randomized, double-blind, placebo-controlled study lasting for 3 months and approved by the local ethics committee and the Swedish Medical Products Agency. Ketoconazole was kindly provided by Janssen-Cilag AB (Västra Frölunda, Sweden) as a powder, which was further dispensed into capsules by the hospital pharmacy. Clinical examinations of the patients were performed at baseline, after 1 month and 3 months, respectively. Each time the severity of the dermatitis was graded according to the SCORAD index [13] and blood samples were collected for determining total serum IgE and specific IgE antibodies to *M. furfur/P. orbiculare*, *C. albicans*, and *D. pteronyssinus*. The liver function was monitored by assessment of the transaminases taken at every clinical visit and also at 2 weeks and at 2 months after the start of the study. At the first clinical visit the patients were randomized and supplied with coded drug packages containing capsules with either 200 mg ketoconazole or placebo and prescribed one capsule daily. The packages were exchanged at the next visit and the compliance was checked. Both the patients and the examining physicians were blinded and the code was kept secret by the hospital pharmacy until all patients had completed the final clinical examination and the case report forms were handed in. At the end of the study the patients were also asked whether they considered their dermatitis had improved or not during the treatment period.

Statistics

The ratios of SCORAD assessments, total IgE and specific IgE of *M. furfur/P. orbiculare*, *C. albicans* and *D. pteronyssinus* at baseline and after 1 and 3 months (0/1, 0/3 and 1/3) were calculated for each individual and compared between the ketoconazole and the placebo groups by means of the Mann–Whitney test. The number of ketoconazole treated individuals with increased vs. decreased values of these parameters after 1 and 3 months of therapy were compared with those from placebo-treated patients using the Fisher's exact, two-tailed test. The correlation between clinical improvement (SCORAD index) and the mass of used betamethasone cream was calculated with the Spearman's correlation test. The statistical

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Table 2 The difference (expressed as a *P*-values, Fisher exact test) in the number of improved patient...

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Table 3 The levels of total and specific IgE (kU/L) in 18 patients treated with ketoconazole shampoo ...

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relation between subjective assessment of the treatment (better/worse or unchanged) and the kind of given therapy was tested with the Spearman's correlation test and the Mann–Whitney test.

Results

Go to: Choose Go

During the study both total and specific IgE as well as the SCORAD index generally decreased in the actively treated group, but were more or less unchanged in the placebo group (Table 1). When the decrease of serum IgE and *M. furfur/P. orbiculare*, and *C. albicans* specific IgE values in the ketoconazole group were compared with those of placebo group it was shown that the reductions of the actively treated patients were more pronounced. The difference was not significant after the first month of the therapy, but at the end of the study the difference was highly significant for *M. furfur/P. orbiculare*-specific IgE and close to the significance limits for total IgE and *C. albicans*-specific IgE (Table 1). The levels of *D. pteronyssinus*-specific IgE in both groups did not change significantly during the study.

The improvement of the clinical score in the ketoconazole-treated group did not differ significantly from that in the placebo group. However, the improvement during the second and third months was correlated to the quantity of used betamethasone ($r = 0.66$, $P = 0.013$) in the placebo group but not in patients treated with ketoconazole ($r = 0.15$, $P = 0.61$). There was neither a significant difference in the number of clinically improved/not improved (according to SCORAD) patients (Table 2) nor in the subjective evaluation of the improvement made by the patients themselves between the groups.

Comparison of total and specific IgE levels between baseline values and those taken during the previous years, revealed a significant reduction of *M. furfur/P. orbiculare*-specific IgE ($P = 0.0016$, Mann–Whitney test) in patients treated with ketoconazole shampoo, but not in patients treated with other treatment modalities ($P = 0.16$). Specific IgE antibodies against *C. albicans* and *D. pteronyssinus* did not decrease significantly in any of the groups (Table 3).

Adverse effects were rather rare during the study and were reported only from patients treated with ketoconazole. Two patients complained of intensive dreams, nausea and abdominal pain. The symptoms disappeared after cessation of the therapy.

Discussion

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This controlled study confirms our previous findings that systemic antimycotic therapy decreases the levels of specific IgE antibodies to the yeasts *M. furfur* and *C. albicans* as well as the levels of serum IgE in yeast allergic patients. [10] However, during the first month of treatment there was no change of the serum antibody titres. This indicates, that the time period is too short to allow the effect of decreased colonization of the yeasts to influence the antibody levels through such a complex sequence of events, including antigen availability, processing and presentation over antibody production and equilibrium with tissue-bound antibodies. This may also explain why topical ketoconazole treatment failed to show clinical improvement in a previously reported 4-week study. [9] Our observations regarding the effect of prolonged topical ketoconazole in the period preceding entry into this study (Table 3) further support the notion that any antimycotic therapy must be long-standing in order to decrease specific antibody production and clinical symptoms.

It is interesting that systemic ketoconazole administration also reduced the total serum IgE levels. This suggests that a considerable fraction of the IgE production ending in serum IgE could be driven by the abundance of yeast antigenic determinants from both *M. furfur/P. orbiculare* and *C. albicans*, including yeast mannans. [14–16] It could be argued that ketoconazole, with many anti-inflammatory effects, [17,18] may suppress IgE production directly, but this is less likely as we could not demonstrate a significant decrease of specific IgE against the unrelated house dust mite allergen (Table 1).

We were not able to show clinical efficacy of oral ketoconazole when the SCORAD indices were compared with the placebo group. This is not surprising as those who entered the study were allowed to use topical betamethasone cream to control their dermatitis. There were problems recruiting patients to the study from the group of patients with generalized and/or head–neck type AD. Almost half of the patient population invited to the study refrained from participation partly because they were satisfied with their treatment with ketoconazole shampoo and intermittent topical steroids and did not approve the requested wash-out period of 2 months before inclusion. In the placebo group there was a negative correlation between the clinical score and the use of topical steroids but not in the ketoconazole group, indicating that ketoconazole at least to some extent improved the dermatitis. In our population of adult AD patients there is a strong correlation between sensitization to *M. furfur/P. orbiculare* and *C. albicans* but also between sensitization to the two yeasts and to house dust mites. Accordingly all patients in the study except five were also allergic to house dust mites. The fact, that ketoconazole did not influence the sensitization to house dust mites and that allergy to mites might contribute to the dermatitis, [19,20] offers another explanation to the clinical outcome.

In conclusion, oral ketoconazole therapy will reduce levels of specific IgE against *M. furfur/P. orbiculare* and *C. albicans* as well as total serum IgE, provided the treatment will last at least 3 months. As indicated by our findings in the patients treated with topical ketoconazole for extended periods prior to entry into the study, similar benefits are achieved with the topical regimen. Antimycotic treatment, topical or systemic, must be considered as a valuable therapeutic alternative for the subpopulation of AD patients with yeast allergy.

Acknowledgements Go to: Choose Go

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References Go to: Choose Go

1 Faergemann J & Fredriksson T. Age incidence of *Pityrosporum orbiculare* on human skin . *Acta Derm Venereol* 1980; **60**: 531 533.
MEDLINE MEDLINE ISI Abstract ISI Abstract

2 Ruiz-Maldonado R, Lopez-Matinez R, Perez Chavarria EL *et al. Pityrosporum ovale* in infantile seborrheic dermatitis . *Pediatr Dermatol* 1989; **6**: 16 20.
MEDLINE MEDLINE

3 Broberg A & Faergemann J. Infantile seborrhoeic dermatitis and *Pityrosporum ovale* . *Br J Dermatol* 1989; **120**: 359 362.
MEDLINE MEDLINE ISI Abstract ISI Abstract CSA Abstract CSA

4 Faergemann J. Lipophilic yeasts in skin disease. *Semin Dermatol* 1985; **4**: 173 184.

5 Clemmensen O & Hjorth N. Treatment of dermatitis of the head and neck with ketoconazole in patients with type I sensitivity to *Pityrosporum ovale. Semin Dermatol* 1983; **2**: 26 29.

6 Wærsted A & Hjorth N. *Pityrosporum orbiculare*– a pathogenic factor in atopic dermatitis of the face, scalp and neck? *Acta Derm Venereol Suppl* 1985; **114**: 146 148.
MEDLINE MEDLINE

7 Svejgaard E, Færgemann J, Jemec G *et al.* Recent investigations on the relationship between fungal skin diseases and atopic dematitis. *Acta Derm Venereol Suppl* 1989; **144**: 140 142.
MEDLINE MEDLINE

8 Rokugo M, Tagami H, Usuba Y, Tomita Y. Contact sensitivity to *Pityrosporum ovale* in patients with atopic dermatitis . *Arch Dermatol* 1990; **126**: 627 632.
CrossRef crossref MEDLINE MEDLINE ISI Abstract ISI Abstract CSA Abstract CSA

9 Broberg A & Faergemann J. Topical antimycotic treatment of atopic dermatitis in the head/neck area. A double-blind randomised study. *Acta Derm Venereol* 1995; **75**: 46 49.
MEDLINE MEDLINE ISI Abstract ISI Abstract

10 Bäck O, Scheynius A, Johansson SGO. Ketoconazole in atopic dermatitis: therapeutic response is correlated with decrease in serum IgE. *Arch Dermatol Res* 1995; **287**: 448 451.
CrossRef crossref MEDLINE MEDLINE ISI Abstract ISI Abstract

11 Lindgren L, Wahlgren C-F, Johansson SGO, Wiklund I, Nordvall L. Occurrence and clinical features of sensitization to *Pityrosporum orbiculare* and other allergens in children with atopic dermatitis . *Acta Derm Venereol* 1995; **75**: 300 304.
MEDLINE MEDLINE ISI Abstract ISI Abstract

12 Hanifin JM & Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl* 1980; **92**: 44 47.

13 Stalder JF & Taïeb A. Severity scoring of atopic dermatitis: The SCORAD Index. *Dermatology* 1993; **186**: 23 31.
MEDLINE MEDLINE ISI Abstract ISI Abstract

14 Johansson S & Karlström K. IgE-binding components in *Pityrosporum orbiculare* identified by an immunoblotting technique . *Acta Derm Venereol* 1991; **71**: 11 16.
MEDLINE MEDLINE ISI Abstract ISI Abstract

15 Savolainen J & Broberg A. Crossreacting IgE antibodies to *Pityrosporum ovale and Candida albicans* in atopic children . Clin Exp Allergy 1992; **22**: 469 474.

16 Doekes G & van Iemperen-van Dijk AG. Allergens of *Pityrosporum ovale* and *Candida albicans*. I. Cross-reactivity of IgE-binding components . *Allergy* 1993; **48**: 394 400.
MEDLINE MEDLINE ISI Abstract ISI Abstract CSA Abstract CSA

17 Tufano MA, Cipollaro G, Ianniello R, Baroni A, Galdiero F. Antimicrobial agents induce monocytes to release IL-1α, IL-6 and TNFα and induce lymphocytes to release IL-4 and IFNγ. *Immunopharmacol Immunotoxicol* 1992; **14**: 769 782.
MEDLINE MEDLINE ISI Abstract ISI Abstract

18 Williams JG & Maier RV. Ketoconazole inhibits alveolar macrophage production of inflammatory mediators involved in acute lung injury (adult respiratory distress syndrome). *Surgery* 1992; **112**: 270 277.
MEDLINE MEDLINE ISI Abstract ISI Abstract

19 Platts Mills TAE, Mitchell EB, Rowntree S *et al.* The role of dust mite allergens in atopic dermatitis. *Clin Exp Dermatol* 1983; **8**: 233 247.
MEDLINE MEDLINE

20 Sanda T, Yasue T, Oohashi M, Yasue A. Effectiveness of house dust-mite allergen avoidance through clean room therapy in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992; **89**: 653 657.

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- Nicholas Aspres and Chris Anderson . (2004) Malassezia yeasts in the pathogenesis of atopic dermatitis. *Australasian Journal of Dermatology* **45**:4, 199-207
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- E. Nivenius, P. G. Montan, E. Chryssanthou, K. Jung, M. van Hage-Hamsten and I. van der Ploeg. (2004) No apparent association between periocular and ocular microcolonization and the degree of inflammation in patients with atopic keratoconjunctivitis. *Clinical & Experimental Allergy* **34**:5, 725-730
  Abstract | References | Full Text Article | PDF
- A. Zargari, G. Midgley, O. Bäck, S. G. O. Johansson, A. Scheynius. (2003) IgE-reactivity to seven Malassezia species. *Allergy* **58**:4, 306-311
  Abstract | References | Full Text Article | PDF
- C. Johansson, M.H. Sandström, J. Bartosik, T. Särnhult, J. Christiansen, A. Zargari, O. Bäck, C.F. Wahlgren, J. Faergemann, A. Scheynius and M. Tengvall Linder . (2003) Atopy patch test reactions to Malassezia allergens differentiate subgroups of atopic dermatitis patients. *British Journal of Dermatology* **148**:3, 479-488
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