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PREDICTORS OF TREATMENT OUTCOME FOLLOWING THE USE OF ANTIFUNGAL AGENTS TO TREAT ONYCHOMYCOSIS

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The variables that can have an effect on the outcomes in the treatment of toenail onychomycosis with an antifungal agent include factors such as those that are local to the nail unit (e.g., area of nail plate involvement at baseline, thickness of nail plate, perfusion of the nail unit), factors that pertain to the patient (e.g., age of patient, presence of diabetes, family history of onychomycosis, history of chronic tinea pedis), causative dermatophyte species (*Trichophyton rubrum* vs. *Trichophyton mentagrophytes*), results of potassium hydroxide and culture examinations at weeks 36 and 48 of the study. A correlation was performed using these variables as independent variables to determine whether any of these factors could predict which patients were more likely to be (1) mycologically cured and (2) effectively cured at week 48 of the study. The results that are available to date (N = 78 patients) indicate that none of these variables are able to provide guidance as to who may be effectively treated. However, when a larger number of patients have been treated, the analysis may provide predictive factors for successful outcomes following treatment of onychomycosis.

Dr. Gupta has been an investigator for Dermik Laboratories.

100% supported by Dermik Laboratories

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SAFETY RESULTS FROM A DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL IN PATIENTS RECEIVING HIGH-DOSE TERBINAFINE

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Background: Oral therapy with terbinafine has been proven to be an effective therapy for the treatment of onychomycosis. Despite an established record of safety, concerns persist among physicians regarding potential hepatic reactions.

Methods: In this double-blind, placebo-controlled, multicenter study, 53 adult patients with chronic rhinosinusitis received terbinafine 625 mg/d or placebo for a period of 6 weeks. Patients with elevated liver enzymes or known liver disease were excluded from participation. Laboratory tests were collected at baseline, week 3, and week 6.

Results: No clinically significant difference between treatment groups was observed in liver function tests at weeks 3 or 6, and all values were less than twice the upper limit of normal. Mean change from baseline at week 6 in SGOT(AST) was −1.38 U/L placebo versus 2.17 U/L terbinafine and −0.04 U/L vs 1.00, respectively, in SGPT. Similar results were observed in mean change at week 6 for alkaline phosphatase (1.33 U/L placebo vs −1.74 terbinafine) and total bilirubin (0.08 mg/dL placebo vs −0.09 terbinafine). Incidence of adverse events (AEs) was low and similar between groups. Most AEs were mild or moderate in severity and consistent with the disease being studied. Two serious AEs (chest pain and pregnancy) were reported in the terbinafine group, but were not considered related to study drug.

Conclusion: Terbinafine, given for 6 weeks at two and a half times the approved dose for treatment of onychomycosis, demonstrated no clinically significant changes in liver function.

Supported by Novartis Pharmaceuticals Corporation.

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SERTACONAZOLE NITRATE HAS A BROAD SPECTRUM OF ACTIVITY *IN VITRO*

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Sertaconazole nitrate has a wide spectrum of antifungal activity, including activity against dermatophytes, yeasts, and opportunistic filamentous fungi. Sertaconazole nitrate also exhibits *in vitro* activity against gram-positive bacteria, including *Staphylococcus* spp. and *Streptococcus* spp.

The antifungal activity of sertaconazole nitrate was evaluated by determining minimum inhibitory concentrations (MICs) against a variety of micro-organisms isolated from clinical specimens.

Sertaconazole was compared with other commonly used antifungal agents, bifonazole and terbinafine. The MIC varied between 0.01 and 8 μg/mL for the dermatophytes tested and 0.09 and 5.04 μg/mL for yeasts. Sertaconazole activity was superior to bifonazole and miconazole for all dermatophytes tested. Sertaconazole demonstrated a lower MIC against all *Candida* species tested than terbinafine.[1]

Sertaconazole was also tested *in vitro* against common cutaneous bacteria such as *Staphylococcus* and *Streptococcus*. MICs of sertaconazole were 4 μg/mL for *Staphylococcus aureus* and 1 μg/mL for *Streptococcus pyogenes*, which may suggest therapeutic activity in the clinical setting. In addition, sertaconazole nitrate has been shown to be active against the yeast *Pityrosporum ovale*, the organism responsible for tinea versicolor.[2]

Results of *in vitro* tests of sertaconazole nitrate demonstrate activity against a wide array of dermatophytes, *Candida* species, and other yeasts. Comparative *in vitro* tests against commonly prescribed topical antifungal agents showed superior activity against common dermatophytes.

References

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100% sponsored by Johnson & Johnson and Ferrer Laboratories

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SERTACONAZOLE NITRATE RAPIDLY ACHIEVES HIGH CONCENTRATIONS IN THE STRATUM CORNEUM WITH PROLONGED RENTENTION TIME

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Sertaconazole nitrate is a new broad-spectrum antifungal agent. Sertaconazole is not soluble in water, but its benzothiophene residue is highly lipophilic, which enhances cutaneous absorption. Topical antifungals should demonstrate rapid penetration, while maintaining a high concentration at the site of superficial fungal infections. Because dermatophytes reside in the stratum corneum, retention in this layer is essential for antifungal activity. In addition, there should be minimal systemic absorption to assure an excellent safety profile. The objective of this study was to determine the rate and extent of sertaconazole penetration into human skin.

A study of the penetration and concentration of sertaconazole in the stratum corneum after a single application of 100 mg of sertaconazole 2% cream to the backs of 12 healthy volunteers was conducted. Sertaconazole and placebo preparations were applied to 10 squares (30 × 30 mm). Preparations were removed from one square of application area at 0 hour, 30 minutes, and 1, 3, 6, 12, 24, 32, and 48 hours. The skin was wiped with ethanol-soaked cotton balls for extraction in the analytical laboratory. Immediately following the removal of residual medication on the surface of the skin, the stratum corneum was stripped from the respective application area with adhesive tape.

Using the amounts extracted and a stratum corneum thickness of 18 μm, an "effective drug level in the target organ" can be estimated. Converting the amounts per 30 × 30 mm to the amounts per millileter, the apparent average drug level per volume can be estimated. Immediately after application a level of 1409 μg/mL was estimated. Thirty minutes after application, 7030 μg/mL were recovered, and these concentrations were maintained or increased over a 48-hour period. The concentrations achieved are significantly higher than the minimum inhibitory concentrations required for inhibition of dermatophyte growth (data on file).

In conclusion, sertaconazole nitrate rapidly achieves and maintains high concentrations in the stratum corneum for at least 48 hours following a single application. These findings suggest that sertaconazole is an ideal agent for the treatment of dermatophyte infections.

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