Clinical trial

Treatment of onychomycosis: a randomized, double-blind comparison study with topical bifonazole-urea ointment alone and in combination with short-duration oral griseofulvin

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A parallel-group double-blind study was carried out which compared the efficacy of chemical avulsion of affected nail by urea 40% and bifonazole 1% cream alone with that of the same local therapy combined with short-term oral griseofulvin in onychomycosis.

A total of 120 patients were included in the study. Patients' characteristics were comparable in both treatment groups. Of the 98 patients fully evaluated, 91 had toenail involvement and only seven had fingernail involvement. Forty-six of the patients were men and 51 were women. The mean age of the patients was 47.14 ± 13.84 years (range 17–80 years). The duration of onychomycosis was for more than 1 year in 96 patients and for 3 months duration in only one patient, who was in the placebo group. Forty patients had received different previous therapies. All topical treatments were discontinued for at least 2 weeks and oral therapy for at least 2 months prior to the beginning of the study.

The diagnosis was confirmed by positive mycologic cultures. *Trychophyton rubrum* was identified as the pathogen in 90 patients, 45 in each group, *T. tonsurans* in four patients, two in each group, and *T. mentagrophytes* in three patients, two in the griseofulvin treated group, and one in the placebo group.

The first phase of treatment given to all patients consisted of occlusive dressing every 24 h with urea 40% and bifonazole 1% ointment until the infected nail became completely detached. Subsequently, in the second phase bifonazole 1% cream was applied to the nail bed every 24 h for 4 weeks. In addition, concomitantly with the bifonazole cream the patients were randomly allocated to a daily oral double-blind treatment with griseofulvin 500 mg or placebo, for 4 weeks. Clinical and mycologic evaluations were carried out at baseline, immediately after removal of the nail, and at 3 days, 4 weeks, and 4 months after the end of treatment with bifonazole cream and griseofulvin/placebo tablets. Mycologic examination included identification of fungi by KOH preparation and culture on potato dextrose agar. Positive cultures were transferred for identification on Sabouraud's.

Criteria for evaluation of efficacy comprised: "cure" defined as clinical and mycologic cure (fresh specimen and culture negative) at both investigation times after the end of treatment; "late cure" defined as mycologic cure at both investigation times after the end of treatment, clinical clearing of the nail only 4 months after the end of treatment; "improvement" defined as mycologic cure and only partial clinical improvement at both times after the end of treatment; "failure" indicating no mycologic cure (fresh specimen and/or culture positive); and "relapse" signifying a change from negative findings 1 month after the end of treatment to positive findings 4 months after the end of treatment. Adverse reactions were evaluated on each visit.

Only those patients who had completed clinical and mycologic evaluation during the entire study were included in the final statistical analysis. Those patients with partial evaluation were included only in the evaluation of adverse events. Based on the assumptions of a failure rate (failure and relapse) of 30% with bifonazole cream alone and

of 10% with bifonazole cream and griseofulvin tablets, $a = 0.05$ and $b = 0.2$, the required sample size was at least 58 patients for each treatment group (Casagrande formula, one-sided test). The primary efficacy variable "assessment of treatment" (cure and improvement versus failure and relapse) was tested for treatment differences by Fisher's exact test ($a = 0.05$, one-sided test; H_0, no advantage with additional systemic therapy of griseofulvin). Additionally, the relapse rates of both treatments were tested exploratively in the same way as the primary efficacy variable. All other data were analyzed descriptively.

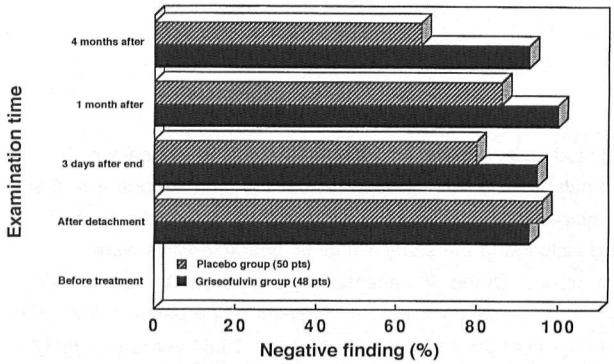

Figure 1 Mycologic cure rate (negative culture and KOH)

Results

Results of 48 patients in the griseofulvin and bifonazole 1% cream group and 50 patients in the placebo and bifonazole 1% cream group were valid for efficacy analysis. The reasons for drop out were bad compliance during the treatment period in 15 patients and during the follow-up period in three patients, all in the placebo group. Mean time to detachment of the nail was 24.9 ± 13 days (6–84 days).

Efficacy

The mycologic cure after detachment of the nail plate was seen in 45 of 48 patients (93%) in the griseofulvin group and in 48 of 50 patients (96%) in the placebo group (Figs 1, 2). At 3 days after the end of the study 95% of the griseofulvin group and 80% of the placebo group were mycologically negative. The corresponding values at 1 month after the end of therapy were 100% and 86% respectively. At 4 months after therapy negative cultures were observed in 45 patients (93%) in the bifonazole and griseofulvin group and in 31 patients (66%) in the bifonazole and placebo group ($P < 0.01$). Based on this data the mycologic relapse rate was 7% (three patients) in the bifonazole and griseofulvin group and 20% (10 patients) in the bifonazole and placebo group ($P < 0.01$).

Clinical and complete cure (clinical and mycologic) (Table 1) was achieved in 21 patients (43.7%) of the bifonazole and griseofulvin group and in 10 patients (20%) of the bifonazole and placebo group. An additional late cure was observed in both groups, in six patients (12.5%) and one patient respectively. Partial improvement was achieved in 12 and eight patients respectively, and relapse occurred in six and 12 patients. The failure rate was 6% (three patients) in the griseofulvin group and 38% (19 patients) in the placebo group.

Adverse events

Six patients (5%) reported adverse events possibly related to the drug, five cases (8.5%) in the bifonazole and griseofulvin group and one case (1.7%) in the bifonazole and placebo group. In three cases the adverse events were related to griseofulvin, all three having gastro-intestinal distress. In two cases the symptoms were classified as severe and in one as moderate. One of these patients also developed a skin eruption. The adverse events in the other three patients were related to the topical treatment; two patients developed an in-grown nail which resolved after local therapy and one patient had severe paronichia with erythema, edema, and pain. All three patients with side-effects due to griseofulvin and the patient with the severe paronichia discontinued therapy permanently.

Discussion

Before the introduction of griseofulvin, onychomycosis was considered as being difficult to treat or even incurable. Griseofulvin is able to cure the majority of patients with fingernail onychomycosis after a treatment period of 6–12 months. However, in a review article[1] on the efficacy of this therapy, griseofulvin alone can cure only a minority of toenail onychomycosis, even after periods of treatment of 12 months or longer. Promising results in both toenail and fingernail infections were achieved when oral griseofulvin was combined with surgical avulsion[2] or with topical antimycotics[3]. With all these therapies the mycologic cure rates seem to be more favorable than the clinical ones.[1]

The mycologic cure rate obtained at the end of follow-up in this study with only chemical avulsion by bifonazole 1% and urea 40% ointment was similar to the 62%

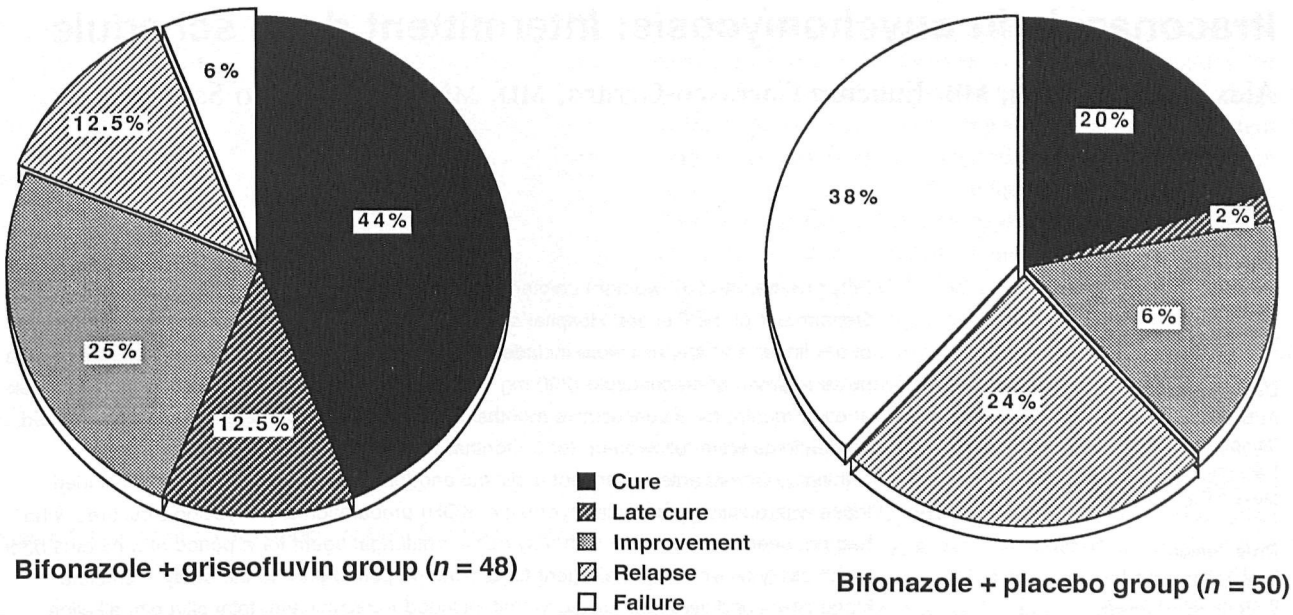

Figure 2 Final evaluation of efficacy

Table 1 Final evaluation of efficacy

	Griseofulvin group (n = 48)	Placebo group (n = 50)
Cure	21 (43.75%)	10 (20%)
Late cure	6 (12.5%)	1 (2%)
Improvement	12 (25%)	8 (16%)
Relapse	6 (12.5%)	12 (24%)
Failure	3 (6.25%)	19 (38%)

negative cultures obtained in previous studies with Mycospore-Onychoset (urea 40% and bifonazole 1% ointment).[4] However, this study indicates that the addition of oral griseofulvin tablets for 4 weeks only has significantly increased the mycologic cure rate and has also reduced the relapse rate.

The clinical cure rate, and thus the complete cure rate, as earlier reported,[1] was less favorable in both groups than the mycologic cure rate. For partial improvement, there was a significant difference in favor of the group treated with the combined topical and oral treatment, as compared with the group treated by chemical avulsion alone.

Only a few patients in both groups reported adverse events. They were mild in most cases and were the reason for discontinuation of therapy in only four patients. This combined treatment scheme offers a good alternative in the treatment of onychomycosis. This is especially true in toenail infections in view of the long treatment period necessary, the limited efficacy of oral griseofulvin tablets, and the possibility of contraindications and possible side-effects with the newer oral antimycotics.

References

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