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Double-blind comparison of amorolfine and bifonazole in the treatment of dermatomycoses

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Summary

A total of 232 patients with mycoses of skin folds, body, or feet were entered into a double-blind, parallel group-study. Therapy with 0·125, 0·25, 0·5% amorolfine cream or 1% bifonazole cream was randomly allocated to patients. The cream was applied once daily for 4 weeks on average. At screening, in 208 patients evaluated for efficacy, a total of 225 fungi were isolated: *T. rubrum* (77), *T. mentagrophytes* (65), other dermatophytes (15), *C. albicans* (34), other yeasts (26) and moulds (8). One to three weeks after ending therapy, the percentage of patients with negative cultures were as follows: 87·3, 91·7, 90·7 and 92·2% in the amorolfine cream 0·125%, 0·25%, 0·5% and bifonazole cream 1% groups respectively. The differences were not statistically significant. Six out of 223 patients evaluated for safety had local adverse events: one (1·7%), two (3·6%) and three (5·4%) in the amorolfine cream 0·125%, 0·25% and bifonazole cream 1% groups respectively. The most common local adverse events were burning and increased itching, erythema or weeping. A once-daily application of amorolfine cream can be recommended for the treatment of dermatomycoses on the basis of the results from this study. However, a further and similar study with a larger number of patients was required to select the concentration of amorolfine cream for therapeutic use.

The new, phenyl-propyl morpholine antimycotic agent, amorolfine (Ro 14-4767), is highly active against dermatophytes and yeasts *in vitro* and *in vivo*.[1–4] Compared with antifungals such as polyenes, imidazoles, griseofulvin, tolciclate or naftifine, amorolfine exhibits between 2·9 and 263 times more potency against *C. albicans* and is 3–66 times more potent against *Trichophyton mentagrophytes* in experimental conditions.[1]

Amorolfine, applied locally, was well tolerated in volunteers. Because of its long skin-retention time (at least 24 h),[4] it is likely that the active agent would be therapeutically effective in dermatomycoses when applied once daily.

The aim of the present multicentre study was to compare the efficacy and tolerability of three concentrations of amorolfine cream (0·125%, 0·25% and 0·5%) and bifonazole cream 1% applied once daily for up to 6 weeks in patients with dermatomycosis.

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Patients and methods

Study design

Patients with the diagnosis of dermatomycosis, aged 16 or over, were entered into this double-blind, randomized, parallel study if they had positive mycological findings (direct microscopic examination and fungus culture). A history was taken from each patient and the patients' demographic characteristics were recorded. Pregnant women and patients with a bacterial infection, onychomycosis or trichomycosis were excluded. Patients who had used other antifungals in the preceding 2 weeks or who required other antimycotic agents during the trial were also excluded.

Therapy with 0·125%, 0·25% or 0·5% amorolfine cream or 1% bifonazole cream was randomly allocated to patients with instructions to apply the cream thinly to the affected skin area once daily in the evening. As dermatomycoses are normally treated for 3–6 weeks, treatment in this study was to last for a minimum of 2 and a maximum of 6 weeks. Compliance was defined as adherence to the correct application of medication and regular attendance at clinical assessments during treatment and at follow-up. Mycological examinations were repeated at the end of treatment and at follow-up 1–3 weeks later. Patients gave verbal or written informed consent and had the right to withdraw from the trial at any time. The study was performed at four centres in West Germany from January to December 1985.

Evaluation of efficacy

Mycological outcome was assessed from cultures taken at follow-up examination (1–3 weeks after the end of treatment) and defined as mycological cure (=negative culture) or mycological failure (=positive culture). In addition, the outcome was assessed according to the type of fungus. Clinical signs and symptoms were assessed at baseline, weekly and at follow-up and scored as: absent, slight, moderate or severe. Size of the target lesion in relation to baseline was assessed weekly and at the post-treatment visit, and was scored as: disappeared, >50% regression, <50% regression, unchanged or increased. At follow-up, investigators recorded their overall assessment of treatment efficacy according to the following scheme: 'cure' (negative mycological findings and clinical signs/symptoms absent), 'improvement' (negative mycological findings and signs improved) or 'failure' (positive mycological findings and signs improved, unchanged or worse). All reasons for premature withdrawal from the trial were noted.

Evaluation of safety

Adverse events were noted together with their duration, severity, relationship to treatment and management. Safety was evaluated if patients had been assessed at least once during treatment or if they withdrew as a result of adverse events after entering the study. Each investigator also made an overall assessment of local tolerability at the end of treatment on a four-point scale.

Statistical analysis

The treatment groups were compared regarding background and relevant prognostic factors. The main efficacy parameter (mycological outcome, i.e. mycological cure or failure at follow-up) was analysed using the Chi-squared test (significance two-sided, $\alpha=0{\cdot}05$). All patients with baseline data and at least one clinical re-examination were included in the intention-to-treat efficacy analysis. A total of 232 patients divided into four groups were included into the study.

Results

From a total of 232 patients entered into the study, nine patients were lost to follow-up and were excluded from the analysis. Thus, 223 patients completed at least one examination and were eligible for the intention-to-treat and safety analyses. The demographic characteristics of these treatment groups were homogeneous (Table 1).

Mycoses occurred most commonly on the feet, followed by the body and skin folds (Table 2), the most frequent diagnosis being tinea pedis (80/223), tinea corporis (32/223) and tinea inguinalis (23/223). Out of a total of 241 fungi identified in 222 patients at baseline, the most common were dermatophytes, including *T. rubrum* (80/165) and *T. mentagrophytes* (67/165) and yeasts, including *C. albicans* (37/67) and *Candida* sp. (20/67). In one patient the culture at baseline was negative. The treatment groups were homogeneous with respect to the fungi isolated.

In all treatment groups the median duration of existing dermatomycosis was 1 month (range 3 days–40 years). Twenty-one patients had previously received antifungal treatment for their condition.

Efficacy

Two hundred and eight out of 223 patients were evaluated in the standard analysis of efficacy, 15 patients having deviated from the protocol. Reasons for deviation were negative culture at baseline (one), completion of less than 2 weeks' treatment (seven), suspected non-

Table 1. Patient demographics

	Amorolfine cream (%)			Bifonazole cream (%)
	0·125	0·25	0·5	1
Patients entered	58	58	58	58
Lost to follow-up	1	2	3	3
Patients eligible for the intention-to-treat and safety analyses	57	56	55	55
Male (%)	42 (73·7)	39 (69·6)	42 (76·4)	43 (78·2)
Female (%)	15 (26·3)	17 (30·4)	13 (23·6)	12 (21·8)
Mean age (s.d.)	36·9 (19·2)	40·4 (18·0)	41·9 (20·4)	35·8 (16·7)
Mean height (s.d.)	174·7 (9·3)	176·1 (7·5)	176·5 (7·6)	177·3 (7·6)
Mean weight (s.d.)	72·8 (11·8)	72·9 (8·6)	74·6 (9·5)	75·4 (10·3)

Table 2. Localization of mycosis

	Amorolfine cream (%)			Bifonazole cream (%)
	0·125	0·25	0·5	1
Localization of mycosis:				
Foot (%)	28 (49·1)*	24 (42·8)	25 (45·4)	27 (49·1)
Large body area (%)	15 (26·3)	17 (30·3)	17 (30·9)	14 (25·4)
Skin fold (%)	13 (22·8)	13 (23·2)	12 (21·8)	11 (20·0)
Other (%)	1 (1·8)	2 (3·6)	1 (1·8)	3 (5·4)
Total patients (%)	57 (100·0)	56 (100·0)	55 (100·0)	55 (100·0)

* Numbers in parentheses are percentages.

compliance (one) and post-treatment assessment not done (six).

The mycological outcome was similar in each treatment group, with negative cultures in around 90% of cases at the follow-up examination (Fig. 1). No statistically significant differences were detected between the four treatments at follow-up. In over 90% of cases (188/202; 93·1%) the results of microscopy and culture were in agreement (both negative or both positive). In 178 out of a total of 188 patients with negative culture at follow-up (1–3 weeks after the end of treatment), microscopic finding was also negative. Five patients with negative cultures (two, one and two in the amorolfine 0·125% and 0·5% groups and bifonazole 1% group respectively) had positive microscopic findings at follow-up; three of them were clinically improved and two cured. In another five patients no microscopy was performed at follow-up (they were clinically cured, with negative microscopy at the end of treatment and repeatedly negative cultures).

At follow-up, the percentage of fungi eradicated in each treatment group is shown in Table 3. There were no statistically significant differences between the four treatments with respect to eradication of *T. rubrum*, *T. mentagrophytes*, total dermatophytes, yeasts and all fungi.

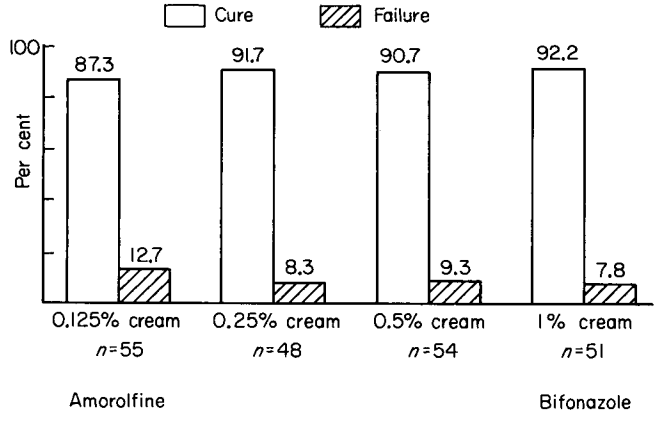

Figure 1. Mycological outcome at follow-up.

Sub-group analysis of mycological outcome showed that there were no statistically significant differences between treatments with regard to localization of the mycoses (feet, body, skin folds).

The clinical signs and symptoms most apparent at baseline (itching, erythema and scaling) were evenly distributed between the four groups, except for itching which was more common in amorolfine-treated patients. At follow-up, the majority of these symptoms were no longer present (no significant differences between treatments). The changes from baseline to follow-up are shown in Table 4. There were no significant differences between treatments in relation to their effect on lesion size. At follow-up, lesions had disappeared or improved by >50% in 49/53 (92·4%), 44/46 (96%), 50/52 (96%) and 45/49 (92%) patients in the 0·125%, 0·25%, 0·5% amorolfine and 1% bifonazole cream groups respectively. According to the investigators' final assessment of efficacy, in a total of 208 patients, more than 90% cure or improvement was observed in each group, with no significant differences between treatments.

Safety

Patients were exposed to medication for a mean of 25·3, 26, 25·9 and 24·8 days in the 0·125%, 0·25%, 0·5% amorolfine and 1% bifonazole groups respectively. During this time, all treatments were generally well tolerated; most of the symptoms reported by patients were of a kind commonly associated with dermatomycoses. According to the investigators' assessment of safety, there was excellent or good local tolerability in 56/57 (98·3%), 52/56 (92·9%), 53/55 (96·4%) and 51/55 (92·7%) patients receiving treatment with 0·125%, 0·25%, 0·5% amorolfine and 1% bifonazole cream respectively.

Six out of 223 patients (2·7%) experienced local intolerance, received a lotion/mixture/cream and discontinued treatment; in each case, association between treatment and event was considered to be possible or probable. The frequency of local adverse events per

Table 3. Eradication of fungi

	Fungi isolated at baseline				Fungi eradicated at follow-up			
	Amorolfine cream (%)			Bifonazole cream (%)	Amorolfine cream (%)			Bifonazole cream (%)
	0·125	0·25	0·5	1	0·125	0·25	0·5	1
Dermatophytes								
T. rubrum	24	13	22	18	20 (83)*	11 (85)	20 (91)	16 (89)
T. mentagrophytes	16	15	16	18	15 (94)	13 (87)	15 (94)	17 (94)
T. terrestre	1				0			
M. canis	1	1		2	1	1		2
E. floccosum	2	3	2	3	2	3	2	3
Yeasts								
C. albicans	8	8	11	7	7	8	9	6
Candida sp.	3	6	5	3	3	6	5	3
Rhodotorula sp.	4	2	2	1	4	2	2	1
Moulds								
A. niger	1	1	1		1	1	1	
A. fumigatus		1				1		
Aspergillus sp.	1	1	1	1	1	1	1	1
Dermatophytes	44	32	40	41	38 (86)	28 (87)	37 (92)	38 (93)
Yeasts	15	16	18	11	14 (93)	16 (100)	16 (89)	10 (91)
Moulds	2	3	2	1	2	3	2	1
Total fungi	61	51	60	53	54 (89)	47 (92)	55 (92)	49 (92)
Total patients	55	48	54	51	48	44	49	47

NB: in 16 patients more than one fungus was isolated at baseline.
* Numbers in parentheses are percentages.

Table 4. The course of itching, erythema and scaling

	At baseline				At follow-up			
	Amorolfine cream (%)			Bifonazole cream (%)	Amorolfine cream (%)			Bifonazole cream (%)
Symptom/ sign	0·125 ($n=55$)	0·25 ($n=48$)	0·5 ($n=54$)	1 ($n=51$)	0·125 ($n=55$)	0·25 ($n=48$)	0·5 ($n=54$)	1 ($n=51$)
Presence of								
Itching (%)	94	85	91	84	11	15	15	12
Erythema (%)	96	94	93	90	22	21	22	16
Scaling (%)	94	98	98	96	24	23	20	16

treatment group and their severity are shown in Table 5. There were no reports of systemic adverse events during the course of the study.

Discussion

A mycological cure rate of about 90% was achieved in 157 patients with dermatomycosis after treatment with amorolfine cream 0·125, 0·25 or 0·5%. The cream was applied once daily for 4 weeks on average and the fungus culture was repeated at the end of treatment and 1–3 weeks thereafter. The mycological cure rate in 51 patients treated with bifonazole cream 1% was similar. The results of treatment with amorolfine as well as bifonazole in this study are comparable with those published for bifonazole in other studies.[5–9]

The most common pathogens isolated in our patients were the dermatophytes, *T. rubrum* and *T. mentagrophytes* and the yeast *Candida* sp. (including *C. albicans*). Relative treatment resistance of *T. rubrum* was not seen in

Table 5. Local adverse events

	Amorolfine cream (%)												Bifonazole cream (%) 1 severity			
	0·125 severity				0·25 severity				0·5 severity							
Local adverse event	*n*	mild	mod.	sev.	*n*	mild	mod.	sev.	*n*	mild	mod.	sev.	*n*	mild	mod.	sev.
Itching/increased itching	1			1	1			1					1			1
Burning					2		1	1					2			2
Local irritation													1			1
Erythema/increased erythema	1			1	2		1	1					2			2
Weeping/increased weeping	1			1	2		1	1					1			1
Oedema	1		1		1		1									
Total adverse events	4				8				0				7			
Total patients with adverse events	1 (1/57=1·7%)				2 (2/56=3·6%)				0 (0/55)				3 (3/55=5·4%)			

NB: mod.=moderate, sev.=severe.

our study; depending on the amorolfine cream concentration, mycological cure rates up to 91% were achieved.

At screening, *Rhodotorula* and/or *Aspergillus* were isolated together with a dermatophyte or *Candida* in a total of 10 patients. *Rhodotorula* and *Aspergillus* are generally considered to be contaminants. So, in another five patients with isolation of *Aspergillus* only, no pathogen was identified. At follow-up, the culture was negative in all these 15 patients. As regards the localization of infection, the patients with mycotic foot infections showed results equally as good as those with mycosis of skin folds or the body (mycological cure rates in amorolfine groups ranged from 87 to 92%). After treatment, the large majority of patients were symptom-free. Erythema and scaling were still present in about 20% of patients (in all amorolfine groups), but in about a half these signs were only slight and residual.

Amorolfine cream can be recommended for the treatment of dermatomycoses and may also replace azoles where these are not well tolerated. This study showed that it is sufficient to apply the cream once daily. However, a further and similar study with a larger number of patients was required in order to select the concentration of amorolfine cream for wide therapeutic use.

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