ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1993, p. 2064–2068
0066-4804/93/102064-05$02.00/0
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Vol. 37, No. 10

Treatment of Tinea Unguium with Medium and High Doses of Ultramicrosize Griseofulvin Compared with That with Itraconazole

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Received 24 March 1993/Returned for modification 28 June 1993/Accepted 20 July 1993

Toenail tinea is a very recalcitrant dermatosis. Griseofulvin at ≥500 mg/day is the current medication of choice, but it is minimally successful. In a controlled open trial ultramicrosize griseofulvin (UMSG) at doses of 660 and 990 mg/day was compared with itraconazole at 100 mg/day in 109 patients. At 4-week intervals, the patients were evaluated for their clinical and mycological statuses and adverse reactions. Treatment was given for up to 18 months. Compliance was checked by tablet counting. Response (cure, partial cure, marked improvement) was analyzed by the intent-to-treat method. Cured and partially cured patients were followed up. Except for one early dropout, the toenails (mean, 6 to 7) were involved. Cure or partial cure was found in 6% (UMSG at 660 mg), 14% (UMSG at 990 mg), and 19% (itraconazole at 100 mg) of patients ($P = 0.2097$); marked improvement was found in 36, 44, and 39% of patients in the three treatment groups, respectively. Most patients had to be treated for 18 months. Failure was related to short medication periods (adverse drug reactions, dropout). While stable cure was not obtained with UMSG at 660 mg, the higher dose of UMSG and itraconazole gave stable cures in the other patients. Side effects of nausea, diarrhea, and headache were found in 20, 26, and 11 patients, respectively ($P = 0.0028$), and the numbers in whom medication had to be discontinued differed, too ($P = 0.0137$). While there was no major difference with glutamic-pyruvic transaminase and γ-GT, total and low-density lipoprotein cholesterol levels declined slightly in the itraconazole group ($P = 0.0357$ and $P = 0.0639$, respectively, at 3 months). More than 70% of the patients had an average compliance of ≥90%; four patients (two dropouts) were poor compliers. In conclusion, it appears questionable whether griseofulvin can continue to be considered the "gold standard" in the treatment of toenail tinea. At present, itraconazole at 100 mg shows better efficacy and is better tolerated.

Despite the introduction of griseofulvin about 30 years ago, tinea unguium remains a major therapeutic problem. Toenail tinea in particular is considered a widely incurable disease (7). Experience with griseofulvin for the treatment of onychomycosis by and large is based on the microsize form administered at fairly low doses of up to 500 (1,000) mg. Pharmacokinetic studies have indicated higher plasma and skin tissue drug levels if ultramicrosize griseofulvin (UMSG) is used. Plasma and skin tissue drug levels following administration of 330 mg of UMSG correspond to those following 500 mg of the microsize form (9, 17, 18). Medium and high doses of UMSG look to be particularly rewarding for the treatment of recalcitrant dermatophytoses.

Some years ago, the imidazole derivative ketoconazole was discussed as an alternative for the treatment of tinea unguium (3, 14, 25). Later, safety concerns made the drug obsolete for that indication (2, 8). The triazole itraconazole seemed to be free of such difficulties (13, 20, 21). Its in vitro activity against dermatophytes (6, 22) and plasma and skin tissue itraconazole levels (1, 16) suggest that itraconazole at 100 mg/day may be useful.

Previous trials of onychomycosis suffered from a variety of shortcomings (7). Thus, the present study design was conceived not only to compare various treatment modalities but also to obtain more insight into the parameters of success in onychomycosis treatment.

In particular the following hypotheses were tested. (i) Conventional doses of griseofulvin, even of the ultramicrosize type (UMSG at 660 mg), are only marginally effective, if at all. (ii) The use of higher doses of griseofulvin (UMSG at 990 mg) is feasible in terms of safety and efficacy. (iii) Itraconazole at 100 mg is at least as effective as UMSG at 990 mg and is better tolerated. (iv) Therapeutic success depends on age, area of involvement, and the number of involved nails. (v) Cure is more likely when culture and potassium hydroxide preparations become negative early in treatment. (vi) Therapeutic failure is linked to irregular drug use.

MATERIALS AND METHODS

Patients. The study described here was a controlled open trial performed at the Department of Dermatology of Munich University. The study protocol was approved by the local Ethical Committee. A total of 109 outpatients with tinea unguium of the toenails, fingernails, or both took part in the study after giving voluntary written informed consent. Inclusion criteria were suggestive clinical appearance, a positive KOH preparation, and a dermatophyte cultured on Kimmig's agar within 3 months before the start of medication. Material was obtained from the border of a lesion by high-speed fraising. Exclusion criteria were severe additional diseases (e.g., impaired liver and kidney function,

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lupus erythematosus, porphyria) and systemic antifungal treatment within the previous 4 weeks. Moreover, all patients aged less than 18 years, pregnant and lactating women, as well as those who were not using suitable contraceptive measures were excluded from the study.

Study protocol. A total of 120 patients referred to the hospital between 1987 and 1990 and diagnosed with tinea unguium were asked to take part in the study. The patients were assigned a study number in the order of their agreement to take part in the study. During the next weeks, baseline values were collected. Eleven patients refused to continue cooperation before the completion of the entrance examination and were excluded.

The study number served for the random assignment of the patients to the three treatment groups (1:1:1 ratio). Therapy was begun after contraindications had been excluded. The patients were to receive UMSG at 660 or 990 mg once a day (tablets with 330 mg of Polygris; Essex Pharma, Munich, Germany) or itraconazole at 100 mg (capsules; Janssen GmbH, Neuss, Germany) once a day. The medication was taken after breakfast. Treatment was continued for up to 18 months. Medication was stopped earlier in patients found to be cured both clinically and mycologically at two consecutive follow-up visits and in patients with intolerable side effects. No additional topical treatment or nail avulsion was performed.

Clinical and mycological investigations. At every visit (before the start of the study, at monthly intervals during treatment, and, if the patient was cured, at 1, 3, and 12 months thereafter), the investigator clinically rated the signs of disease (dyschromasia, subungual hyperkeratosis, nail dystrophy, paronychia) and recorded the involved area of every nail (5). One of the nails with the most extensive lesions, if possible, the toenail of the big toe, was defined as the test nail which served for the rating of improvement. All toenails, fingernails, or both were documented photographically in a standardized fashion. Culture identification was based on macroscopic and microscopic findings (19). Except for the follow-up period, a blood sample was taken for a complete blood count and the check of glutamic-pyruvic transaminase (GPT), gamma glutamyltransferase (γ-GT), alkaline phosphatase, total bilirubin, cholinesterase, creatinine, and total protein as well as blood lipids. Patients were also asked to report subjective adverse reactions to treatment.

The clinical response to treatment was assessed in a way similar to the one described by Walsoe and coworkers (23). Patients were rated cured when they showed complete clinical remission with negative culture and microscopy and partially cured when microscopy alone remained positive. Marked improvement was recorded if there was only minimal clinical involvement of the test nail and no dermatophyte could be grown. Other cases in which the area of involvement of the test nail plate had declined by at least 50% of the baseline condition were called improved.

Medication compliance. Compliance was determined by the tablet or capsule counting method. On each visit, the patients received the drug for the following 35 days (and in some cases 70 days) and were instructed to return the unused medication on the next visit. Compliance with medication was calculated as described previously (11, 15). Average compliance (AC) was expressed as the percentage of the scheduled dose taken by the patient during the study period (not including periods when no return of the remainder was made). In poor compliers (AC, <75%) and patients who repeatedly failed to return the medication (suspected poor compliance), the regression of the involvement of the test nail was evaluated for a coincidence of a failure to improve and a (possible) low level of drug intake.

Additional investigations. The in vitro susceptibilities of all dermatophytes cultured were determined by a broth microdilution test. All blood samples were analyzed for drug levels. The results will be reported separately, as will the clinical photodocumentation series.

Statistical analysis. The present study was exploratory in nature. Results are reported for all subjects enrolled in the study except for those who dropped out before the completion of baseline parameters (intention-to-treat analysis). All statistical tests were performed as two-tailed tests by using the IDV program package (IDV, Gauting, Germany). The treatment groups were evaluated for comparability by the R×C test. This also served for the evaluation of treatment response, adverse drug reactions, and dropout because of intolerable adverse reactions. In case of an asymptotic P (Pearson) level of ≤ 0.05, the respective groups were analyzed two by two. Changes between baseline and treatment values for hepatic, renal, and blood lipid indices were compared by the sign test and Bowker's test (3rd and 12th follow-ups under treatment).

RESULTS

Patients' characteristics at baseline. The groups assigned to the different treatment regimens were well matched (Table 1). There were no significant differences between the three groups with respect to sex, age, or body weight or the duration of onychomycosis, which ranged from 6 months to 35 years. In more than 50% of the patients of each group, onychomycosis had been treated previously: 4 to 9 patients of each group had previously received griseofulvin and 10 to 17 had received local therapy (mostly with an azole antifungal agent). Except for one patient who presented with fingernail involvement only and who had to stop treatment within 1 week because of gastrointestinal disturbances on taking UMSG at 990 mg (this patient was included in the safety analysis only), all the other subjects suffered from tinea of the toenails. On average, six toenails in each patient were involved, and the area of involvement of the most severely affected nail was about 90% of the entire nail plate. Only in 12 patients did this figure not exceed 50%. At the start of treatment, a dermatophyte was cultured from nail material from 90 patients (*Trichophyton rubrum* from 85 patients, *Trichophyton mentagrophytes* from 5 patients), but a dermatophyte was detected by culture in all of them within 3 months prior to the study and recurred during therapy in 10 patients who were negative at the baseline.

Clinical and mycological cure. Seventy-nine patients complied with the trial protocol in full. The remainder were lost to follow-up. The numbers of patients cured of toenail tinea, partially cured, much improved, or improved are given in Table 2. Cure or partial cure was obtained in 6% of the patients who received UMSG at 660 mg, 14% who received UMSG at 990 mg, and 19% of those on itraconazole at 100 mg ($P = 0.2097$). The corresponding figures for major improvement were 36, 44, and 39%. In a few patients, a treatment period of less than 18 months was required, as shown in Table 3. There was no clear-cut relation between outcome and age, body weight, area of involvement, or number of nails involved. An unfavorable outcome (improvement only or no essential change), however, was predominantly seen in patients who were treated for a short duration because of either side effects requiring a premature

TABLE 1. Patient characteristics at baseline[a]

Treatment group	Sex (no. of patients)[b]	Age (yr)	Wt (kg)	Toenails[c]			Fingernails[c]			No. of yr of previous treatment (treatment, no. of patients)[d]
				No.	Min	Max	No.	Min	Max dis.	
UMSG, 660 mg	F,15;M,21	45.9 ± 10.5	71.5 ± 12.2	7 ± 3	18.3 ± 23.6	89.7 ± 21.3	0.7 ± 1.8	13.6 ± 29.3	19.2 ± 36.3	7.9 ± 37.1 (Gris, 8; topical, 13)
UMSG, 990 mg	F,20;M,17	47.9 ± 12.6	71.1 ± 12.8	6 ± 3	25.0 ± 30.2	83.1 ± 27.9	0.8 ± 1.5	12.0 ± 25.3	20.8 ± 35.4	7.4 ± 5.0 (Gris, 4; topical, 17)
Itraconazole, 100 mg	F,18;M,18	44.9 ± 15.8	70.2 ± 13.2	7 ± 3	34.4 ± 36.5	90.6 ± 21.8	0.7 ± 1.9	11.4 ± 29.1	16.7 ± 35.1	8.1 ± 6.5 (Gris,9;topical, 10)

[a] Values are means ± standard deviations.
[b] F, female; M, male.
[c] Mean numbers of involved nails (No.) and lesional area (percent of total surface area) of the nail plates with minimum (min) and maximum (max) involvement in each patient.
[d] Gris, oral griseofulvin treatment.

TABLE 2. Therapeutic outcomes at the end of treatment in patients with toenail tinea[a]

Treatment group	No. of patients				
	Cured	Partially cured	Markedly improved	Improved	No change
UMSG, 660 mg	2	0	13	14	7
UMSG, 990 mg	2	3	16	5	10[b]
Itraconazole,100 mg	3	4	14	5	10

[a] $P = 0.1631$ (R×C test).
[b] This value does not include one patient who suffered exclusively from fingernail involvement.

end of treatment or loss to follow-up. This explains the result for 12 patients each in the groups of patients on UMSG at 660 and 990 mg and in 11 patients on itraconazole (including a female patient who became pregnant; see below) treated for up to 1 year only.

The fates of the patients who were cured or partially cured are also given in Table 3. Interestingly, a few patients on UMSG at 990 mg or itraconazole who were only partially cured at the end of the treatment period were found to be completely cured later on. Two additional patients on UMSG at 990 mg and rated as much improved were also found to be cured when they voluntarily returned for follow-up 3 months after the end of treatment. The rates of negative KOH and cultural findings within the first 6 months of treatment were not related to the therapeutic outcome.

Safety. Side effects were noted in 20 patients in the group receiving UMSG at 660 mg, 26 in the group receiving UMSG at 990 mg, and 11 taking itraconazole ($P = 0.0028$). Itraconazole was better tolerated compared with the high dose ($P = 0.0007$) and even the low dose ($P = 0.0322$) of griseofulvin. In all groups, side effects primarily concerned the gastrointestinal tract, the central nervous system, or both. In particular, nausea, diarrhea, and headache were reported.

TABLE 3. Patients cured or partially cured at the end of the treatment[a]

Treatment group and patient no.	End of treatment		Follow-up after the end of treatment			
			1–3 mo		6–12 mo	
	Week	Status	Week	Status	Week	Status
UMSG, 660 mg						
4	44	c	4	pc	18	Relapse
40	76	c				
UMSG, 990 mg						
18	77	pc	13	pc	38	Relapse
28	68	c	13	c	38	c
91	79	c	12	c	52	c
102	84	pc	4	c		
110	45	pc				
Itraconazole, 100 mg						
2	34	c	4	c	54	c
19	36	c				
63	89	pc	13	pc	52	c
86	78	c	5	c	50	c
99	79	pc	5/13	pc/c		
100	62	pc				
114	77	pc	6/14	pc/c		

[a] c, cured; pc, partially cured.

TABLE 4. Reasons for the end of treatment

Treatment group	No. of patients				
	Regular treatment period		Reason for premature end of treatment		
	18 mo	<18 mo (cured)	Side effects	Lost for follow-up	Pregnancy
UMSG, 660 mg	17	1	8	10	0
UMSG, 990 mg	12	1	16	8	0
Itraconazole, 100 mg	16	2	5	12	1

Discontinuation of treatment because of side effects was necessary in different proportions of the various treatment groups (Table 4). Statistical comparison of the numbers of patients removed from treatment because of adverse drug reactions and those not removed for this reason indicates a difference between the treatment groups ($P = 0.0137$). Better tolerability of itraconazole and possibly also UMSG at 660 mg compared with that of UMSG at 990 mg was suggested by the results of the respective two-by-two comparisons ($P = 0.0056$ and 0.0559).

On the whole, there were no remarkable differences concerning pharmacological safety parameters before or during treatment. Repeatedly elevated GPT values were found in three patients on UMSG at 660 mg, in all of whom the baseline value was normal. The corresponding figures for patients on UMSG at 990 mg and itraconazole were 3 and 1 and 2 and 1, respectively. With γ-GT the situation in the three treatment groups was as follows: 15 and 12, 13 and 7, and 7 and 7, respectively. In the itraconazole group, slight decreases in total and low-density lipoprotein cholesterol levels were detected ($P = 0.0357$ and 0.0639, respectively, at 3 months).

Clinical side effects potentially related to liver damage were recorded in one of the patients in each of the groups UMSG at 660 mg and UMSG at 990 mg. In the former instance, treatment had to be discontinued. The same applied to a female patient who became pregnant after 7 months of itraconazole treatment. She later gave birth to a healthy child.

Medication compliance. All study medications were, by and large, taken regularly, and there was no major difference in compliance between the various treatment groups. More than 70% of the patients in all treatment groups had an average compliance of at least 90%, and only three patients (two dropouts) were poor compliers (Fig. 1). A total of 44 and 62 patients returned unused medication for at least 90 and 80% of the treatment periods, respectively. In general, the return rates decreased at the end of the study. An interruption of drug intake for 2 to 3 weeks was reported by four patients. The reason was suspicion of pregnancy in one female patient and tetracycline treatment for influenza inducing intolerance in a male patient.

Compliance could not be calculated for eight patients who stopped drug intake during the first month (intolerable side effects in six patients), and these patients did not return the remainder of their medications. Incomplete return of medication was also seen for some other patients, most of whom were lost to follow-up later on or were removed from therapy because of adverse drug reactions. In patients treated for more than 1 year, a coincidence of slow regression or an increase in the involved area of the test nail and suspected insufficient medication was detected in one and two patients on UMSG at 660 mg and UMSG at 990 mg, respectively, and in one poor complier on itraconazole.

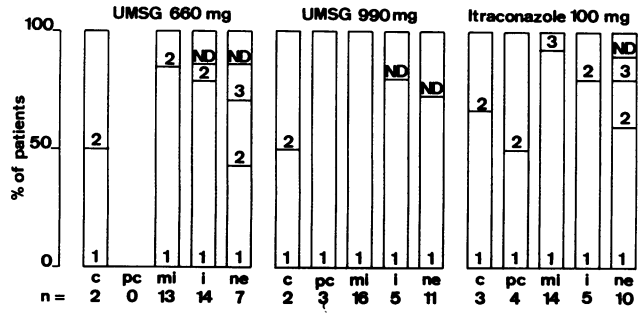

FIG. 1. AC (in percent) among the patients receiving UMSG at 660 and 990 mg and itraconazole at 100 mg once daily. 1, AC >90%; 2, AC >75 to ≤90%; 3, AC >50 to ≤75%; 4, AC ≤50%; ND, AC not determinable. Patients were classified as cured (c), partially cured (pc), much improved (mi), improved (i), and no essential effect (ne).

DISCUSSION

Tinea unguium of the toenails is amenable to long-term cure by treatment with either UMSG or itraconazole. With griseofulvin, however, particularly high doses (990 mg a day) are required. This type of medication necessitates discontinuation of treatment because of side effects more often than treatment with itraconazole at 100 mg does (Table 4). As expected from the well-documented short-term application experience in patients with superficial mycoses (13, 21), the long-term application of itraconazole at the dose used in the present study is safe. This confirms the initial observations of Tucker and coworkers (20). The findings concerning griseofulvin at 660 mg are consistent with previous experience. Somewhat higher cure rates published elsewhere may be due to less rigid tests of cure. Moreover, it must be kept in mind that data evaluation in the present study was based on the intent-to-treat method, which was not the case in many older studies. Although the severity of infection does not delineate the prognosis according to our data, it would be helpful to know to what extent the nails were involved in previous studies.

Previous trials whose results have been published recently have indicated that itraconazole is effective against onychomycosis involving the toenails (5, 15, 23). Except for one trial (23), however, griseofulvin either was not investigated in parallel as a reference drug or the numbers of patients were fairly small and the dose of griseofulvin used was low (500 mg of the microsize of drug). In that trial (23), the treatment period was limited to 6 months, and only marked improvement of toenails was obtained at best, with cure observed only in patients with fingernail tinea. This was true for both itraconazole and griseofulvin (23). In future, it might be worth knowing whether higher doses of itraconazole are as well tolerated and even more efficacious, possibly even during shorter periods of treatment. The clinical and mycological outcomes of the patients taking part in a study on itraconazole penetration into the nail plate indeed point in this direction (24). Further comparative evaluation of itraconazole should also study terbinafine, which has recently been found to be effective for this indication (4, 26).

Considering a recent survey of the literature (7) and the experience presented here, it seems questionable that conventional griseofulvin treatment can any longer be considered a "gold standard." If griseofulvin is to be considered

further at all, a dose of 990 mg of UMSG must be recommended. Yet, itraconazole at 100 mg seems to be preferable, in particular because of its better tolerability. With effective treatment protocols (UMSG at 990 mg and itraconazole at 100 mg) applied for prolonged periods of time, complete cure occurs in some cases several weeks to months after the end of application. This hints at the deposition of active drug in the horny layer, as demonstrated for itraconazole (24). Hence, the need for alternative treatment should not be considered too hastily.

In clear contrast to a belief shared by many dermatologists, old age, extended areas of nail involvement, and the involvement of high numbers of nails are not rational reasons for practitioners to avoid systemic treatment because of a fear of lower rates of treatment success. Moreover, a positive KOH preparation and/or culture within the first months of treatment are not good indicators of ultimate treatment failure.

Noncompliance is of major concern in topical dermatomycosis treatment, in which about half of the patients neglect the proper daily dosage schedules (12). Previous onychomycosis studies, however, have ignored this problem. At present, there is no method which allows the estimation of medication compliance without uncertainty. Tablet counting may overestimate patient compliance. Recently, however, a rather close relationship of this method compared with two others has been described (10). By and large, in our patients compliance did not differ between cured and noncured subjects. Good compliance was observed in those who completed the study, although a mild deterioration in medication compliance as well as a decreasing return rate occurred at the end of the study period. This hints at motivational problems when residual minor lesions do not improve for months. Decreasing medication compliance was also reported in other long-term studies (11). An influence of poor compliance on therapeutic outcome was suspected in four patients. Thus, other reasons must contribute considerably to the rather low cure rates.

To make comparisons between various treatment regimens for onychomycosis easier in future, it would be helpful to adopt a generally acknowledged trial design. The present one might be considered as a pertinent proposal.

ACKNOWLEDGMENTS

We thank K. Domschky, Janssen GmbH, Neuss, Germany, for the supply of the study medication and W. Junge, Kiel, Germany, for safety pharmacology analysis. We are grateful to K. Fanderl and A. Kerschnitzki for technical support in the Mycology Laboratory and P. Bilek and J. Gumina from the Photography Department.

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