Randomised double blind comparison of terbinafine and itraconazole for treatment of toenail tinea infection

M Bräutigam, S Nolting, R E Schopf, G Weidinger for the Seventh Lamisil German Onychomycosis Study Group

Abstract

***Objective*—To compare the efficacy and tolerability of terbinafine and itraconazole in the treatment of toenail tinea unguium.**

***Design*—Multicentre, double blind, parallel group study.**

***Setting*—17 university hospitals, one army hospital, and five dermatology practices.**

***Patients*—195 patients with clinically suspected toenail tinea and growth of dermatophytes in baseline culture; data on 86 patients in the terbinafine group and 84 patients in the itraconazole group were fully evaluated for efficacy.**

***Interventions*—Daily dose of 250 mg terbinafine or 200 mg itraconazole for 12 weeks, with follow up for a further 40 weeks.**

***Main outcome measures*—Mycological cure (negative results on microscopy and culture) and clinical improvement (length and area of unaffected nail) at week 52 or at discontinuation of treatment.**

***Results*—At the end of the study mycological cure rates were 81% (70 out of 86) for terbinafine and 63% (53 out of 84) for itraconazole ($2P < 0.01$). Negative culture was achieved in 92% (79 out of 86) in the terbinafine group and 67% (56 out of 84) in the itraconazole group ($2P < 0.0001$). Length of unaffected nail was 9·44 mm in the terbinafine group and 7·85 mm in the itraconazole group ($2P < 0.05$).**

***Conclusion*—Terbinafine is more effective than itraconazole in the treatment of toenail tinea infection.**

Introduction

Dermatophyte nail infection is fairly common. A computer search in the United Kingdom showed a prevalence of 2·8% in men and 2·6% in women,[1] and the prevalence of onychomycosis in an epidemiological study in the United States was 2·2%.[2] Topical antifungal treatments for onychomycosis have been disappointing,[3] although the more recently developed antifungal nail lacquers may be effective in less severe cases.[4,5] As soon as the fungus has spread to the nail matrix, however, systemic treatment is imperative.[6] Until recently only two systemic drugs were available for treatment of tinea unguium—namely, griseofulvin and ketoconazole. With griseofulvin the therapeutic results were unsatisfactory in toenail infections[7] and ketoconazole is associated with the risk of hepatic injury and drug interactions.[8] Two new systemic antimycotic agents have since been added to the therapeutic arsenal: the allylamine terbinafine and the triazole itraconazole. These drugs differ in their chemical structure and in their mode of action,[9,10] but their pharmacokinetics are similar. Both drugs persist for weeks in the nail plate after treatment has been stopped and treatment need not be continued for several months until the infected nail plate has grown out.[11–15] In addition, the primary fungicidal effect on dermatophytes may be the reason for the convincing effectiveness of short term treatment with terbinafine.[16] We investigated the efficacy of these two drugs in what we believe to be the first double blind long term comparison in the treatment of toenail tinea unguium, the most recalcitrant dermatophyte infection.

Patients and methods

The study was performed in men and women aged 18 or over who had a clinical diagnosis of distal subungual or proximal onychomycosis and a growth of dermatophytes in a mycological culture up to 12 weeks after the start of the treatment. Women of childbearing age were asked to use a reliable contraceptive method until four weeks after stopping taking the study drugs. We excluded from the study pregnant or breast feeding women and patients with pre-existing renal, hepatic, or gastrointestinal disease, bacterial or yeast infections of the nails or the periungual area, or psoriasis and psoriatic changes of the toenails. All patients had stopped taking systemic antifungal treatments three months before giving samples for baseline mycological culture; they had all stopped applying topical treatments one month before. No patients received systemic immunosuppressive treatments during the study or in the two weeks before.

Patients were screened up to 12 weeks before the start of the study treatment and those with clinically suspected toenail tinea unguium and proved mycological growth of dermatophytes entered the study. The patients were randomly allocated to receive a daily dose of either 250 mg terbinafine or 200 mg itraconazole for 12 weeks. To keep the treatment double blind the patients additionally took a placebo of the comparative drug. Drugs were taken after dinner to ensure good absorption of itraconazole. Patients were followed up for an additional 40 weeks after the end of treatment. They were assessed at weeks 2, 4, 8, and 12 and then every eight weeks during the 40 weeks of follow up.

MYCOLOGICAL AND CLINICAL ASSESSMENTS

At each visit nail clippings were taken and sent to a central laboratory in Münster for mycological investigation. This consisted of direct microscopy in 20% potassium hydroxide and culture on Sabouraud-dextrose-agar (with chloramphenicol 0·05% and actidione 0·5%) at room temperature for up to four weeks. Clinical response to treatment was monitored by observing the movement of a scratch at the border between infected and normal areas on the patient's most affected nail, excluding the little toe.[17] In addition, the nails were examined for onycholysis, hyperkeratosis, brittleness, and paronychial inflammation

A complete list of the members of the study group is given at the end of the paper.

Department of Clinical Research, Sandoz AG, 90429 Nuremberg, Germany
M Bräutigam, *head of dermatology*
G Weidinger, *head of clinical research*

Department of Dermatology, University of Münster, 48149 Münster, Germany
S Nolting, *professor of dermatology and allergy*

Department of Dermatology, University of Mainz, 55131 Mainz, Germany
R E Schopf, *professor of dermatology*

Correspondence to:
Dr Bräutigam.

BMJ 1995;311:919-22

by means of a four point scale (0=absent, 1=mild, 2=moderate, 3=severe). The area of the affected nail was assessed as 0, 0-30%, 30-60%, and more than 60%. Adverse events were evaluated using standardised questions at each visit. The following haematological and biochemical laboratory values were evaluated at the screening visit, at baseline, and at each visit during treatment: packed cell volume, haemoglobin concentration, erythrocyte and leucocyte counts, erythrocyte indices, and concentrations of creatinine, cholesterol, triglyceride, γ glutamyltransferase, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase, bilirubin, and potassium.

The study was approved by an independent ethics committee and was performed according to the guidelines of the declaration of Helsinki. All patients gave informed consent before they were recruited.

STATISTICS

The patients were randomly assigned to treatment with either terbinafine or itraconazole according to a computer generated randomisation schedule in the order of obtaining informed consent. A restricted form of randomisation was used to provide blocking over time. All centres received multiple complete blocks of length four; thus the assignments of each treatment were balanced after each block.

Two populations were defined for evaluation of the study. All the patients except two who did not have any follow up visits were included in the analyses of drug tolerance. All patients who completed the study as planned and all those patients who stopped treatment because of adverse events or ineffectiveness of treatment were included in the analysis of efficacy. One last result was used in patients who withdrew from the study.

Sample size was calculated on the basis of the assumption that at the end of the study the mycological cure rate should be 75% in the terbinafine group and 50% in the itraconazole group. With a type I error of 0·05 and a type II error of 0·20 at least 132 patients (2×66) had to be included in the study to detect a significant difference.

The main measure of efficacy was mycological cure, which was defined as negative results of microscopy and no growth of dermatophytes in culture. The treatment groups were compared by means of Fisher's exact test for differences in mycological cure rates and in percentages of negative cultures.

Secondary measures of efficacy were area of the affected nail and the length of the unaffected nail. Group differences in nail length were assessed by Student's independent t test, and differences in the area were compared by a χ^2 test according to the percentage of nail affected. In addition, 95% confidence intervals were calculated for group differences in mycological cure rates and unaffected nail length.

Results

A total of 195 patients were recruited from 17 university hospitals and one army hospital and from the practices of five dermatologists. Eleven patients in each group were excluded from the evaluation of drug efficacy because the protocol had not been followed, mainly because they had not attended appointments during the study. Three further patients in the itraconazole group were excluded because they had concomitant disease. Thus data on 86 patients in the terbinafine group and 84 in the itraconazole group were used to analyse efficacy.

Distribution of sex, age, height, and weight were identical in both treatment groups. Sixty four per cent of patients were men. The mean age was 49 years (range 21-70), mean height 174 cm (range 153-193 cm), and mean weight 75 kg (range 48-134 kg). Most patients had severe onychomycosis with more than 60% of the toenail affected (table I). Fifty two of the patients receiving terbinafine (60%) and 50 of those taking itraconazole (60%) had previously been treated with antimycotic drugs. Sixteen and 11 of them respectively had been treated systemically, mainly with griseofulvin, although three patients in the terbinafine group and two in the intraconazole group had been treated with terbinafine or itraconazole. Previous antimycotic treatment had been successful in only two patients in the terbinafine group and five patients in the itraconazole group. In most cases (76 patients given terbinafine (88%) and 74 given itraconazole (88%)) the nail of the big toe was the index nail.

TABLE I—*Area of nail plate clinically affected by dermatophyte infection. Values are numbers (percentages) of patients*

	Terbinafine (n=86)	Itraconazole (n=84)
Baseline		
Area of affected nail plate (%):		
<30	0	7 (8)
30-60	30 (35)	27 (32)
>60	56 (65)	50 (60)
*End of study**		
Area of affected nail plate (%):		
0	42 (49)	30 (36)
<30	27 (31)	33 (39)
30-60	14 (16)	8 (10)
>60	3 (4)	13 (15)

*2P < 0·05 for terbinafine *v* itraconazole.

Trichophyton rubrum was identified as the pathogen in 83 patients in the terbinafine group (97%) and in 78 of those in the itraconazole group (93%). *T mentagrophytes* was observed in two (2%) and six (7%) patients respectively. *T violaceum* was grown at baseline in cultures from one patient in the terbinafine group.

Mycological cultures gave negative results after treatment in 79 patients given terbinafine (92%) and 56 given itraconazole (67%) (95% confidence interval of the difference (13·5% to 36·9%); 2P<0·0001). The success rates in both groups, on the basis of the results of culture, were about 50% of the final value after four weeks, with a continued increase until study week 20 (fig 1). The mean time taken to achieve negative results on culture was 8·5 (SD 6·6) weeks in the terbinafine group and 11·6 (9·1) weeks in the itraconazole group. Because the disappearance of the hyphae from the nail plate took more time than fungal viability, the mycological cure rate increased more slowly (fig 2). Again terbinafine proved to be superior to itraconazole, with a mycological cure rate of 81% (70 out of 86) compared with 63% (53 out of 84) at the end of the study (5·2% to 31·4%; 2P<0·01). Figure 3 shows the length of the unaffected nail, which increased in the terbinafine

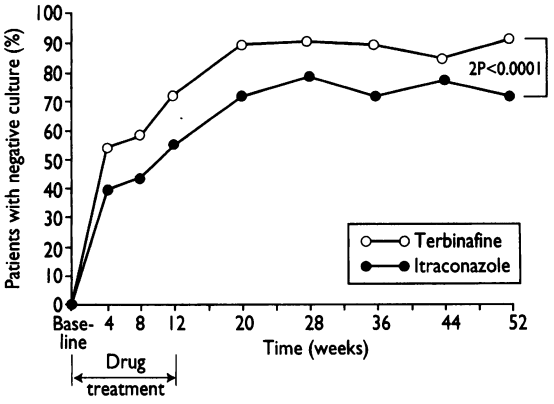

FIG 1—*Proportion of patients with mycological cure (negative results for fungus on microscopy and culture) during study*

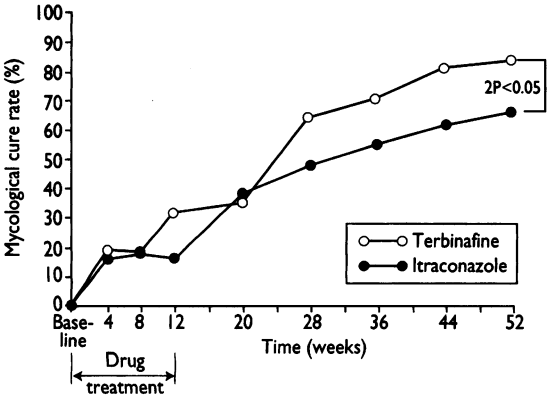

FIG 2—*Percentages of mycological cultures with no growth of dermatophytes during study*

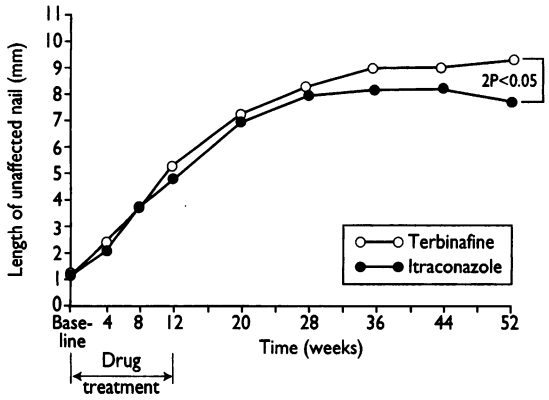

FIG 3—*Increase in length of unaffected nail during study*

group from 1·3 mm to 9·4 mm and in the itraconazole group from 1·2 mm to 7·9 mm (0·02 mm to 3·16 mm; $2P < 0·05$). The clinical response was also reflected by the decrease of the affected area of the nail plate (table I).

The mean global symptom score proved to be less sensitive in differentiating between the two drugs than the variables related to area and fell from 5·8 to 1·9 in the terbinafine group and from 5·5 to 2·2 in the itraconazole group.

ADVERSE EVENTS

During the study period of about 52 weeks, 75 adverse events were reported by 38 of the 95 patients given terbinafine (40%) and 87 adverse events by 47 of the 98 patients given itraconazole. Table II shows the most common adverse events according to drug and organ system. We believe that adverse events were probably related to terbinafine and itraconazole in six (6%) and nine (9%) patients, respectively.

Adverse events were the reason for discontinuation of treatment in three patients receiving terbinafine and four receiving itraconazole. One patient in each group was withdrawn from the study because of increases in liver enzyme activity; one patient given itraconazole withdrew because of paraesthesia and the remaining four patients were withdrawn because of gastrointestinal complaints.

Tolerability of treatment was assessed as good or excellent by participating dermatologists for 81 patients in the terbinafine group (93%) and 78 patients in the itraconazole group.

TABLE II—*Frequency of reporting of most common* adverse effects of treatment during study*

	Terbinafine group	Itraconazole group
Headache	10	9
Dyspepsia	8	5
Diarrhoea	1	7
Taste disorders	4	3
Constipation	2	5
Influenza-like symptoms	4	2
Nausea	3	3
Abdominal pain	2	3
Fatigue	3	1

*Reported by at least three patients.

LABORATORY TESTS

The only significant differences in laboratory variables between the groups were in γ-glutamyltransferase and cholesterol concentrations. γ-glutamyltransferase concentrations were unchanged in the itraconazole group, but there was a slight increase of 1·0 U/l in the terbinafine group. Cholesterol concentration increased insignificantly by 0·16 mmol/l with terbinafine, but it decreased significantly by 0·67 mmol/l with itraconazole ($2P < 0·00001$). The maximum cholesterol lowering effect of itraconazole was observed after two weeks of treatment, and it was no longer evident in the 14 patients with additional laboratory tests after treatment within four weeks after the end of treatment.

Discussion

Both drugs were equally well tolerated, but terbinafine proved to be significantly more effective in terms of clinical improvement and in the eradication of fungal pathogens. The mycological cure rate after 12 weeks of terbinafine treatment and a total observation time of one year was 81% (70 out of 86 patients). This corresponds well with the results of former trials, in which longer treatment times of 24 to 48 weeks resulted in cure rates of 82% to 88% after 48 weeks.[14 18-20] The mycological cure rate of 63% (53 out of 84 patients) in the itraconazole group was lower than the 79% (15 out of 19 patients) reported recently.[15] However, the results in that trial were based on only 19 evaluable patients, and three false negative results on culture could increase the cure rate from the 63% seen in our trial to the 79% reported by Willemsen *et al.*[15]

We know of only one published report of a clinical trial comparing terbinafine and itraconazole in onychomycosis.[21] Although treatment durations and doses were similar to those in our study, it was an open comparison with only 53 patients and a shorter follow up time, which failed to show significant differences between the treatments. In contrast, we found that terbinafine was more effective than itraconazole. This corresponds to the favourable results of terbinafine in comparison with itraconazole in the treatment of tinea pedis, another dermatophyte infection.[22] Recently itraconazole interval treatment (three to four cycles of treatment for one week every month at a dose of 200 mg twice daily) was recommended for the treatment of onychomycosis. There are almost no clinical data published about this new modality. However, published nail concentrations of itraconazole are no higher than with conventional treatment as investigated in our study[23] Hence our conclusions probably apply to itraconazole interval treatment as well.

DIFFERENCE IN EFFICACY

The most likely explanation for the better efficacy of terbinafine is the higher antimycotic activity of terbinafine against dermatophytes,[9 10] as both drugs rapidly penetrate the nail plate and nail concentrations lie within the same range.[11 15] It cannot be ruled out that the fungicidal mode of action of terbinafine has also some clinical relevance. This issue is controversial, but it is in accordance with our finding of a shorter time to obtain negative culture results with terbinafine.

We believe that previous systemic treatment does not account for the efficacy of the two agents or

Key messages

- Tinea unguium has a prevalence of 2-3% in the adult population
- Severe toenail onychomycosis that affects the matrix of the nail is almost incurable with topical antifungal agents and older systemic antifungal agents are ineffective and poorly tolerated
- This study showed that 12 weeks of treatment with a daily dose of 250 mg terbinafine or 200 mg itraconazole was well tolerated and effective in treating severe toenail tinea
- Itraconazole lowered serum cholesterol concentrations, which suggests that sterol inhibition is not completely fungus specific
- Terbinafine had a higher efficacy in terms of eradication of the fungus and improvement in clinical symptoms

their differences in efficacy. Firstly, less than 20% of the patients in each group had previously taken systemic antimycotic drugs. Most had been treated with griseofulvin, which does not persist in the nail plate and must therefore be given until a clinical cure is achieved. Secondly, only five patients overall had been previously treated with terbinafine or itraconazole. Finally, to exclude any possible influence of previous treatment with antimycotic agents, we requested that dermatophytes should be present and growing in the screening culture before patients could be included in the study.

ADVERSE EFFECTS

The number of adverse events was fairly high in both groups, but even with placebo, similar figures have been obtained in other studies with diligent questioning on adverse events and comprehensive patient information about potential side effects.[13 14 19 20 24] The above reasons can also explain the implausibly high frequency of dysgeusia in four patients taking terbinafine and three taking itraconazole. Reversible taste disturbances are usually a rare side effect of terbinafine, with an approximate incidence of 1 per 800 people,[25] and they have not yet been observed with itraconazole treatment.

Biochemical tests showed a significant effect of terbinafine on γ-glutamyltransferase, but the median change was only 1 U/l, and other liver related variables either remained unchanged or were significantly decreased. These findings suggest that there is little risk of relevant hepatotoxicity with either drug.

The cholesterol lowering effect of itraconazole was surprising because it was not recorded in the product information. However, the difference between the two treatments as well as the comparison of values at baseline and after treatment was highly significant ($2P < 0{\cdot}00001$). Serum cholesterol concentration decreased with itraconazole treatment in 81% of patients. The observed decrease was certainly clinically relevant and in the range of that which is seen with lipid lowering drugs such as fibrates.[26] Interestingly, a recently published comparison between itraconazole and griseofulvin in tinea unguium also found a significant decrease in cholesterol concentrations in the itraconazole group.[24] These findings suggest that the inhibition of sterol synthesis by itraconazole is not completely fungus specific, and the clinical implications have to be carefully considered.

CONCLUSIONS

We have shown that with the availability of terbinafine and itraconazole, therapeutic nihilism is no longer indicated in patients with severe toenail tinea. Both drugs are well tolerated and highly effective, but terbinafine is therapeutically superior.

Members of the Seventh Lamisil German Onychomycosis Study Group are:

Principal investigator: S Nolting (Münster).

Central mycological laboratory: M Brockmann (Münster).

Clinical centres: J Knop, B Morsches, R Schopf (Mainz); E G Jung, M Schliz (Mannheim); A Rosinus, B Schäfer (Wiesbaden); R Happle, I Effendy, C Enschedé (Marburg); E Schöpf, A Pfister-Wartha (Freiburg); G Falker (Frankenberg); F A Bahmer, J Pönnighaus (Homburg); M Landthaler, A Götz, T Vogt (Regensburg); K Gründer, P Mayser, M Thomas, A Langrock (Giessen); H Mensing, C Dahm, D Reinel, R Ulrich (Hamburg); S Borelli, H Hofmann, H Bruckbauer (Munich); P J Frosch, U Beiteke, F Bleckmann (Dortmund); C Scherwitz, B Hook, Knauss-Scherwitz (Tübingen); P Altmeyer, U Matthes, R Hartwig (Bochum); W Berns (Duisburg); E Haneke, T Lacour (Wuppertal); H Jacobi, I Hackert (Dresden); I Tausch, A Hutschenreuther, I Buchholtz (Berlin); H Dietz, P Gregor (Magdeburg); B Knopf, H Roth (Jena); G Niedergesäss (Potsdam); E Schell, D Schweiss (Nuremberg).

Monitoring and technical help: G Petry (Seligenstadt); R Tanke (Dortmund); H Heinrich (Berlin); and U Geisler (Nuremberg).

Funding: Sandoz AG Nuremberg, Germany.

Conflict of interest: MB and GW are employees of Sandoz.

1 Roberts DT. Prevalence of dermatophyte onychomycosis in the United Kingdom: results of an omnibus survey. *Br J Dermatol* 1992;126(suppl 39):23-7.
2 Prevalence, morbidity and cost of dermatological diseases [editorial]. *J Invest Dermatol* 1979;73:395-401.
3 Zalas N. Onychomycosis. In: *The nail in health and disease.* Lancaster: MTP, 1980:91-113.
4 Reinel D, Clarke C. Comparative efficacy and safety of amorolfine nail lacquer 5% in onychomycosis, once-weekly versus twice-weekly. *Clin Exp Dermatol* 1992;17(suppl 1):44-9.
5 Effendy I, Gasse A, Stangier U, van de Venne C. When is exclusive topical treatment indicated in onychomycoses? *Zeitschrift für Hautkr* 1991;66:620-7.
6 Greer DL. Dermatophytosis (Ringworm). In: Jacobs PH, Nall L, eds. *Antifungal drug therapy: a complete guide for the practitioner.* New York: Marcel Dekker, 1990:5-22.
7 Anderson DW. Griseofulvin: biology and clinical usefulness. *Ann Allergy* 1965;23:103-10.
8 Lewis JH, Zimmerman HJ, Benson GD, Ishak KG. Hepatic injury associated with ketoconazole therapy: analysis of 33 cases. *Gastroenterology* 1984;86:503-13.
9 Balfour JA, Faulds D. Terbinafine. A review of its pharmacodynamic and pharmakokinetic properties, and therapeutic potential in superficial mycoses. *Drugs* 1992;43:259-84.
10 Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic and pharmakokinetic properties, and therapeutic potential in superficial and systemic mycoses. *Drugs* 1989;37:310-44.
11 Schatz F, Bräutigam M, Dobrowolski E, Habel H, Weidinger G, Stütz A, *et al.* Nail incorporation kinetics of terbinafine in onychomycosis patients. *Clin Exp Dermatol* (in press).
12 Faergemann J, Zehender H, Millerioux L. Levels of terbinafine in plasma, stratum corneum, dermis-epidermis (without stratum corneum), sebum, hair and nails during and after 250 mg terbinafine orally once daily for 7 and 14 days. *Clin Exp Dermatol* 1994;19:121-6.
13 Goodfield MJD. Short-duration therapy with terbinafine for dermatophyte onychomycosis: a multicentre trial. *Br J Dermatol* 1992;126(suppl 39):33-5.
14 Van der Schroeff JG, Cirkel PKS, Crijns MB, van Dijk TJA, Govaert FJ, Groeneweg DA, *et al.* A randomized treatment duration-finding study of terbinafine in onychomycosis. *Br J Dermatol* 1992;126 (suppl 39):36-9.
15 Willemsen M, De Doncker P, Willems J, Woestenborghs R, van de Velde V, Heykants J, *et al.* Posttreatment itraconazole levels in the nail. *J Am Acad Dermatol* 1992;26:731-5.
16 Clayton YM. Relevance of broad-spectrum and fungicidal activity of antifungals in the treatment of dermatomycoses. *Br J Dermatol* 1994;130 (suppl 43):7-8.
17 Zaias N, Drachman D. A method for the determination of drug effectiveness in onychomycosis. *J Am Acad Dermatol* 1983;9:912-9.
18 Goodfield MJD. Clinical results with terbinafine in onychomycosis. *Journal of Dermatological Treatment* 1990;1(suppl 2):55-7.
19 Baudraz-Rosselet F, Rakosi T, Wili PB, Kenzelmann R. Treatment of onychomycosis with terbinafine. *Br J Dermatol* 1992;126(suppl 39):40-6.
20 Hofmann H, Bräutigam M, Weidinger G, Zaun H. Treatment of toenail mycosis—a randomized, double-blind study with terbinafine and griseofulvin. *Arch Dermatol* 1995;131:919-22.
21 Arensas R, Dominguez-Cherit J, Fernandez LMA. Open randomized comparison of itraconazole versus terbinafine in onychomycosis. *Int J Dermatol* 1995;34:138-43.
22 De Keyser P, de Backer M, Massart DL, Westelinck KJ. Two-week oral treatment of tinea pedis, comparing terbinafine (250 mg/day) with itraconazole (100 mg/day): a double-blind, multicentre study. *Br J Dermatol* 1994;130(suppl 43):22-5.
23 Roseeuw D, de Doncker P. New approaches to the treatment of onychomycosis. *J Am Acad Dermatol* 1993;29:S45-50.
24 Korting HC, Schafer-Korting M, Zienicke H, Georgii A, Ollert MW. Treatment of tinea unguium with medium and high doses of ultramicrosize griseofulvin compared with that with itraconazole. *Antimicrob Agents Chemother* 1993;37:2064-8.
25 Beutler M, Hartmann K, Kuhn M, Gartmann J. Taste disorders and terbinafine. *BMJ* 1993;307:26.
26 Monk JP, Todd PA. Bezafibrate—a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hyperlipidaemia. *Drugs* 1987;33:539-76.

(Accepted 7 September 1995)