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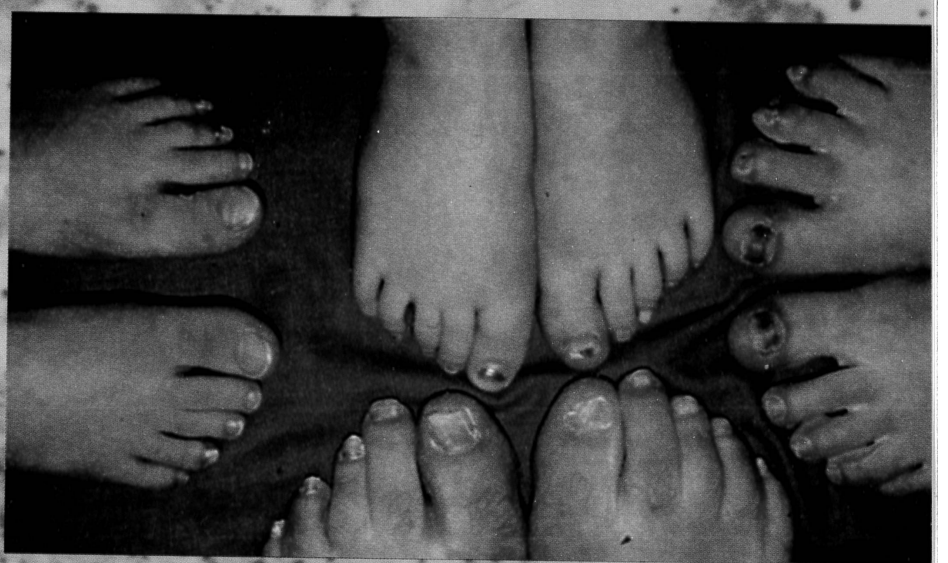

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Cover picture: The feet of an entire family with onychomycosis. See pp 1–4. Photograph courtesy of Dr D.T.Roberts, Department of Dermatology, Southern General Hospital, Glasgow, UK.

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Onychomycosis: current treatment and future challenges

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Summary Onychomycosis is a fungal infection of the nails, more often of the toenails. It is a common condition, with an estimated overall prevalence of 3–10% in European populations. Dermatophytes, especially *Trichophyton rubrum* and *Trichophyton mentagrophytes*, are the usual pathogens. Some 50% of infected patients fail to seek medical advice. Medically confirmed onychomycosis should be treated. This recommendation is based on several disease-specific considerations: cosmetic and functional disability, lack of spontaneous remission, impairment of health and wellbeing in elderly patients and the need to reduce contamination in communal bathing places. Current treatments for onychomycosis include oral antifungal agents such as terbinafine (Lamisil®) and itraconazole (Sporanox®). They offer significantly improved rates of cure, shorter treatment regimens and a lower level of adverse events than was previously the case. Comparative studies have shown that terbinafine is more effective than griseofulvin, fluconazole or itraconazole in the treatment of this condition, providing a cure rate of 70–80% and an excellent tolerability profile. Terbinafine is also the most cost-effective agent. However, several problems remain that will provide future challenges in the treatment of onychomycosis, not least the consistent treatment failure rate of 20%. In many of these cases, surgery may need to precede drug therapy in order to maximise the prospects of clinical and mycological cure. In addition, duration of treatment also needs to be more closely adjusted to the individual case by prior identification of severity and extent of toenail infection, and combined oral and topical therapy also requires further investigation.

Onychomycosis comes from the Greek *onyx*, a nail, and *mykes*, a fungus. It is the term used to describe a fungal infection of the nails caused predominently (in about 90% of cases) by anthropophilic dermatophytes: *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the usual pathogens. Yeast and non-dermatophyte mould infections are much less common. Toenails are more often affected than fingernails by a ratio of about 4:1.

Infection usually begins in the toe clefts, with subsequent spread to the hyponychium and thence into the distal area of the nail bed. The whole width of the nail may be affected, but involvement of the lateral edges is more frequently seen. Subsequent spread of infection is proximal towards the posterior nail fold and medially to encompass the whole nail bed. The nail can become grossly thickened, sometimes completely broken. Involvement of the nail plate leads ultimately to complete destruction of the nail, a process that can take several years from initial infection.

Onychomycosis is common. Prevalence studies[1,2] have suggested that 3% of the population in developed countries are affected. Both studies also showed that almost 50% of infected patients had never sought medical advice, and that among those who had, few had been prescribed systemic therapy. More recently, smaller mycologically controlled studies[3] have suggested a prevalence approaching 10%. These data suggest that onychomycosis would constitute a significant healthcare challenge, both logistically and financially, if treatment – systemic and/or topical – were to be made available to all sufferers.

Why onychomycosis should be treated

An excellent case can be made out for treating mycologically confirmed onychomycosis, based on four disease-specific considerations. First, fingernail infection results in increasing cosmetic and functional disability. Second, the well-documented lack of spontaneous remission totally invalidates any 'wait and watch' policy. Third, no improvement in the contamination levels of communal bathing places can be envisaged unless the general pool of infection is reduced. Last,

family members can fall easy victim to transmission from an infected parent or sib (Fig. 1).

To these disease-specific considerations can be added several general, but in some ways more important, reasons. Onychomycosis becomes more common with age, and can impair the quality of life and wellbeing of elderly persons. In those with intercurrent diabetes mellitus or significant peripheral vascular disease, the presence of onychomycosis can aggravate management. In these and similar cases it may be more cost effective to treat the initial disease than the later complications.

Currently available drug therapy

The medical management of onychomycosis has improved considerably over the last 10 years. Oral antifungal agents now available offer significantly increased rates of cure, shorter treatment regimens and a lower level of adverse events. Terbinafine (Lamisil®) and itraconazole (Sporanox®) are now available in many countries, and are generally considered to be the treatments of choice for this condition. Is there any evidence to suggest that one or other of these agents has greater efficacy?

In vitro *evidence*

Table 1, compiled from data collected in several studies,[4–8] shows mean inhibitory concentration (MIC) and mean fungicidal concentration (MFC) values and peak nail concentrations for terbinafine and itraconazole (and for several other drugs where values are available). The MIC values for both agents are low. The MFC value for itraconazole, though still low, is two orders of magnitude higher than that for terbinafine. The relevance of these figures relates to the data in the third column on peak nail concentrations, which for maximum efficacy should be consistently higher than the MFC value. This status is comfortably achieved by terbinafine, but is not always achieved by either itraconazole or fluconazole. Nails affected by dermatophyte infection are not kinetically homogenous, so this difference may be crucially important.

In vivo *evidence*

This is conventionally based on two comparisons of efficacy: mycological cure rates at completion of the study and relapse rates at long-term follow-up. Nails have no power of regeneration, and must therefore be given the time to grow out completely if cure (absence of relapse) is to be properly assessed. For a toenail the time span can be 12–18 months. Thus a follow-up time of 12 months from the start of a study is desirable, but 12 months from cessation of treatment may be even better. Beyond 2 years it is difficult to distinguish between relapse and reinfection.

Table 1. Minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values (in μg/mL), and peak nail levels (in μg/g) of five agents used orally in the treatment of dermatophyte infection. Not all values are provided. Data from references 4–8 Courtesy of Dr Neil Ryder, Novartis Research Institute, Vienna, Austria

Agent	MIC	MFC	Peak nail concentration
Griseofulvin	0·5–2·0	na	nr
Ketoconazole	0·04–6·0	na	nr
Itraconazole	0·08	0·6	0·5–1·0
Fluconazole	6·25–200	na	8·0
Terbinafine	0·004	0·004	0·5–1·5

na: Not applicable as these drugs are fungistatic only, nr: not reported

Comparative studies have shown that terbinafine is more effective than griseofulvin, fluconazole and itraconazole in the treatment of fungal nail infections. Griseofulvin has a low cure rate and high relapse rate in toenail disease, coupled with a more significant adverse event profile than newer agents. Three studies[9–11] comparing griseofulvin with terbinafine have shown consistent advantages for terbinafine in terms of mycological and clinical cure rates, increase in length of the unaffected nail and number of adverse events.

Fluconazole has been less well evaluated than either terbinafine or itraconazole in onychomycosis, and the optimum dose and duration of treatment remain uncertain. To date, only one study (V. Havu, personal communication) has directly compared the efficacy of terbinafine with fluconazole. The results in terms of negative microscopy at week 60 were statistically in favour of terbinafine. The doses of fluconazole used in this study were probably too low, but the higher doses needed would tend to increase terbinafine's advantage in terms of cost-effectiveness.

Terbinafine at a dose of 250 mg daily has been shown to be more effective than continuous itraconazole 200 mg daily in two studies in toenail infection. In a double-blind study[12,13] over 3 months and with a follow-up extending to 52 weeks, Bräutigam *et al.* showed that the mycological cure rate for terbinafine

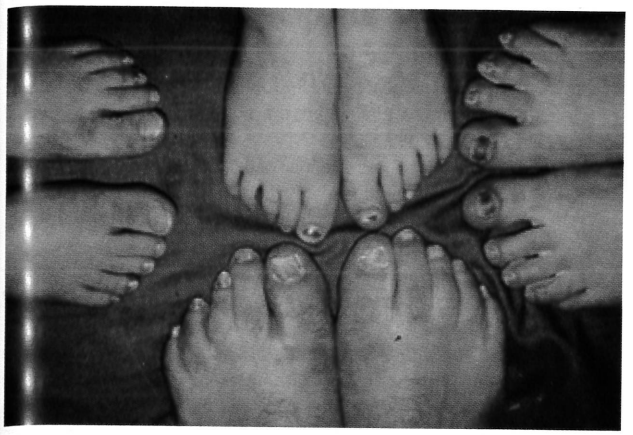

Figure 1. The feet of an entire family (mother, father, and two children) with onychomycosis. In this case there is no doubt that one family member was responsible for infecting the others.

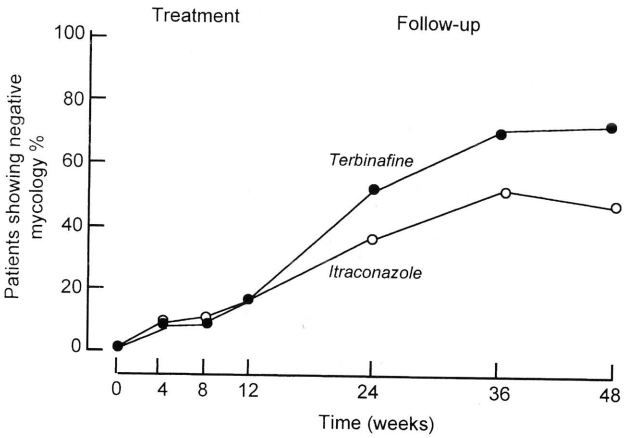

Figure 2. Mycological cure rates (determined by negative mycology on culture) during treatment with either terbinafine 250 mg daily or itraconazole 200 mg daily for 12 weeks and subsequently over a follow-up period extending to 48 weeks. The difference at 48 weeks between terbinafine (l) (73% culture negative) and itraconazole (○) (45·8% culture negative) is significant, $P<0·0001$. After de Backer *et al.*[14]

was 81%, significantly better than the 63% seen in the itraconazole group, $P<0·01$. Mean time to first negative culture was 8·52 weeks for terbinafine, compared to 11·64 weeks for itraconazole, $P<0·05$. At the end of the follow-up period there was an overall greater percentage of cures in the terbinafine group, and a smaller percentage of unchanged or deteriorated nails. In another double-blind study[14] over 3 months with a follow-up of 48 weeks, De Backer *et al.* recorded a mycological cure rate of 73% with terbinafine, compared to only 45·8% with itraconazole, $P<0·0001$ (Fig. 2). At the end of the study, 76·1% of the terbinafine group had normal nails (or minimal signs), compared to 58·1% in the itraconazole group: failure of treatment was 12·8% and 29·1%, respectively, both findings significantly in favour of terbinafine, $P<0·001$. These findings, showing terbinafine to be the more effective agent, are in keeping with the *in vitro* data.

Itraconazole is now more usually given in an intermittent fashion, at a dose of 400 mg daily for 7 days each month for 3 or 4 months. An open randomised study[15] in 63 patients compared continuous (250 mg/day) and intermittent (500 mg/day for 7 days each month) terbinafine with intermittent itraconazole (400 mg/day for 7 days each month) over 16 weeks. Mycological cure rates 6 months after completion of therapy were 94·1%, 80% and 75·5%, respectively. In patients where mycological cure was achieved without nail deformities, there was a significant difference between the cure rates in favour of continuous terbinafine over intermittent itraconazole, $P<0·05$. The results of the L.I.ON. (Lamisil® vs. Itraconazole in ONychomycosis) study, which compared terbinafine 250 mg/day for 12 or 16 weeks with intermittent itraconazole 400 mg/day for 7 days every 4 weeks for 12 or 16 weeks, are presented later in this supplement.

For the present it seems reasonable to conclude that terbinafine, taken at a dose of 250 mg daily for 3 months, is the most effective currently available treatment for onychomycosis, with a cure rate of 70–80% and an excellent tolerability profile.

Reasons for a continuing failure rate

Despite the high cure rates that can now be achieved, some 20% of patients still fail to benefit from therapy. Leaving aside inadequate compliance, the usual reasons are dermatophyte resistance; inadequate drug absorption into the affected area, often associated with the presence of a dermatophytoma; lack of any nail growth; and immunosupression. It seems likely that the majority of treatment failures are related to kinetic problems within the affected nail that prevent adequate penetration of drug into the fungal mass or dermatophytoma. Surgical removal of such areas prior to drug therapy may be the answer. In general, physicians need to identify these patients early in the treatment cycle, to ensure that they receive treatment appropriate to their needs.

Dystrophic nails that yield non-dermatophyte moulds in culture are unlikely to respond adequately to treatment if the moulds are secondary pathogens of previously damaged nail. However, the commonest cause of previous nail damage is primary dermatophyte

infection, which will respond, leading to outgrowth of saprophytic moulds and restoration of the nail to normal. Thus, improvement in cure rates is likely to follow a better understanding of treatment failure rather than manipulation of drugs and drug regimens.

Economic considerations

Effective treatment for onychomycosis has three aspects: rapid onset of action, sustained effect and a favourable adverse events profile. But economic considerations cannot be ignored, and several studies have attempted to evaluate the cost-effectiveness of the available agents. Einarson *et al.* compared terbinafine, ketoconazole and griseofulvin, and showed that terbinafine was the most cost-effective, providing the highest percentage success rate in both toenail and fingernail infection, and the greatest number of disease-free days.[16] Meta-analysis of data from 12 European countries and Canada, undertaken by the same group, confirmed the findings.[17] In the USA, a comparison of the costs of treatment with terbinafine, griseofulvin, itraconazole and ketoconazole – including on this occasion costs related to adverse events and relapses as well as the drug acquisition and clinical and laboratory costs – showed once again that terbinafine was the most cost-effective.[18]

Future challenges

There are several issues in the treatment of onychomycosis that remain to be overcome. First, the consistent failure rate of some 20% in all studies needs to be addressed. As suggested above, the most frequent explanation is likely to be kinetic: patients with a fungal mass effectively impenetrable to an antifungal agent need to be offered surgery before medical treatment. Second, the duration of treatment needs to be more closely adjusted to the individual case. Perhaps some 40% of those with toenail infection require only 6 weeks of treatment, but the challenge is to identify this population prior to therapy. Third, the combination of oral and topical therapy has hardly been investigated, and may be the route by which the duration of systemic therapy can be reduced. Last, there is the challenge to produce the ideal drug, one with a 100% cure rate and no adverse events!

Conflict of interest: Dr Roberts and his department have carried out drug studies for, given advice to and received educational funding from Novartis Pharma, Janssen Pharmaceuticals and Pfizer.

References

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 Sais G, Juggla A, Peryi J. Prevalence of dermatophyte onychomycosis in Spain: a cross-sectional study. *Br J Dermatol* 1995; **132:** 758–61.
3 Heikkila H, Stubb S. The prevalence of onychomycosis in Finland. *Br J Dermatol* 1995; **133:** 699–703.
4 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.
5 Troke PF. *In vitro* and experimental *in vivo* activities of fluconazole against some fungi causing cutaneous mycoses. In: *Cutaneous Antifungal Agents: Selected Compounds in Clinical Practice and Development* (Rippon JW, Fromtling RA, eds), New York: Marcel Dekker, 1993:199–214.
6 De Doncker P, Decroix J, Pierard GE *et al.* Antifungal pulse therapy for onychomycosis. A pharmacokinetic and pharmacodynamic investigation of monthly cycles of 1-week pulse therapy with itraconazole. *Arch Dermatol* 1996; **132:** 34–41.
7 Faergemann J, Zehender H, Denouël J, 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 per day for four weeks. *Acta Derm Venereol (Stockh)* 1993; **73:** 305–9.
8 Schatz F, Bräutigam M, Dobrowolski E *et al.* Nail incorporation kinetics of terbinafine in onychomycosis patients. *Clin Exp Dermatol* 1995; **20:** 377–83.
9 Faergemann J, Andresen C, Hersle K *et al.* Double-blind, parallel group comparison of terbinafine and griseofulvin in the treatment of toenail onychomycosis. *J Am Acad Dermatol* 1995; **32:** 750–3.
10 Haneke E, Tausch I, Bräutigam M *et al.* Short duration treatment of fingernail dermatophytosis: a randomized double-blind study with terbinafine and griseofulvin. *J Am Acad Dermatol* 1995; **32:** 72–7.
11 Hofmann H, Bräutigam M, Weidinger D *et al.* Treatment of toenail onychomycosis. A randomized, double-blind study with terbinafine and griseofulvin. *Arch Dermatol* 1995; **131:** 919–22.
12 Bräutigam M, Nolting S, Schopf RE *et al.* Randomized double-blind comparison of terbinafine and itraconazole in the treatment of toenail tinea infection. *Br Med J* 1995; **311:** 919–22. [See also published erratum, *Br Med J* 1995; 311: 1350.]
13 Bräutigam M, Nolting S, Schopf RE *et al.* German randomized double-blind multicentre comparison of terbinafine and itraconazole for the treatment of toenail tinea infection. *Br J Dermatol* 1996; **134** (Suppl.46): 18–21.
14 De Backer M, De Kayser P, De Vroey C, Lesaffre E. A 12-week treatment for dermatophyte toe onychomycosis: terbinafine 250 mg/day vs. itraconazole 200 mg/day: a double-blind comparative trial. *Br J Dermatol* 1996; **134** (Suppl.46): 16–7.
15 Tosti A, Piraccini BM, Stinchi C *et al.* Treatment of dermatophyte nail infections: an open randomized study comparing intermittent terbinafine therapy with continuous terbinafine treatment and intermittent itraconazole therapy. *J Am Acad Dermatol* 1996; **34:** 595–600.
16 Einarson TR, Arikian SR, Shear NH. Cost-effectiveness analysis for onychomycosis therapy in Canada from a government perspective. *Br J Dermatol* 1994; **130** (Suppl.43): 32–4.
17 Arikian SR, Einarson TR, Kobelt-Nguyen G *et al.* A multinational pharmacoeconomic analysis of oral therapies for onychomycosis. *Br J Dermatol* 1994; **130** (Suppl.43): 35–44.
18 Marchetti A, Piech CT, McGhan WF *et al.* Pharmacoeconomic analysis of oral therapies for onychomycosis: a US model. *Clin Ther* 1996; **18:** 757–777.