Response to the Letter by Dr Safer

Sir,

Statement 1: In previous studies (De Backer et al.), the duration of follow-up was 46 weeks and the mycological cure rates for itraconazole declined after week 36 as those of terbinafine increased.

Response: The total duration for both trials was 48 weeks with a post-treatment follow-up period of 36 weeks (not 46 weeks as you mention). Both trials were double blind and had a comparable design and methodology and a large patient sample.

The results of our trial show a mycological cure of 61% for itraconazole and 67% for terbinafine, while the results of the De Backer trial indicate a lower cure for itraconazole (45.8% at week 48) but a comparable cure for terbinafine (73%). The cure rates of itraconazole were in the range of the cure rates reported in other trials.

We do not have as such an explanation for the difference in outcome. The only major difference in inclusion criteria that we found was the fact that in our trial only patients with a nail involvement more than 50% of the whole nail surface could be included (severe type) while in the De Backer trial no minimum severity criterion was required.

The findings of this study do not support a decline in mycological cure rates within 1 year of evaluation. This has also been confirmed in a number of other trials using pulse dosing and continuous dosing (1, 2).

It would have been of interest to have longer post-treatment data in our patient sample in order to predict the relapse after more than 1 year.

The pharmacokinetic properties of itraconazole support the long-term protection as therapeutic levels are found in toenails up to 9 months after stopping a 3-month treatment.

Based on these pharmacokinetic/pharmacodynamic studies, it is expected that cure rates of itraconazole within a 12-month period will not decrease.

Statement 2: Black-box warning.

Response: A black box warning is a US-only issue as in other countries there is no such warning on the label. For the sake of completeness, it is of interest to note that a red-box warning exists for terbinafine in Japan for blood dyscrasia and liver monitoring.

The safety data indicate that the prevalence of nuisance side-effects is comparable for both drugs (3, 4). Hepatic side-effects are uncommon, some hematological side effects are reported for terbinafine, drug interactions are present for the azole derivatives, but recent data suggest also the potential interaction of terbinafine with CYP 2D6.

The symptomatic hepatotoxicity with terbinafine is estimated to be 1:54,000 to 1:120,000 (Canadian product monograph of terbinafine). In a pharmacovigilance study of 25,884 patients completed by Novartis, Hall et al. (3) report that 10 patients experienced symptomatic hepatobiliary events. Two cases of cholestatic hepatic dysfunction were considered potentially related to terbinafine (2 out of 25,884 patients).

Statement 3: Fungicidal.

Response: The minimal inhibitory concentrations (MICs) of terbinafine and itraconazole for most isolates of the dermatophytes are low. Terbinafine demonstrates an excellent fungicidal activity *in vitro* against dermatophytes, whereas itraconazole has a poorer fungicidal activity.

Clayton (5) has shown that the minimal fungicidal concentration (MFC) for terbinafine is 0.004 mg/l against dermatophytes and for itraconazole is 0.595 mg/l. Indeed, the MFCs are clearly higher for itraconazole, but based on the itraconazole drug levels in the nail (approx. 1 μg/g tissue), these drug levels are sufficient for fungicidal activity (on condition we believe that having a fungicidal claim is clinically relevant).

More studies are needed to establish the true relevance of this fungicidal activity. If fungicidal activity would implicate a direct killing effect, treatment should be even shorter, as the current 3 months of treatment for onychomycosis.

That other factors may determine the clinical efficacy of antifungal is shown for the treatment of tinea capitis. Terbinafine shows *in vitro* a fungicidal activity against *Microsporum canis*, yet *in vivo* griseofulvin, a so-called fungistatic drug, remains in most countries the golden standard for this type of tinea capitis caused by *M. canis*, with even better cure rates for this type of infection than terbinafine (6).

REFERENCES

1. Havu V, Brandt H, Heikkilä H, Hollmen A, Oksman R, Rantanen T, et al. A double blind randomized study comparing itraconazole pulse therapy with continuous dosing for the treatment of toenail onychomycosis. Br J Dermatol 1997; 136: 230–234.
2. Haneke E, Abeck D, Ring J. Safety and efficacy of intermittent therapy with itraconazole in finger- and toenail onychomycosis: a multicentre trial. Mycoses 2000; 41: 521–527.
3. Hall M, Monka C, Krupp P, O'Sullivan D. Safety of oral terbinafine. Arch Dermatol 1997; 133: 1213–1219.
4. Amichai B, Grunwald M. Adverse reactions of the new oral antifungals – terbinafine, itraconazole and fluconazole. Int J Dermatol 2000; 37: 410–415.
5. Clayton Y. Relevance of broad spectrum and fungicidal activity of anti-fungals in the treatment of dermatomycosis. Br J Dermatol 1994; 130: 7–8.
6. Hazen KC. Fungicidal versus fungistatic activity of terbinafine and itraconazole; an in vitro comparison. J Am Acad Dermatol 2000; 38: 537–541.

Accepted April 5, 2000.

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