Terbinafine in fungal infections of the nails: a meta-analysis of randomized clinical trials

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Authors' objectives
To compare the safety and efficacy of terbinafine with placebo, itraconazole and griseofulvin.

Searching
MEDLINE was searched up to March 2000 using the terms listed in the review. Reviews were examined for additional studies.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) that were double-blinded were eligible for inclusion.

Specific interventions included in the review
Comparisons of terbinafine with placebo, itraconazole or griseofulvin were eligible for inclusion. The daily doses used in the included studies were for terbinafine, 250 mg; for itraconazole, 200 mg (3 trials) or 400 mg daily for one in every 4 weeks and 200 mg otherwise (1 trial); and for griseofulvin, 500 or 1,000 mg. The duration of treatment in the included studies generally ranged from 3 to 6 months, although one study of griseofulvin treated patients for 11 months.

Participants included in the review
Criteria were not defined in terms of the participants, but studies of people with onychomycosis appeared to be eligible.

Outcomes assessed in the review
The primary outcome assessed in the review was mycological cure. The included studies usually defined this as negative microscopy or culture at the end of the trial. Other outcomes assessed in the review were tolerability (assessed by patients and physicians) and adverse event rates. There were no details of the methods used to assess tolerability or adverse events.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The tabulated information included author, intervention details, treatment duration, and mycological cure rates at the end of the study. Where possible, the data were extracted on an intention-to-treat basis.

Methods of synthesis
How were the studies combined?
The studies were grouped by (placebo, itraconazole and griseofulvin) and data in each group were combined in a meta-analysis. The pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated for mycological cure rates.

How were differences between studies investigated?
The text of the review did not mention any testing for statistical heterogeneity. Forest plots of terbinafine versus
itraconazole and terbinafine versus griseofulvin were presented. A potential reason for the significant heterogeneity of terbinafine versus itraconazole was considered in the text.

**Results of the review**

Nine RCTs (2,227 patients) were included in the review.

Terbinafine versus placebo (3 RCTs, 588 patients): compared with placebo, terbinafine significantly improved the cure rates at 12 weeks; the RR was 9.07 (95% CI: 5.14, 16.02).

Terbinafine versus itraconazole (4 RCTs, 1,264 patients): compared with itraconazole, terbinafine significantly improved the cure rates at the end of treatment (12 to 16 weeks); the RR was 1.64 (95% CI: 1.48, 1.81). The forest plot showed significant heterogeneity with one RCT showing greater efficacy than the other 3 RCTs. The authors suggest this may be due to the one RCT using a higher dose of itraconazole (400 mg) for one in every 4 weeks. Terbinafine was reported as being better tolerated by patients and physicians than itraconazole (RR 1.22, 95% CI: 1.14, 1.31). However, it was unclear how the reported RR for this outcome was assessed. There was no significant difference between the treatments in terms of the adverse event rates; further details were not presented.

Terbinafine versus griseofulvin (2 RCTs, 375 patients): compared with griseofulvin, terbinafine significantly improved the cure rates at 24 weeks; the RR was 1.31 (95% CI: 1.10, 1.56).

**Authors’ conclusions**

Terbinafine significantly increased the mycological cure rates compared with placebo, itraconazole and griseofulvin.

**CRD commentary**

The review question was clear in terms of the study design, intervention, and outcomes of interest. The participants were defined in terms of diagnosis, but no diagnosis criteria were reported. The search was limited to published studies listed in one database, which may have resulted in the omission of other relevant studies and raises the possibility of publication bias. It was not possible to assess the adequacy of the methods used to select the studies or to extract the data since no details were reported of either process. The included studies were restricted to blinded RCTs but their quality was not assessed further.

The studies were appropriately grouped by comparator treatment. Testing for statistical heterogeneity was not mentioned in the text of the review, although forest plots for two of the three comparisons were presented. A potential reason for the significant heterogeneity among studies comparing terbinafine with itraconazole was discussed in the text. Where adverse events were not mentioned, it was unclear whether they were not reported in the review or were not reported in the primary studies. Where adverse events were mentioned, no details were given of either adverse event rates or specific adverse events reported by the patients.

In view of the limited investigation of heterogeneity and insufficient information on the included studies, it is not possible to adequately assess the evidence. Hence, the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors state that more long-term studies with adequate follow-up time are required.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.