Economic evaluation of antifungal agents in the treatment of toenail onychomycosis in Germany


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of antifungal agents in the treatment of patients with toenail onychomycosis. The agents considered were as follows:

(1) itraconazole, continuous regimen,
(2) itraconazole, 1-week pulse dosage regimen,
(3) oral terbinafine,
(4) topical ciclopirox nail varnish.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients with toenail onychomycosis.

Setting
Hospital. The economic study was carried out in Germany.

Dates to which data relate
The data for the effectiveness analysis were obtained from studies published between 1989-1996. The date related to the resource use data was not specified. The prices were those prevailing in 1995.

Source of effectiveness data
Effectiveness data were derived from a synthesis of previously completed studies, assumptions made based on expert opinion, and a decision tree model.

Modelling
A decision tree was used to estimate benefits and costs of alternative agents.
Outcomes assessed in the review
Clinical response rates (defined as clinical cure plus marked improvement in the appearance of the nails) were assessed in the review.

Study designs and other criteria for inclusion in the review
Clinical trials, three studies reported as randomized clinical trials. The inclusion criteria were reported as follows: onychomycosis should be diagnosed on the basis of both clinical and mycological evaluation; the infecting pathogen should be identified; clear report of the drug used; clear report of duration of treatment, which must be at least 12 weeks; definitions of endpoints 'cure' and 'response'; specification of the site of the infection as toenail; no antimycotic treatment other than the primary drug should be administered during the study; rejection of studies performed using suboptimal continuous dosing schedules of 50-150 mg/day for itraconazole; response rates based on a minimum period of 6 months of follow up for itraconazole and terbinafine; adequate description of patients' status during follow up; continuous therapy at a dose of itraconazole 200 mg/day; at least 10 evaluable patients in the clinical trial; efficacy rates "not available for follow-up beyond six months". Due to the scarcity of study reports on fingernail onychomycosis and the low numbers of patients in most of those reports, the study focused only on toenail onychomycosis.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
The methods used to judge relevance and validity were not stated. The data were extracted by means of summary statistics in the primary studies.

Number of primary studies included
Seventeen studies were included, three of which were reported to be randomized clinical trials.

Methods of combining primary studies
Meta-analysis. The method of pooling of results from each primary study was based on that of DerSimonian and Laird, and that of Velanovich.

Investigation of differences between primary studies
Not reported.

Results of the review
The clinical response rates, at 12 months from initiation of therapy, were as follows: Itraconazole continuous therapy, 77.5% (+/- 9%), itraconazole 1-week pulse therapy, 89.8% (+/- 3%); oral terbinafine, 79.4% (+/- 10%); ciclopirox nail varnish, 55.0% (+/- 4%).

Methods used to derive estimates of effectiveness
Estimates of effectiveness were also based on authors' assumptions.

Estimates of effectiveness and key assumptions
The efficacy rate of the second line therapy was assumed to be an average of the two most effective antifungal agents (pulsed itraconazole and oral terbinafine). Relapse rates were not included in the analysis because of lack of sufficient data on itraconazole therapies.

**Measure of benefits used in the economic analysis**
The measure of benefits was the number of successes (clinical response rates times 1,000 hypothetical patients). A decision tree was used to calculate the expected benefits once the efficacy rate of first line therapy was obtained. The valuation of benefits was at 12 months after initiation of treatment.

**Direct costs**
Only drug doses were reported as quantities. The cost items were not fully reported. The costs measured were operating costs (drug acquisition costs of initial therapy, physician visit and diagnostic tests costs). The boundary adopted was the health care payer. The estimation of quantities was based on actual data and experts' opinion ('recommended clinical practice'). The grounds on which the estimation of costs on each branch of the decision tree was carried out were not reported. The source of costs was not reported. The prices used were those of 1995. The costs of complications were excluded due to insufficient data.

**Indirect Costs**
Not included.

**Currency**
German marks (DM).

**Sensitivity analysis**
The parameters varied in the analysis were the efficacy rates of first-line therapies and the definition of efficacy (complete cures defined as clinical cure and mycological cure instead of clinical response). A threshold analysis was performed.

**Estimated benefits used in the economic analysis**
The number of successes at 12 months, in a hypothetical group of 1,000 patients with onychomycosis were as follows:

- itraconazole (1-week pulse) 898;
- terbinafine, 794;
- itraconazole (continuous), 775;
- ciclopirox, 550.

**Cost results**
The total costs at 12 months, in a hypothetical group of 1,000 patients with onychomycosis were as follows:

- itraconazole (continuous), DM1,905,901; itraconazole (1-week pulse), DM993,954; terbinafine, DM972,498; ciclopirox, DM734,290.

**Synthesis of costs and benefits**
Cost per success and incremental cost per additional success ratios were calculated for each strategy. The cost per success ratios were as follows: itraconazole (1-week pulse), DM1,107; terbinafine, DM1,224; itraconazole (continuous),
DM2,460; ciclopirox, DM1,335.

The incremental cost effectiveness ratios were as follows: itraconazole (continuous) with respect to ciclopirox, DM5,214; terbinafine with respect to the former, <0; itraconazole (1-week pulse) with respect to terbinafine, DM207.

The sensitivity analysis showed no conclusive results in favour of either itraconazole (1-week pulse) or terbinafine, since in the baseline case the former had the lowest cost effectiveness ratio using clinical response, whereas terbinafine had the lowest ratio using 'clinical cure' as outcome measure and this ranking was transposed once the upper confidence limits in efficacy rates were used.

Authors' conclusions
Itraconazole is an effective, broad-spectrum triazole used as continuous or pulse therapy in the treatment of onychomycosis. Itraconazole (1-week pulse) and terbinafine are the most cost-effective therapies for toenail onychomycosis.

CRD COMMENTARY - Selection of comparators
No single agent was specifically considered as the comparator as all were considered to be the most commonly used agents in Germany in the context in question.

Validity of estimate of measure of benefit
The internal validity of the benefit results is likely to have been weakened by the lack of randomisation, and a systematic review of the literature.

Validity of estimate of costs
Resource quantities were not fully reported and adequate details of methods of cost estimation were not given. The sources of cost data were not reported.

Other issues
In view of the lack of randomisation, a systematic review of the literature, and statistical analysis of the costs, the results need to be treated with some caution. The issue of generalisability to other settings/countries was not addressed.

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