Pharmacoeconomic analysis of oral antifungal therapies used to treat dermatophyte onychomycosis of the toenails: a US analysis

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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
Antifungal agents used in the treatment of dermatophyte onychomycosis of the toenails. Specifically the agents examined were griseofulvin, itraconazole (continuous and pulse), terbinafine and fluconazole.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
A hypothetical cohort of patients requiring treatment for dermatophyte onychomycosis of the toenails.

Setting
Community. The economic analysis was conducted in Toronto, Ontario, Canada.

Dates to which data relate
Effectiveness data were derived from literature published between 1960 and 1997. The resource use data were derived from a panel of experts and may reflect patterns of US practice at the time of the study. 1997 prices were used in the analysis.

Source of effectiveness data
Effectiveness data were derived both from review or synthesis of previously completed studies and assumptions (relapse rates for itraconazole pulse).

Modelling
A decision analytical model, incorporating initial cure rates and relapses, was used to estimate the costs and effectiveness of the different treatment alternatives over a three year period.

Outcomes assessed in the review
The review assessed mycological cure and relapse rates for dermatophyte onychomycosis of the toenails for each of the comparators.

Study designs and other criteria for inclusion in the review
The analysis included randomised controlled trials and uncontrolled, prospective studies measuring mycological cure rates identified between 1960 and 1997 which were published in the English language.

Specific criteria for inclusion were:

onychomycosis had to be diagnosed both by clinical and mycological evaluation, and an etiological organism had to be identified;

duration of therapy should be more than 6 months for griseofulvin, 3 months for itraconazole (continuous), 3 pulses over 7 weeks for itraconazole (pulse), and 3 months for terbinafine and 6 months for fluconazole.

Specific dosages for the regimens were 500mg or more per day for griseofulvin, itraconazole (continuous) 200 mg per day, itraconazole (pulse) 200 mg twice daily for one week each month, terbinafine 250 mg per day and fluconazole 300 mg per day once per week. Patients were required not to be on any other drug therapy. The duration of follow up for itraconazole and terbinafine had to be at least 6 months.

Sources searched to identify primary studies
Medline/Embase was searched between 1966 and 1997. In addition the references of all articles meeting the inclusion criteria were also examined.

Criteria used to ensure the validity of primary studies
Although double blind and controlled studies were preferred, open and uncontrolled trials were considered if they met the criteria. All studies needed to have a minimum sample size of 10 to be included in the analysis.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Overall, 32 studies were included in the meta-analysis of cure rates.: griseofulvin (8 studies), itraconazole continuous (9 studies), itraconazole pulse (5 studies), terbinafine (9 studies) and fluconazole (1 study).

For griseofulvin, 2 studies were described as 'open', 2 as 'open controlled', 1 as a 'double-blind comparative', 1 as an 'open comparative randomised', 1 as a 'double-blind parallel group', and 1 as a 'randomised double-blind' study.

The estimate of itraconazole continuous was derived from 2 'open' studies, 2 'randomised double-blind' studies, 2 'double-blind placebo controlled' studies, 1 'open comparative' and 1 'double blind-parallel-group' study.

The corresponding value for itraconazole pulse was derived from 3 'open' studies, 1 'placebo-controlled study' and 1 'double-blind parallel group'.

The effect of terbinafine was estimated from 4 'double-blind placebo-controlled' studies, 2 'double-blind comparative' studies, 1 'open comparative' study, and 2 'open' studies.

The relapse rates for griseofulvin, itraconazole continuous, terbinafine and fluconazole, were derived from one study each (overall 4 studies). Two of these were studies whose design was not reported. The other two studies included a multi-centred 'randomised double-blind' study of fluconazole, which was also used to determine the cure rate for fluconazole, (as this was a new treatment with little available information) and an overview of itraconazole continuous studies which was also included in the analysis of cure rate ('double-blind placebo controlled').

Methods of combining primary studies
A meta-analysis was conducted to combine the results of the studies to determine mycological cure rates. The sample
size weighted average value was determined for each comparator for each mycological cure rate. Relapse rates were taken from individual articles in the literature and no weighting was derived.

Investigation of differences between primary studies
Not stated.

Results of the review
The mycological cure rates (95% CI in brackets) by comparator were as follows:

- griseofulvin, 24.3% (11.3 - 37.7%);
- itraconazole (continuous), 66.4% (54.4 - 78.4%);
- itraconazole (pulse), 76.0% (57.8 - 94.2);
- terbinafine, 74.0% (60.2 - 87.7).
- fluconazole, 59%.

The relapse rates reported for the drugs were: griseofulvin (40%), itraconazole continuous (21%), terbinafine (15%) and fluconazole (4.8%).

Methods used to derive estimates of effectiveness
The base case estimate of the rate of relapse for itraconazole pulse therapy was based on opinion.

Estimates of effectiveness and key assumptions
The relapse rate of itraconazole pulse therapy was assumed to be the same as that of itraconazole continuous therapy, namely, 21%.

Measure of benefits used in the economic analysis
The benefit measures were symptom-free days gained and patients cured. Benefits were not reported as discounted in spite of the 3-year period covered by the analysis.

Direct costs
Costs were not reported as discounted even though the period of analysis was greater than 1 year. The direct costs of drug acquisition, medical management and adverse events associated with each regimen were estimated. These costs included those for the initial consultation, return visits, mycology and other laboratory tests. The resource use associated with treatment regimens was determined in consultation with an expert panel of five dermatologists. The costs of adverse events were also estimated with the help of this panel. Costs and resources were estimated by adopting the view of a third party payer whilst also including out of pocket expenses (over the counter medications) paid by patients. Average wholesale prices for drugs were taken from the 1997 Mosby Physicians Drug reference book. Medical management costs were taken from the 1995 Health Care Finance Administration's Physician Fee Schedule and the Clinical Diagnostic Laboratory Fee Schedule. 1997 prices were used to report results.

Currency
Canadian dollars (Can$).

Sensitivity analysis
A threshold analysis was conducted. The parameters examined included mycological cure rate, clinical cure rate, relapse rates, drug acquisition costs and duration of therapy.

**Estimated benefits used in the economic analysis**
The mycological cure rates for initial therapy with griseofulvin was 24.5%, with itraconazole continuous was 66.4%, with itraconazole pulse was 76%, with terbinafine was 0.74, and with fluconazole was 59%.

The numbers of symptom-free days per patient over the 3 year treatment and follow up period for each of the regimens were:

- griseofulvin, 408,
- itraconazole (continuous), 929,
- itraconazole (pulse), 942 days,
- terbinafine, 945 days
- and fluconazole, 680 days.

Adverse events were included in the analysis.

**Cost results**
The total costs per patient, including adverse events of the treatment regimens, over the 3 year treatment and follow up period were:

- griseofulvin, Can$2,880,
- itraconazole (continuous), Can$2,022,
- itraconazole (pulse), Can$1,182,
- terbinafine, Can$1,211
- and fluconazole, Can$1,443.

The average costs per mycological cure for these same treatments were Can$8,089, Can$1,877, Can$991, Can$1,125 and Can$1,506 respectively. The duration of treatment for these regimens were 18 months, 3 months, 1 week, 3 months and 6 months respectively.

**Synthesis of costs and benefits**
The following figures represent 1997 prices, and no discounting was reported.

The cost per mycological cure rate was:

- griseofulvin, Can$8,089,
- itraconazole continuous, Can$1,877,
- itraconazole pulse, Can$991,
- terbinafine, Can$1,125,
- fluconazole, Can$1,506.
The (average) cost per symptom-free day (SFD) gained over the 3 year period was estimated to be as follows:

griseofulvin Can$7.05,
itraconazole (continuous) Can$2.18,
itraconazole (pulse) Can$1.26,
terbinafine Can$1.28 and
fluconazole Can$2.12.

In an incremental analysis griseofulvin, itraconazole (continuous) and fluconazole were dominated by itraconazole (pulse) and terbinafine. The incremental cost per symptom-free day for terbinafine compared with itraconazole (pulse) was Can$9.67. Sensitivity analysis found that the rank ordering of itraconazole (pulse) and terbinafine changed with minor variations.

Authors' conclusions
Itraconazole pulse and terbinafine were the most cost effective treatments for dermatophyte onychomycosis of the toenails and are similar to results reported by other authors. The high sensitivity of the ranking between those two strategies was considered to point to their equivalent efficiency. The authors felt that the widespread use of griseofulvin was due to lack of information and custom on the part of physicians, and that, consequently, an education programme may be required.

CRD COMMENTARY - Selection of comparators
No justification was given for the comparators used in the analysis. All of the antifungal treatments, with the exception of fluconazole, which is under consideration, are available for use in the United States for the treatment of dermatophyte onychomycosis of the toenail.

Validity of estimate of measure of benefit
The estimate of benefits was based on a meta-analysis of data taken from a systematic literature review using Medline. Inclusion criteria for this search were stated, although the authors themselves noted the inconsistency in reported measures of efficacy among the studies retrieved. In addition, information on fluconazole was based on a single randomised controlled trial, as this drug had only recently been developed. Only a few studies in the analysis were randomised controlled trials due to the paucity of studies matching the inclusion criteria. Most of the information came from less well controlled, or uncontrolled, studies and this could have introduced bias into the estimates. The literature search was restricted to English language papers, which may have led to the omission of important clinical studies. The authors noted that their relapse rates may not be accurate due to the lack of quality data. They also noted that the effects of compliance with therapy, and interactions with other drugs being taken by patients, were not examined.

Validity of estimate of costs
Although sufficient details were provided of the methods used to derive costs, the analysis only examined costs from the perspective of the third party payer and excluded costs related to others in society such as patients. Costs were not reported as discounted. No information was provided on the methods by which the expert panel arrived at their estimates of resource use and the impact of adverse events.

Other issues
The cost data may not be generalisable outside the United States.

Implications of the study
There is a need for well-designed clinical and economic studies to consider the different treatments from a societal perspective and to take into account compliance and drug interactions. In addition there is a need to evaluate relapse rates and to conduct further clinical trials with fluconazole, as information on this drug is limited.
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