Cost effectiveness of continuous terbinafine compared with intermittent itraconazole in the treatment of dermatophyte toenail onychomycosis: an analysis based on results from the LION Study

Jansen R, Redekop W K, Rutten F F H

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 study compared two oral anti-fungal treatment regimens for patients with dermatophyte toenail onychomycosis. The treatment regimens compared were continuous terbinafine and intermittent itraconazole over a 12 or 16-week treatment period.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was people with dermatophyte onychomycosis. The study sample comprised men and women aged 18 to 75 with a clinical and mycological diagnosis of dermatophyte onychomycosis who participated in the Lamisil versus Itraconazole in Onychomycosis (LION) Study. The authors reported that the use of drugs known or believed to interact with either of the study agents was an exclusion criterion. The authors did not report any other details about the study sample or the inclusion and exclusion criteria used in the clinical trial.

Setting
The setting was secondary care. The study was carried out in six European countries: Finland, Germany, Iceland, Italy, the Netherlands, and the UK.

Dates to which data relate
The effectiveness and resource use data were taken from the LION study published in 1999. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The authors applied costs estimated from expert opinion to the patient sample used in the effectiveness study.

Study sample
The authors did not report details about sample selection, sample size calculations or the appropriateness of the sample for the evaluation. The authors reported that 496 patients were randomised to treatment. However, the table of adverse
events suggests that 506 patients were allocated to treatment; 126 to the T12 treatment group, 123 to the T16 treatment group, 131 to the I3 treatment group, and a further 126 to the I4 treatment group.

**Study design**
The study was a prospective, double-blind, double-dummy, multi-centred, randomised, controlled trial carried out in six European countries (Finland, Germany, Iceland, Italy, the Netherlands, and the UK). The duration of follow-up was 72 weeks. The authors did not report details about the method used for randomisation and treatment allocation, or the loss to follow-up.

**Analysis of effectiveness**
The outcome measures used in the clinical trial included mycological cure and complete cure. The authors did not report whether the clinical trial was based on the intention to treat or treatment completer cohort.

**Effectiveness results**
The study reported the mycological and complete cure rates in each of the four treatment groups. The results for mycological cure were:

- group T12, 76% (81/107);
- group T16, 81% (80/99);
- group I3, 38% (95% CI: 41 to 107);
- group I4, 49% (53/108).

The results for complete cure were:

- group T12, 45.8% (95% CI: 36.4 to 55.3);
- group T16, 55.1% (95% CI: 45.0 to 65.0);
- group I3, 23.4% (95% CI: 15.4 to 31.3);
- group I4, 25.9% (95% CI: 17.7 to 34.0).

The percentage of patients completely cured at week 72 in the terbinafine groups (T12, T16) was significantly greater (p<=0.0046) than those in the itraconazole groups (I3, I4).

**Clinical conclusions**
The authors concluded that continuous terbinafine was a more effective treatment strategy than intermittent itraconazole in the treatment of dermatophyte toenail onychomycosis.

**Measure of benefits used in the economic analysis**
The authors used the percentage of patients completely cured (mycological cure plus 100% toenail clearing) and number of disease free days as the measure of benefit.

**Direct costs**
The authors reported that only direct medical costs were assessed, because no data on direct non-medical or indirect costs were available. Medical resource consumption was divided into 3 categories: routine medical management, management of adverse events, and management of relapse or failure. Costs were calculated through determining the
levels of medical resource consumption in each of the six countries, and then applying country specific unit cost estimates to the data. Medical resource use was estimated from expert opinion and the trial investigators. The author's reported that resource consumption during routine medical management consisted mainly of the costs associated with antifungal medication, visits to a general practitioner and dermatologist, and laboratory tests. Based on previous toenail onychomycosis cost estimate studies the number of physician visits varied between 1 and 3, and the number of laboratory tests varied between 0 and 2 for mycology (fungal culture and direct microscopy) and were either 0 or 1 each for biochemistry and haematology.

Data relating to adverse events were obtained from the LION study. However, because most adverse events were reported to be mild and with only a low incidence, only those considered relevant from a cost perspective were included. The costs associated with treating adverse events were added in the cost calculations. The costs of treatment failure or relapse were included. Patients who relapsed following a period of complete cure, or who failed drug therapy during the 72-week study period were assumed to receive an extra course of antifungal therapy identical to the initial course.

The costs of different antifungal regimens were calculated using published retail prices for 1998 in the 6 countries. It was assumed that all patients had received a complete course of antifungal therapy (terbinafine or itraconazole) according to randomisation. The source of unit costs of other resource use was not reported. The price year was 1998. The authors did not report whether the costs were discounted. No indirect costs were included in the analyses.

**Statistical analysis of costs**
The authors used bootstrap statistical methods to generate mean costs and 95% confidence intervals (95% CI).

**Currency**
Costs were given in the currency of each of the 6 countries, namely: Finnish marks (Fmk); German marks (DM); Icelandic kroner (Isk); Italian Lira (L); Dutch guilders (Dfl), and UK pounds sterling (). 

**Sensitivity analysis**
The authors conducted one-way and two-way sensitivity analyses to assess the impact of changing the number of physician visits and the number of laboratory tests performed. Firstly, the authors varied the number of physician visits or laboratory visits simultaneously. Secondly, the number of physician visits or laboratory tests were varied in the terbinafine groups only, with the numbers in the itraconazole group remaining constant.

**Estimated benefits used in the economic analysis**
The authors used complete cure to proxy overall health benefit. The reader is referred to the effectiveness results for complete cure reported previously.

The authors also used the number of disease-free days in each patient group at week 72 as a measure of health benefit. The results were as follows:

group T12, 95.7 days (95% CI: 74.4 to 117.1);
group T16 114.8 (95% CI: 91.0 to 138.5);
group I3, 55.5 days (95% CI: 37.9 to 73.0);
group I4, 58.5 days (95% CI: 39.5 to 77.5).

Patients treated with continuous terbinafine over a 12 or 16-week period had significantly more disease-free days (p<0.0046) than those treated with intermittent itraconazole over a 12 or 16-week period. The duration of follow-up was 72 weeks.
Cost results
The mean treatment costs per patient in each of the six countries, for each of the 4 treatment groups were as follows:

Finland: T12 = Fmk 3665, T16 = Fmk 5,132, I3 = Fmk 2,955, I4 = Fmk 3,649.
Germany: T12 = DM 1,263, T16 = DM 1,817, I3 = DM 1,605, I4 = DM 2,081.
Iceland: T12 = Isk 55,490, T16 = Isk 79,739, I3 = Isk 64,208, I4 = Isk 83,040.
Italy: T12 = L 874,252, T16 L 1,187,431, I3 = L 989,545, I4 = L 1,210,563.
The Netherlands: T12 = Dfl 854, T16 = Dfl 1,197, I3 = Dfl 1,041, I4 = Dfl 1,316.
UK: T12 = 298, T16 = 405, I3 = 323, I4 = 397.

The incremental costs were:

Finland: T12-I3 = Fmk710 (443, 976), T16-I4 = Fmk 1,483 (913, 2,052).
Germany: T12-I3= DM -342 (-439, -244), T16-I4 = DM-264 (-473, -55).
Iceland: T12-I3= Isk -8,719 (-12,853, -4,585), T16-I4 = Isk -3,302 (-12,188, +5,584).
Italy: T12-I3= L -115,293 (-183,189, -47,397), T16-I4 = L -23,232 (-157,680, +111,416).
The Netherlands: T12-I3= Dfl -187 (-253, -121), T16-I4 = Dfl -118 (-256, +19).
UK: T12-I3= -26 (-48, -3), T16-I4 = -8(-54, +79).

The side effects of treatment and adverse events that occurred within 72 weeks of treatment initiation were included in the economic analysis.

Synthesis of costs and benefits
The authors conducted an incremental analysis, and presented incremental cost-effectiveness ratios (ICERs). In 5 of the 6 countries T12 showed dominance relative to itraconazole regimens, as it was both less expensive and, more effective. In contrast T16 was more effective but also more costly than T12. The authors reported that the results of the sensitivity analyses were robust. They stated that, even if the number of physician visits or laboratory tests were made unrealistically higher (more than 300%) in the terbinafine groups than in the itraconazole groups, continuous terbinafine would still remain more cost-effective than intermittent itraconazole in all the countries.

Authors' conclusions
The authors concluded that, from the perspective of the healthcare system, continuous terbinafine is less costly and more effective than intermittent itraconazole in the treatment of dermatophyte toenail onychomycosis.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of comparator by reference to current practice and uncertainty about the relative cost effectiveness of the alternatives. You, as a user of this database, should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a prospective, double-blinded, multi-centred, randomised, controlled trial, which was appropriate for the study question. The authors did not provide sufficient information to determine whether the study
sample was representative of the study population, whether the patient groups were comparable at baseline, whether the study had sufficient power to detect statistically significant differences in outcome or whether the analysis was based on an intention to treat or treatment completers cohort. However, the number of patients used for the analysis of adverse events was greater than for the analysis of cure rates, suggesting the use of a treatment completers cohort. The authors also noted that one of the exclusion criteria was the use of drugs believed to interact with itraconazole, which may have biased the results in favour of this drug. These factors mean that it is not possible to assess the validity of the effectiveness evaluation.

Validity of estimate of measure of benefit
The authors used complete cure rates and number of disease free days as the measures of benefit. The number of disease free days was not clearly justified. The authors stated that the nature of toenail onychomycosis means that quality-adjusted life years are not an appropriate measure. The authors did not consider other measures to value the outcomes of treatment to patients. The number of disease free days was estimated from the trial database as the time between the last visit when a cure was not observed and the first visit when a cure was observed. This is likely to over-estimate the number of disease free days. The authors used Monte Carlo simulation analysis to estimate the uncertainty associated with this approach. However, this might not be sufficient if there were systematic differences between the groups in the actual time of cure between visits.

Validity of estimate of costs
All categories of cost relevant to the perspective adopted (healthcare system) appear to have been included in the analysis. The authors did not report costs and quantities separately. A sensitivity analysis of quantities was performed and the ranges used appear to have been appropriate. However, no sensitivity analysis of prices was conducted. The authors did not report any currency conversions, although the cost-effectiveness analysis was conducted in Euros. Since all costs were incurred over only a 72-week period, discounting was unnecessary.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The authors report that a central assumption of their study was that the only difference in medical management between the treatment groups was the choice of antimycotic cure and the duration of treatment. However, the authors also stated that other studies have shown possible differences in medical management between patients receiving terbinafine and itraconazole. Consequently this implies that there may be between-country differences in relation to medical management, and also differences in terms of the number of physician visits and the frequency of laboratory tests. However, this must be qualified by the fact that the sensitivity analysis conducted by the authors showed that differences between terbinafine and itraconazole in relation to both the number of physician visits and the number of laboratory tests had only a minimal impact on the results and did not affect the main conclusions of the study.

Implications of the study
The authors conclude that continuous terbinafine is more cost-effective than intermittent itraconazole in the treatment of dermatophyte toenail onychomycosis. However, the authors also state that, even under the most dominant treatment strategy, continuous terbinafine for 12 weeks, 54% of patients will still remain uncured after 72 weeks, and consequently there remains considerable room for improvement.

Source of funding
Financially supported by Novartis Pharma (Switzerland)

Bibliographic details
PubMedID
11383756

Indexing Status
Subject indexing assigned by NLM

MeSH
Antifungal Agents /adverse effects /economics /therapeutic use; Cost-Benefit Analysis; Foot Dermatoses /drug therapy; Humans; Itraconazole /adverse effects /economics /therapeutic use; Multicenter Studies as Topic; Naphthalenes /adverse effects /economics /therapeutic use; Onychomycosis /drug therapy /economics; Randomized Controlled Trials as Topic

AccessionNumber
22001008089

Date bibliographic record published
28/02/2002

Date abstract record published
28/02/2002