Pharmacoeconomic analysis of sequential treatment pathways in the treatment of onychomycosis
Frankum L E, Nightengale B, Russo C L, Sarnes M

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 ciclopirox (CIC) nail lacquer, itraconazole pulse treatment (ITRA pulse), terbinafine (TERB) and itraconazole continuous treatment (ITRA cont) for the treatment of onychomycosis was examined. Recommended regimens were 250 mg/day TERB for 12 to 16 weeks, 200 mg/day ITRA cont for 12 to 16 weeks, 200 mg ITRA pulse twice daily for one week per month, and CIC no more than once daily for up to 48 weeks. Each agent could be used as first-, second- or third-line therapy. Thus, 12 sequential treatments were considered:

CIC/ITRA pulse/TERB;
CIC/TERB/ITRA pulse;
CIC/TERB/ITRA cont;
ITRA pulse/CIC/TERB;
ITRA pulse/TERB/CIC;
TERB/CIC/ITRA pulse;
CIC/ITRA cont/TERB;
TERB/ITRA pulse/CIC;
TERB/CIC/ITRA cont;
TERB/ITRA cont/CIC;
ITRA cont/CIC/TERB; and
ITRA cont/TERB/CIC.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with toenail onychomycosis.
Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1992 and 2003. The price year appears to have been 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
A decision model of sequential treatments was constructed to examine the costs and benefits of alternative strategies for the treatment of toenail onychomycosis in a hypothetical health plan covering 1 million lives. A sequential treatment pathway was described, where patients were given a first-line treatment. Some of the patients who responded to treatment could experience relapse, and these received another course of the first-line therapy. Patients failing treatment were switched to the second-line agent. Patients who failed initial first-line treatment switched directly to a second-line agent, and again the model considered response rates and relapse rates. Those who failed the second-line agent switched to the third-line therapy. A time horizon of one to three years was considered.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the clinical response rate,
the relapse rate,
the frequency of adverse events resulting in discontinuation of treatment,
adverse events that required care, and
disease prevalence.

Study designs and other criteria for inclusion in the review
A review of the literature was carried out to identify relevant studies assessing clinical response rates. A description of each study was provided. The inclusion criteria were:

efficacy measured by clinical response end points;
diagnosis confirmed by microscopy or culture;
greater than 50% of isolated organisms of dermatophyte etiology; and
greater than 50% of infections involved in onychomycosis of toenail only.
The exclusion criteria were:
the inclusion of immunocompromised patients;
the inclusion of patients with concurrent psoriasis;
clinical response not defined; and
definition of clinical response included mycological evaluation of 100% reduction of the affected area.

Other clinical inputs appear to have been identified selectively.

Sources searched to identify primary studies
Not stated.

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

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

Number of primary studies included
Eighteen primary studies were used in the review. Other model inputs came from four studies.

Methods of combining primary studies
The response rates were combined by calculating an average, weighted by sample size.

Investigation of differences between primary studies
The authors stated that differences in study design had no large effects on the difference in clinical response.

Results of the review
The clinical response rate was 66.9% (range: 42 - 86) with CIC, 85.7% (range: 65 - 97) with ITRA pulse, 78.9% (range: 63 - 97) with TERB, and 70% (range: 58 - 82) with ITRA cont.

The relapse rate was 20.7% with CIC, 10.4% with ITRA pulse, 15% with TERB, and 21% with ITRA cont.

The frequency of adverse events resulting in discontinuation of treatment was 1% with CIC, 11% with ITRA pulse, 4.2% with TERB, and 11% with ITRA cont.

The rate of adverse events that required care was 0% with CIC and 1% with ITRA pulse, TERB and ITRA cont.

The prevalence of disease was 4% (and 20% of patients would seek treatment). Thus, in a cohort of 1 million individuals, the treated population would consist of 8,000 patients.

Measure of benefits used in the economic analysis
The summary benefit measure was the number of responders. This was obtained using the decision model.

Direct costs
Discounting was not relevant since the costs were incurred during short periods of time. The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were antymyotic treatments, office visits, liver function test, complete blood count and an assessment of potassium hydroxide. The cost/resource boundary of the health care system was adopted. Resource consumption was derived from a study published in 2000. The costs were estimated using data derived from the Centers for Medicare and Medicaid Services Relative Resource Value Scale and the Price-Check in 2003.
Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
Univariate and multivariate sensitivity analyses were performed to examine the robustness of the model results to variations in the base-case inputs. The low and high values of each input were used. When published ranges of values were not available, the inputs were varied by +/- 20% of their base-case value. A Monte Carlo simulation was also carried out whereby all inputs were varied simultaneously using 1,000 iterations. This yielded a mean and 95% confidence interval for the costs and benefits.

Estimated benefits used in the economic analysis
In a cohort of 8,000 cases, the number of responders was:

7,834 with CIC/ITRA pulse/TERB,
7,776 with CIC/TERB/ITRA pulse,
7,688 with CIC/TERB/ITRA cont,
7,834 with ITRA pulse/CIC/TERB,
7,870 with ITRA pulse/TERB/CIC,
7,776 with TERB/CIC/ITRA pulse,
7,605 with CIC/ITRA cont/TERB,
7,870 with TERB/ITRA pulse/CIC,
7,688 with TERB/CIC/ITRA cont,
7,697 with TERB/ITRA cont/CIC,
7,605 with ITRA cont/CIC/TERB, and
7,697 with ITRA cont/TERB/CIC.

Cost results
In a cohort of 8,000 cases, the total costs (in millions) were:

$6.0 with CIC/ITRA pulse/TERB,
$6.2 with CIC/TERB/ITRA pulse,
$6.6 with CIC/TERB/ITRA cont,
$7.9 with ITRA pulse/CIC/TERB,
$8.3 with ITRA pulse/TERB/CIC,
$8.6 with TERB/CIC/ITRA pulse,
$8.5 with CIC/ITRA cont/TERB,
$9.1 with TERB/ITRA pulse/CIC,
$9.0 with TERB/CIC/ITRA cont,
$10.5 with TERB/ITRA cont/CIC,
$15.3 with ITRA cont/CIC/TERB, and
$16.1 with ITRA cont/TERB/CIC.

**Synthesis of costs and benefits**
Average cost-effectiveness ratios (ACERs; i.e. the cost per responder) were calculated to combine the costs and benefits.

In a cohort of 8,000 cases, the estimated ACERs were as follows:

$757.89 with CIC/ITRA pulse/TERB,
$796.13 with CIC/TERB/ITRA pulse,
$854.37 with CIC/TERB/ITRA cont,
$1,008.04 with ITRA pulse/CIC/TERB,
$1,052.96 with ITRA pulse/TERB/CIC,
$1,103.56 with TERB/CIC/ITRA pulse,
$1,119.69 with CIC/ITRA cont/TERB,
$1,151.45 with TERB/ITRA pulse/CIC,
$1,165.32 with TERB/CIC/ITRA cont,
$1,373.94 with TERB/ITRA cont/CIC,
$2,008.63 with ITRA cont/CIC/TERB, and
$2,093.25 with ITRA cont/TERB/CIC.

The Monte Carlo simulation showed the robustness of the base-case results. The univariate sensitivity analysis suggested that when CIC was the first-line agent, the total costs were mostly affected by variations in the clinical response rate of CIC. When ITRA pulse was the first-line agent, the cost of ITRA was the variable with the greatest impact on the model results.

**Authors’ conclusions**
A treatment pathway for toenail onychomycosis that used ciclopirox (CIC) nail lacquer solution 8% as a first-line agent
was a cost-effective strategy from the perspective of the health care system.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators, which represented commonly used agents for the treatment of onychomycosis. Dosages were reported and all possible combination therapies were considered. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from published evidence. The key clinical input (clinical response rate) was estimated from a review of the literature, which could have been systematic (although it was not stated so). Some of the methodology used to conduct the review was described. For example, the inclusion and exclusion criteria and method of combining the primary estimates. Other estimates could have been identified selectively. All clinical inputs were varied in the sensitivity analysis in order to address the impact of each estimate on the model results.

**Validity of estimate of measure of benefit**
The benefit measure was specific to the disease considered in the study and is not comparable with the benefits of other health care interventions. The impact of the interventions on quality of life was not assessed, although the authors stated that this represented an important dimension of care for patients with onychomycosis.

**Validity of estimate of costs**
The categories of costs included in the analysis were consistent with the perspective of the study, which was explicitly stated. Extensive details of the unit costs, resource use, source of data and price year were provided, which enhances the possibility of replicating the analysis and performing reflation exercises in other settings. The cost estimates were varied in the sensitivity analysis.

**Other issues**
The authors compared their findings with those from a published model, and observed similar results. In addition, the results of other studies were compared and possible explanations for the observed differences in the results were discussed. The authors stated that the external validity of their results was addressed by making comparisons with other studies. Some sensitivity analyses were also carried out to identify key model inputs. The authors noted some limitations of their study. First, the model did not address compliance for any of the comparators. Second, oral dosages were compared with topical therapies, which might reduce the validity of clinical data. Finally, several primary studies used per protocol analysis rather than intention to treat.

**Implications of the study**
The study results supported the use of CIC as first-line treatment for toenail onychomycosis. The authors highlighted that their analytic framework could be useful for formulary decision-makers.

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