A multicentre, randomized, controlled study of the efficacy, safety and cost-effectiveness of a combination therapy with amorolfine nail lacquer and oral terbinafine compared with oral terbinafine alone for the treatment of onychomycosis with matrix involvement


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 oral terbinafine 250 mg with and without amorolfine 5% nail lacquer for the treatment of onychomycosis with matrix involvement.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Men and women aged 18 to 70 years with dermatophytic onychomycosis affecting at least one great toenail (target nail) and matrix involvement were screened. Eligible patients were required to have dermatophytes from both direct microscopic and mycological culture examinations. The patients were required to have washout periods of at least 6 months for oral antifungals and 3 months for antimitotic nail lacquers. Exclusion criteria prohibited the enrolment of patients with any of several predisposing conditions (e.g. diabetes), patients with known sensitivities to treatments, patients requiring interfering treatment, patients with impaired liver or kidney function, and women who were pregnant, breastfeeding or planning pregnancy.

Setting
The setting was secondary care in nine European countries.

Dates to which data relate
The clinical trial took place between February 2002 and September 2004. The price year was not reported. The exchange rate used to standardise the costs was that for January 2006.

Link between effectiveness and cost data
The resource use for costing was prospectively collected and drawn from the same sample of patients as that used for the effectiveness analysis.

Study sample
A sample size of 125 patients per group could detect a 20% difference in efficacy, assuming a drop-out rate of 20%. A convenience sample of 249 patients was randomised to either the combined amorolfine-terbinafine therapy (A-T) or terbinafine alone (T). Of these, 120 received A-T and 129 received T. A total of 83.5% of the patients completed the study, 105 in the A-T group and 103 in the T group. Discontinuation rates were higher in the T group (20.2%) than in
the A-T group (12.5%), and were mainly driven by lack of efficacy and patient request. The baseline characteristics were similar in both groups. Major protocol deviations (27%) were higher in the T group (34%) than in the A-T group (19%), and were most commonly associated with the 18-month visit not being completed or being outside the defined timeframe.

**Study design**
An 18-month, multi-centre (20), randomised, open-label and parallel-group study was conducted. A 1:1 randomisation list was generated. Patients in the A-T group continued in the trial after treatment was completed for a 6-month treatment-free period. Similarly, patients in the T group continued in the trial for a 15-month treatment-free period. This resulted in a total follow-up time of 18 months for both groups.

**Analysis of effectiveness**
The primary analysis was an intention to treat analysis of the overall response at the end of 18 months, using a dichotomous scale of success or failure. Success was defined as the combination of clinical cure (disappearance of all lesions or residual disease of maximum 10% of the original diseased surface) and negative mycology (comprising both negative microscopy and negative culture). The last-observation-carried-forward method was used to impute missing data. The secondary end points included clinical response, mycological examination and total percentage diseased surface. The presence of streaks and of onycholysis on the target nail was assessed at baseline, and a onychomycosis quality of life questionnaire was administered to a sub-set of patients (n=39). Sub-group analyses of the primary end point were also performed.

**Effectiveness results**
After 18 months, A-T was associated with a significantly higher success rate compared with T alone, (59.2% versus 45.0%; p=0.03).

A-T patients had a higher rate of clinical cure than T patients, (66.7% versus 53.5%; p<0.04).

Both groups showed important reductions in disease surface area, with mean reductions of 85.1% in the A-T group and 78.5% in the T group at 18 months.

The sub-groups were insufficiently powered for conclusions to be drawn about the exploratory variables.

The quality of life assessment was performed in 15.7% of patients. Both groups showed improvement but no difference was found between treatments.

**Clinical conclusions**
The authors concluded that A-T enhances clinical efficacy compared with T alone, and that both treatments were safe and well tolerated.

**Measure of benefits used in the economic analysis**
The primary efficacy criterion, overall response at last visit, was chosen as the efficacy measure in the cost-effectiveness evaluation.

**Direct costs**
Only direct drug acquisition costs were included. Other costs were not included because they were protocol-driven and because only a few adverse events occurred. The mean quantity of amorolfine nail lacquer used per patient was drawn from a previous study. For terbinafine, the quantity used per patient was based on the protocol indication. Local public prices and the lowest priced pack size were used.
Statistical analysis of costs
The data were treated deterministically.

Indirect Costs
Inline with the perspective adopted, productivity costs were not considered in the study.

Currency
The currency was unclear, although it is likely to have been Euros.

Sensitivity analysis
No sensitivity analysis was conducted.

Estimated benefits used in the economic analysis
See the Effectiveness Results section.

Cost results
The total costs were not reported separately.

Synthesis of costs and benefits
The cost per patient cured was reported for the A-T and T groups, using prices from each of the nine countries studied. It was numerically lower in the A-T group in all price settings. A statistical analysis was not reported.

The cost-effectiveness results were presented in a graph, the title of which stated that costs were in Euro (EUR), while the Y-axis showed UK pounds sterling (£). The exchange rates used were referenced to the European Central Bank, 6 January 2006.

Authors’ conclusions
The authors concluded that the trial supported existing data for the efficacy of the combination of amorolfine and terbinafine (A-T). They stated that A-T provided enhanced efficacy, did not present an increased safety risk, and was more cost-effective than terbinafine alone.

CRD COMMENTARY - Selection of comparators
The comparator (T alone) was justified as the most commonly used oral antifungal for treatment of onychomycosis. You should decide whether it is appropriate in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised controlled trial, which was appropriate. Although treatment was not blinded, all other aspects of the trial appear to have been conducted adequately. Blinding is unlikely to have had an impact on the primary end point, although it could have had an effect on the difference in the groups' perception of care and hence their assessment of quality of life (in the sub-group where this end point was evaluated). The method of randomisation was not described, thus it is not possible to judge the validity of the method used. The study sample appears to have been representative of the study population although, since a convenience (chronological) sample was used, it is likely to be truly representative only of that patient population seeking specialist care for their disorder. The study design was well reported, which suggests that the internal validity was likely to be good. The analysis was credible and the study was appropriately powered to detect clinically significant differences.
Validity of estimate of measure of benefit
The authors used the primary efficacy end point in the clinical trial, that is, the overall response at 18 months (success or failure). While relevant, a disease-specific measure like this does not capture all the health benefits of the intervention, so it is almost impossible to compare with the benefits of other interventions, certainly outside this disorder.

Validity of estimate of costs
The authors reported that the payer perspective was adopted in the study, but only drug costs were included. The authors justified this omission on the basis that all other resource use was protocol-driven and common to both treatment groups, and adverse events were rare. It is possible that the omissions had an effect on the results. For example, treatment continued for 12 months in the A-T group but for only 3 months in the T group. It seems possible that the rate of use of non-drug health care resources might be different in each group in clinical practice, but it is not possible to judge whether a longer or shorter treatment period might result in, for example, more physician contacts. The mean drug resource use per patient was reported. The costs were quoted as being derived from public drug prices for each country, but no specific unit costs, sources or dates were given. The source of the exchange rates was given but not the rates themselves.

Other issues
The authors compared their findings with those from other studies, which were generally in agreement. The authors did not acknowledge potential variation in patient population or service provision, but did account for variation in unit costs by calculating the costs for the nine different countries participating in the trial. The authors presented only the final cost-effectiveness results, whereas more detail of the costing would have been useful. The authors did not report any limitations to their study.

Implications of the study
The authors suggested that further study is warranted around the hypothesis of a possible predictive relationship between streaks and/or onycholysis and response. They also noted that the sample in the present study was too small for a meaningful statistical analysis of the quality of life data, which suggests that the impact should be confirmed by a larger study.

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