Topical amorolfine for 15 months combined with 12 weeks of oral terbinafine: a cost-effective treatment for onychomycosis

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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
The use of amorolfine nail lacquer plus oral terbinafine, a combination treatment for severe onychomycosis of the toenail.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with severe onychomycosis of the toenail. This was defined as onychomycosis involving more than 80% of the surface and/or matrix of at least one toenail (not including the little toenail).

Setting
The setting was primary care. The economic study was carried out in France.

Dates to which data relate
The dates during which the effectiveness and resource data were gathered were not provided. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations to determine the sample size were not performed. The method used to select the sample was not reported. An initial sample of 147 individuals was included in the analysis, but two patients withdrew before the analysis took place. Consequently, the final sample included 50 patients in the AT-6 group, 47 patients in the AT-12 group, and 48 patients in the T-12 group.

Study design
This was an open randomised controlled trial with three parallel groups. The centres where the study was conducted were not specified. Patients in the AT-6 and AT-12 groups were supplied with a total of three bottles of amorolfine lacquer. Patients in the AT-6 group received 42 tablets of terbinafine, while patients in the AT-12 and T-12 groups received 84 tablets. The length of follow-up was 18 months and both mycological and clinical assessments were performed every 3 months. Data at 3 months were available for 40 patients in the AT-6 group, 40 patients in the AT-12 group, and 41 patients in the T-12 group.

**Analysis of effectiveness**

Although not explicitly stated in the paper, the clinical study appears to have been analysed on an intention to treat basis. The primary health outcome assessed in the analysis was the result of the mycological examination after 3 months of therapy. The secondary health outcome measures were the results of mycological testing and clinical evaluation at all visits, and a joint mycological-clinical evaluation (global cure) at the end of the study. Mycological cure was defined as a negative direct microscopy and a negative in vitro culture. Clinical response was classified as success (disappearance of all lesions or more than 90% reduction in total diseased nail surface area), improvement (more than 20% reduction in the total disease surface area) or failure. Adverse events were also reported. The comparability of the study groups was not reported.

**Effectiveness results**

At the 3-month visit, 121 patients were available for the primary outcome assessment. Of these, 14 of the 40 patients (35%) in the AT-6 group, 11 of the 40 patients (27.5%) in the AT-12 group, and 7 of the 41 patients (17.1%) in the T-12 group had negative mycological results.

At the final assessment, the overall clinical cure rate was 46% (95% confidence interval, CI: 32 - 61) in the AT-6 group, 74% (95% CI: 60 - 86) in the AT-12 group, and 42% (95% CI: 28 - 57) in the T-12 group.

At the end of the study, the global cure rate was 44% (95% CI: 30 - 59) in the AT-6 group, 72.3% (95% CI: 57 - 84) in the AT-12 group, and 37.5% (95% CI: 24 - 53) in the T-12 group.

The author highlighted the fact that there was no overlap between the 95% CIs for the AT-12 and T-12 groups.

Overall, 34 treatment-related adverse events (mainly gastro-intestinal disorders and pain) were reported. These occurred similarly in the three study groups.

**Clinical conclusions**

The effectiveness analysis showed that, although all the treatments were safe and well tolerated, the AT-12 treatment was the most effective intervention for severe onychomycosis of the toenail.

**Measure of benefits used in the economic analysis**

The benefit measure was the overall cure rate, as reported in the effectiveness analysis.

**Direct costs**

Discounting was irrelevant as the time horizon of the study was 18 months. The unit costs and the quantities of resources were not reported. The analysis of the costs included only the costs of the drugs. The cost/resource boundary adopted in the study was that of the French National Health Insurance System, as reimbursement prices were used in the economic analysis. The source of the cost data was not reported. The quantities of resources were estimated alongside the trial. No price year was reported.

**Statistical analysis of costs**

The costs were treated deterministically.
Indirect Costs
The indirect costs were not included in the analysis.

Currency
The costs were reported in French francs (Ffr) and Euros (EUR). The fixed rate of 0.152 was used to convert Ffr into EUR.

Sensitivity analysis
No sensitivity analyses were conducted.

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

Cost results
The total costs were not reported. The costs were reflected in the 'Synthesis of Costs and Benefits' field.

Synthesis of costs and benefits
The cost and benefits of the interventions were combined by calculating the cost per patient cured. This was Ffr 2,541.4 (EUR 386.3) in the AT-6 group, Ffr 2,320.8 (EUR 357.8) in the AT-12 group, and Ffr 3,016 (EUR 458.4) in the T-12 group.

Authors’ conclusions
The combined treatment of amorolfine nail lacquer (once weekly) for 15 months plus oral terbinafine (250 mg once daily) for the first 12 weeks proved to be a cost-effective intervention for patients with severe onychomycosis of the toenail, compared with a single oral therapy or a shorter combined treatment.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. The single oral therapy was selected as it represented the actual alternative treatment for patients with severe onychomycosis of the toenail. Two regimens of combined treatments were then used to reflect dosages used in a clinical setting. You should decide whether they represent widely used interventions in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a randomised controlled trial, which was appropriate for the study question. In addition, it enhances the validity of the results in terms of eliminating bias and confounding. The study sample appears to have been representative of the study population. However, neither the method of sample selection nor the method of randomisation was reported. In addition, power calculations were not conducted and there was no evidence that the initial study sample was adequate for the study question. Further, the study groups were not shown to be comparable at baseline and the patient demographics were not reported. These latter issues tend to limit the internal validity of the analysis.

Validity of estimate of measure of benefit
The benefit measure was derived directly from the effectiveness analysis.
Validity of estimate of costs
The perspective of the analysis was clearly stated in the study. However, only limited details of the pharmacoeconomic assessment were reported, as the author stated that this was a preliminary study. The quantities of resources were estimated during the trial, but neither the unit costs nor a detailed breakdown of the costs were provided. No price year was reported and no statistical analyses of the costs were performed. Overall, the cost analysis has a number of limitations, which make the internal and external validity of the results problematic.

Other issues
The author made some comparisons of the study findings with those from other published studies. The issue of the generalisability of the study results to other settings was not addressed and no sensitivity analyses were conducted. Thus, the external validity of the findings is quite low. The study enrolled a sample of patients with severe onychomycosis of the toenail, and this was reflected in the conclusions of the study. Consequently, the author stressed that the study findings should not be generalised to patients with moderate disease.

Implications of the study
The author noted the lack of widely accepted guidelines, whose development could help the conduct and credibility of more rigorous studies. Further studies should focus on patient stratification according to a common severity scoring scale.

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