Economic evaluation of voriconazole in the treatment of invasive aspergillosis in the Netherlands


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 examined three first-line treatments for invasive aspergillosis. These were voriconazole (VOR), conventional amphotericin B (CAB) and itraconazole (ITRA). All treatments were assumed to be given up to 12 weeks. VOR and ITRA were given intravenously (IV) for 14 days and as oral treatment in the following 50 days, while CAB was assumed to be given IV initially for 21 days and then as step-down therapy. The dosages considered were:

for ITRA, 400 or 600 mg per day IV or 400 mg orally;
for VOR, 8 or 12 mg/kg IV per day or 200 mg orally twice daily;
for CAB, 1 mg/kg per day.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with confirmed or probable aspergillosis in individuals with allogeneic haematopoietic cell transplantation, autologous haematopoietic cell transplantation, acute leukaemia, and other haematologic cancers. The average patient had a weight of 65 kg.

Setting
The setting was a hospital. The economic study was carried out in the Netherlands.

Dates to which data relate
Most of the effectiveness and resource use data were derived from studies published in 2001 and 2002. The price year was 2003.

Source of effectiveness data
The clinical data used in the model were effectiveness, toxicity, non-response, mortality, switch rates, and all other transition rates used in the decision model.

Modelling
The decision model consisted of a 12-week decision tree followed by a Markov model with weekly cycles. Treatment
Pathways for ITRA were derived from the literature and then assumed to be similar for the other two treatments. One of the key factors of the model was that patients experiencing toxicity were switched to other licensed antifungal agents. In addition to CAB, ITRA and VOR, these included caspofungin and liposomal amphotericin B. Treatment switch occurred also in the case of lack of effectiveness. All pathways in the decision tree and the health states included in the Markov model were reported. The time horizon of the model was lifetime.

Sources searched to identify primary studies
Most of the clinical data for VOR and CAB were derived from the 12-week Pfizer Global Comparative Aspergillosis (GCA) study, a randomised controlled trial. Input parameters for ITRA were obtained from another clinical trial and three experts in the Netherlands. Mortality rates were obtained from Dutch registries. Little information on the other studies was given. Treatment pathways were mainly derived by means of expert opinion and authors' assumptions.

Methods used to judge relevance and validity, and for extracting data
The primary studies appear to have been identified selectively. No systematic search for studies was reported. Much of the evidence was derived from a head-to-head trial of CAB versus VOR, but it would appear that no study directly comparing all three agents under analysis was found. Justification was provided for most of the assumptions made in the decision model. However, the approach used to elicit the opinions of experts was not described.

Measure of benefits used in the economic analysis
The summary benefit measures used were the proportion of successfully treated patients in the 12-week model and survival in the lifetime model. Both measures were estimated using a modelling approach. No discounting of benefits was performed in the base-case analysis.

Direct costs
The cost analysis included only direct medical costs associated with antifungal therapy, prophylaxis and treatment of side effects related to antifungal therapy, monitoring for side effects, screening for fungal infection, hospitalisation and outpatient care. A breakdown of the cost items was given. The unit costs were reported separately from the quantities of resources used for some items. Resource consumption was mainly derived from the GCA study, as well as from expert opinion. The costs were derived from National Health Tariffs Authority, the Dutch costing manual, and the Z-Index Taxe (only for drugs). Discounting was not relevant given the short timeframe of the analysis in the 12-week model. However, the future costs of invasive aspergillosis were not discounted in the lifetime model either. The price year was 2003.

Statistical analysis of costs
A range of values for resource use parameters was constructed, reflecting 80% and 120% of the mean value.

Indirect Costs
Productivity costs were not considered. The authors assumed that patients with invasive aspergillosis were not employed because of the severity of the disease.

Currency
Euros (EUR).

Sensitivity analysis
The issue of uncertainty was investigated by presenting mean values and confidence intervals for both the expected benefits and costs. Cost-effectiveness acceptability curves were generated to indicate the probability that a treatment was cost-effectiveness in comparison with the alternative strategies. This aspect of uncertainty was addressed through a
Monte Carlo simulation. The probabilistic distributions assigned to model inputs were reported. In a deterministic sensitivity analysis, a 4% discount rate was applied to both the costs and benefits. In addition, the impact of reducing the clinical efficacy of ITRA to that of CAB was analysed.

**Estimated benefits used in the economic analysis**
In the 12-week model, the expected proportion of successfully treated patients was 0.53 (range: 0.48 to 0.58) with VOR, 0.32 (range: 0.28 to 0.35) with CAB and 0.43 (range: 0.30 to 0.59) with ITRA.

In the lifetime model, mean survival was 174.0 life-weeks (range: 160.1 to 188.9) with VOR, 116.1 life-weeks (range: 104.8 to 128.0) with CAB and 150.4 life-weeks (range: 109.1 to 194.4) with ITRA.

Thus, over a patient’s lifetime, VOR led to a gain of 58.0 life-weeks (range: 39.2 to 76.6) over CAB and 23.6 life-weeks (range: -22.0 to 68.0) over ITRA.

**Cost results**
In the 12-week model, the total treatment costs were EUR 26,794 (range: 24,939 to 28,512) with VOR, EUR 24,509 (range: 22,815 to 26,324) with CAB and EUR 22,007 (range: 19,475 to 22,420) with ITRA.

In the lifetime model, the total treatment costs were EUR 32,651 (range: 30,037 to 36,869) with VOR, EUR 33,616 (range: 30,920 to 36,869) with CAB and EUR 29,115 (range: 23,537 to 61,414) with ITRA.

Thus, the incremental acquisition cost of VOR was completely or partially offset on a lifetime horizon by a reduction in the costs of treating adverse events and costs associated with invasive aspergillosis.

**Synthesis of costs and benefits**
Average and incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative strategies.

In the 12-week model, the average cost per successfully treated patient was EUR 50,759 (range: 44,382 to 57,674) with VOR, EUR 77,666 (range: 69,012 to 87,543) with CAB and EUR 51,929 (range: 37,386 to 76,553) with ITRA.

The incremental cost per additional successfully treated patient with VOR was EUR 10,881 over CAB and EUR 47,870 over ITRA.

The cost-effectiveness acceptability curve showed that the probability that VOR was cost-effective was 95% over CAB and 10% over ITRA for a willingness-to-pay of EUR 20,000 for each additional successfully treated patient.

In the lifetime model, the average cost per life-week gained was EUR 187.65 (range: 168.04 to 218.20) with VOR, EUR 289.68 (range: 258.69 to 349.68) with CAB and EUR 193.55 (range: 139.08 to 423.64) with ITRA.

The incremental cost per incremental life-week gained with VOR was EUR 150.02 over ITRA (about EUR 7,800 per life-year gained), while VOR dominated CAB, which was both less effective and more expensive.

The cost-effectiveness acceptability curve suggested that VOR was likely to dominate CAB in almost 70% of simulations.

The results of the sensitivity analysis showed that the use of a discount rate did not alter the conclusion of the analysis. As expected, reducing the efficacy of ITRA substantially reduced the incremental cost-effectiveness ratio for VOR compared with ITRA.

**Authors’ conclusions**
Voriconazole (VOR) used for the treatment of invasive aspergillosis was preferred over conventional amphotericin B
(CAB) and was cost-effective in comparison with itraconazole (ITRA).

**CRD COMMENTARY - Selection of comparators**
The authors provided a justification for their choice of the comparators. CAB was considered the first choice of treatment for life-threatening invasive fungal infections. ITRA was the azole of choice for empiric therapy of neutropenia in patients with suspected fungal infections and was commonly used as first-line treatment in the authors’ country, although there was no formal indication for invasive aspergillosis. VOR was introduced in 2003 as a superior alternative to CAB. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data were derived from studies that might have been identified selectively as no systematic search for data was reported. The parameters for the model were mainly derived from a published clinical trial involving a comparison between CAB and VOR, which could be expected to have high internal validity. However, no head-to-head trials for VOR versus ITRA were found, and ITRA efficacy was mainly derived from a separate study. Expert opinion was also used. No details of homogeneity in the original studies were provided. However, the authors addressed the issue of uncertainty around key clinical parameters by means of an extensive sensitivity analysis.

**Validity of estimate of measure of benefit**
The estimation of health benefits (success rate and survival) was modelled using a decision model. Success rate was used as a disease-specific measure, whereas survival can be compared with the benefits of other health care interventions. Extrapolation techniques were used to assess the lifetime benefits of the treatments. Discounting was investigated in the sensitivity analysis. The impact of the interventions on quality of life was not evaluated since the analysis focused on unadjusted survival.

**Validity of estimate of costs**
The perspective adopted in the study was not stated clearly, but only direct medical costs were included. The authors provided a justification for the exclusion of indirect costs. The unit costs were reported for all items, but resource quantities were given only for medications. The sources of the resource use and unit cost data were reported. The price year was given, which will facilitate reflation exercises in other time periods. Statistical analyses of the costs were carried out, but the cost estimates were specific to the study setting. In effect, alternative sources of costs were not considered.

**Other issues**
The authors did not compare their findings with those from other studies. The issue of the generalisability of the study results to other settings was not clearly addressed. However, the use of a probabilistic sensitivity analysis enhances the external validity of the study. The authors noted that some assumptions were required in the model. The most critical assumption was that weekly transition probabilities to success and mortality beyond week 12 were constant over time, which may be unrealistic. However, a panel of experts validated all assumptions. Another potential limitation of the analysis was that no head-to-head comparisons of VOR with ITRA were available, thus an indirect comparison was required to derive clinical data. However, no statistical technique for indirect comparison (e.g. test of homogeneity) was applied.

**Implications of the study**
The study results support the use of VOR as a cost-effective first-line treatment for invasive aspergillosis.

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Other publications of related interest
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MeSH
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