An economic evaluation of voriconazole versus amphotericin B for the treatment of invasive aspergillosis in Canada
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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 study compared the use of voriconazole and conventional amphotericin B deoxycholate (CAB). Voriconazole was administered at a dose of 6 mg/kg intravenously (IV) twice a day on day 1, followed by 4 mg/kg IV twice a day for at least 7 days, at which time patients could switch to oral voriconazole 200 mg twice daily. CAB was administered at a dose of 1.0 to 1.5 mg/kg IV once a day.

In the event of an inadequate response or severe toxicity, patients were switched from an initial therapy to other licensed antifungal therapy (OLAT), which included CAB and oral itraconazole or a combination of liposomal amphotericin (L-AMB) and oral itraconazole.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised immunocompromised patients with definite or probable invasive aspergillosis.

Setting
The study setting was secondary care. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness data were mainly derived from a study published in 2002. The price year was 2002.

Source of effectiveness data
The effectiveness and resource use data were mainly derived from the GCA study (Herbrecht et al. 2002, see 'Other Publications of Related Interest' below for bibliographic details). When there were insufficient data on resource use in the GCA study, an independent expert panel was consulted.

Link between effectiveness and cost data
The cost data were derived from the same clinical trial that derived the effectiveness results, and also from a panel of experts.

Study sample
The authors reported limited information on the GCA study as it had been published already (Herbrecht et al. 2002). The study sample comprised 277 patients, of which 144 were randomised to voriconazole and 133 to CAB. No further details of the study sample were reported.

**Study design**
The GCA study was a randomised multi-centre trial. All of the patients in the trial were followed for 12 weeks, whether they continued to take their initial randomised treatment or switched to an OLAT.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on an intention to treat basis. The primary objective of the GCA study was to demonstrate the non-inferiority of voriconazole at week 12, as assessed by an independent and blinded data review committee. The GCA study provided the following data to populate the model:

- clinical success rate,
- morbidity and mortality,
- treatment duration,
- OLAT use for each patient, and
- resource use.

Information on days of IV and oral therapy, hospital length of stay, and time spent on initial therapy before switching to an OLAT, was also derived from the GCA trial.

**Effectiveness results**
Of the 144 patients randomised to voriconazole, 140 had no early switch to OLAT. Of these 140 patients, 19 switched later to OLAT because of no response, 4 because of hepatotoxicity, and a further 14 for other reasons. A total of 103 patients were not switched to OLAT.

Of the 133 patients randomised to CAB, 107 had no early switch to OLAT. Of these 107 patients, 25 later switched to OLAT because of no non-response, 41 because of renal toxicity, 3 because of hepatotoxicity, and a further 8 for other reasons. A total of 35 patients were not switched to OLAT.

At the end of 12 weeks, 52.8% of voriconazole-treated patients exhibited complete or partial responses compared with 31.6% of CAB-treated patients (95% confidence interval, CI, for the difference between groups: 10.4 - 32.9).

Survival was improved in the voriconazole group (70.8% versus 57.9% for CAB; hazard ratio 0.59, 95% CI: 0.40 - 0.80).

Significantly fewer adverse events, (p=0.002), including nephrotoxicity, (p<0.001), were reported in the voriconazole group.

**Clinical conclusions**
Voriconazole was shown to be more clinically efficacious than CAB.

**Modelling**
A cost-consequences model was used to compare the cost outcomes of initiating voriconazole versus CAB as primary therapy for proven or probable aspergillosis. The model was based on a decision tree designed to reflect the treatment pathway relevant for clinical practice.
Methods used to derive estimates of effectiveness
In the instances where there was insufficient information in the GCA study, an independent Canadian expert panel, consisting of 12 physicians and 3 hospital pharmacists, was consulted (Canadian Voriconazole Advisory Board for the Pharmaco-economic Model Validation). The authors also supplemented data from the GCA study with their own assumptions.

Estimates of effectiveness and key assumptions
Following recommendations by the expert panel, the distribution of OLAT days (i.e. the total number of patient days spent on each OLAT by the total number of days patients spent on all OLAT) was based on North American switch patterns. Patients initially assigned to CAB who switched treatment (73.5% of all CAB patients) spent 45.7% of all OLAT days on L-AMB (n=524 days), 31% of all OLAT days on itraconazole (n=356 days), and 14.1% of all OLAT days on a combination of the two (n=62 days). For voriconazole patients who switched to an OLAT, OLAT days were primarily composed of L-AMB (64.8%; n=278 days), itraconazole (15.4%; n=66 days) or CAB (12.1%; n=52 days).

The model assumed a full course of treatment for those patients remaining on one of the two initial randomised treatments. The model considered a switch as a failure of initial therapy. Therefore, patients who switched were assumed to have received initial therapy up to the time they were switched. These patients were also assumed to have started therapy over with an OLAT, with all of the clinical, resource use and cost sequelae associated with the new therapy.

Measure of benefits used in the economic analysis
The measures of benefits used were the number of successfully treated patients and the number of lives saved. Treatment success was defined as the complete or partial resolution of signs and symptoms of aspergillosis, and the requirement of patient survival at 12 weeks.

Direct costs
The direct costs to the Canadian health service were included in the analysis. These included:

the cost of voriconazole, which was obtained from the manufacturer;

the cost of CAB, obtained from the Ontario Drug Benefit List;

the cost of L-AMB, obtained from Fujisawa Canada, Inc.;

the cost of itraconazole, acetaminophen, granulocyte-colony stimulating factor, diphenhydramine and meropenem, which were obtained from the Quebec Formulary;

the cost of meperidine, obtained from the Saskatchewan formulary;

the costs of hospital stays, intensive care unit (ICU) and general ward, obtained from the Cost List of Manitoba Health Services; and

the costs of outpatient visits, monitoring and screening, which were obtained from the Ontario Ministry of Health and Long-Term Care Schedule benefits.

Resource use and costs were reported separately. In the instances where there was insufficient information on resource use in the GCA study, the independent Canadian expert panel was consulted. As the costs were incurred over a 12-week period, discounting was appropriately not performed. The study reported the average costs. The price year was 2002.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).
Indirect Costs
The indirect costs were not included.

Currency
Canadian dollars (Can$).

Sensitivity analysis
A sensitivity analysis was carried out to assess how changes in key input variables would affect the final outcome of the model. The variables investigated were the treatment success rates, hospital length of stay, hospital costs, treatment switches and antifungal costs. The following scenarios were tested:

- CAB total length of stay and ICU bed days for non-switch patients increased;
- the costs per day for a general ward bed increased by 50%;
- the costs per day for an ICU bed decreased by 50%;
- CAB time to switch increased;
- voriconazole time to switch decreased; and
- cost of itraconazole, L-AMB and CAB decreased by 50%.

Estimated benefits used in the economic analysis
The probability of success without switch was 0.053 for CAB and 0.403 for voriconazole. The probability of successful treatment, including switches, was 0.309 for CAB and 0.521 for voriconazole.

The probability of survival was 0.579 for CAB and 0.708 for voriconazole.

Cost results
The total average cost per patient was Can$42,495 for those treated with CAB and Can$38,319 for those treated with voriconazole.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-effectiveness ratio (i.e. the additional cost per successfully treated patient or per life saved). Voriconazole was found to be dominant as it was both more effective (the probability of treatment success and survival was higher) and less costly than CAB.

The results of the sensitivity analysis showed that a 50% reduction in the cost of L-AMB was the only scenario in which voriconazole no longer saved costs. However, it was only $698 greater than with CAB. The model was also found to be sensitive to changes in hospital costs and time to switch.

Authors’ conclusions
The use of voriconazole as a primary treatment for invasive aspergillosis increased the chances of successful treatment, improved survival, and could represent a potential cost-saving strategy in Canada.

CRD COMMENTARY - Selection of comparators
A justification was given for using CAB as the comparator. It was the current 'gold' standard treatment of invasive...
aspergillosis. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was mainly based on data from a randomised controlled trial (RCT). This was appropriate as well-conducted RCTs are considered the ‘gold’ standard study design when comparing health interventions. However, the authors provided very few details of the trial. The authors supplemented clinical data from the trial with the opinions from a 15-member expert panel, comprising 12 physicians and 3 hospital pharmacists, in order to derive the proportion of days on each particular OLAT. Appropriate sensitivity analyses were performed by varying success rates and treatment switches.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled using a decision tree analysis. This was appropriate for the study question.

**Validity of estimate of costs**
All the categories of cost relevant to the perspective adopted were included in the analysis. The authors reported that only the direct costs of inpatient and outpatient hospital care were included in the analysis since invasive aspergillosis is predominantly treated in secondary care settings. The costs and the quantities were reported separately, which will enhance the generalisability of the authors’ results to other settings. Resource use was derived from the GCA study and from an expert panel consisting of 15 Canadian physicians and pharmacists. The unit costs were derived from a variety of sources, with the majority of prices being derived from provincial ministries of health. Appropriate sensitivity analyses of the costs and resource use were performed. As all the costs were incurred during a short time period, discounting was appropriately not performed. The price year was reported, which will aid any future inflation exercises.

**Other issues**
The authors made appropriate comparisons of their findings with those from another study that found similar cost-savings when voriconazole was compared with CAB in the USA. The issue of generalisability to other settings was addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. First, the structure of the decision tree model assumed a simplified switch pattern which, according to the authors, biased the results against voriconazole. Second, the model resource use was not broken down by success and failure of each type of switch because the numbers were too small. Third, the authors assumed that L-AMB was the sole lipid formulation of amphotericin B employed as an OLAT. Finally, caspofungin acetate was not considered as one of the OLAT antifungals because it was not available at the time of the GCA study.

**Implications of the study**
The authors report that substantial economic benefits could arise from the use of voriconazole as primary therapy for invasive aspergillosis. According to the authors, these benefits would be achieved despite the choice of best available therapy (CAB followed by other approved antifungal therapies such as L-AMB or oral itraconazole).

**Source of funding**
Supported by a grant from Pfizer Canada Inc.

**Bibliographic details**

**Other publications of related interest**
Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive


Indexing Status
Subject indexing assigned by CRD

MeSH
Acetaminophen /therapeutic use /economics; Amphotericin B /adverse effects /therapeutic use /administration & dosage /economics; Antifungal Agents /adverse effects /therapeutic use /administration & dosage /economics; Aspergillosis /prevention & control /drug therapy; Clinical Trials as Topic; Cost Control; Cost-Benefit Analysis; Costs and Cost Analysis; Diphenhydramine /therapeutic use /economics; Drug Hypersensitivity /complications /drug therapy; Granulocyte Colony-Stimulating Factor /therapeutic use /economics; Itraconazole /adverse effects /therapeutic use /administration & dosage /economics; Meperidine /therapeutic use /economics; Randomized Controlled Trials as Topic; Survival; Treatment Outcome

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