Pharmacoeconomic evaluation of voriconazole versus posaconazole for antifungal prophylaxis in acute myeloid leukaemia

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Background: Voriconazole and posaconazole are used prophylactically against invasive fungal infection (IFI) in patients with acute myeloid leukaemia (AML). The current study attempted to evaluate the economics of voriconazole versus posaconazole for prophylaxis in AML.

Methods: A 6 year (2003–09) retrospective chart review of AML patients was performed at a major Australian tertiary hospital. Patients were followed through the induction stage of chemotherapy, estimating outcome probabilities and prescribing patterns of antifungal prophylaxis. Cost inputs were obtained from the latest Australian sources. A decision analytical model was developed to depict options and consequences involved in the prophylaxis, including success, survival, possible and proven IFIs, and discontinuations due to intolerance. A cost–benefit analysis and an uncertainty study through sensitivity analyses were performed.

Results: Fifty-six and 38 patients were evaluated in the voriconazole and posaconazole groups, respectively. Baseline demographic characteristics were not significantly different between the study cohorts. Posaconazole was associated with an overall cost saving of AU$17458 (29%) per patient over voriconazole. The posaconazole group was associated with lower rate of death, as well as lower probability of discontinuation because of possible infections and intolerance to oral administration. The voriconazole group was associated with fewer proven infections. As per sensitivity analyses, results were highly robust over variations in all costs and probabilities in the model. Monte Carlo simulation suggested a 91.6% chance for posaconazole to cost less than voriconazole.

Conclusions: This is the first economic evaluation of voriconazole versus posaconazole; where posaconazole appears to be more cost-beneficial than voriconazole as antifungal prophylaxis in AML.

Keywords: cost–benefit, model, AML

Introduction

In the absence of preventive therapy, the risk of developing invasive fungal infection (IFI) can be up to 50% in some groups of patients with haematological malignancies, particularly among patients with acute myeloid leukaemia (AML).1,2 Once established, IFIs are associated with a mortality rate of 30%-90%.3 Antifungal prophylaxis is often administered to patients who are at risk of IFIs,4 the rationale being the lack of sensitive and specific tools for the early diagnosis of infections, as well as poorly effective and costly curative therapies.5

A variety of antifungal agents are commonly available for prophylactic use. These include voriconazole, posaconazole, liposomal amphotericin B (LAmB), itraconazole and fluconazole. In Australia, for patients with intermediate to high risk for IFIs, including AML patients, the prophylactic use of voriconazole, posaconazole, intermitted LAmB, itraconazole and fluconazole is suggested as per guidelines.6,7

Voriconazole (Vfend®; Pfizer) and posaconazole (Noxafl®; Schering-Plough) are two high-cost, new-generation triazole antifungals that are currently prescribed for prophylactic antifungal therapy.8 A major difference between voriconazole and
posaconazole is that posaconazole is the only non-ampoter Cin B antifungal with an acceptable activity against zygomycosis. In addition, in a recent clinical trial, posaconazole was shown to be superior to fluconazole or itraconazole, with higher clinical success rate and lower mortality rate. Clinical trials that help define the benefits and risks of prophylactic use of voriconazole are yet to be performed. Voriconazole has been available since 2002, and is available in oral and intravenous (iv) forms, administered twice daily. Posaconazole was launched in 2006, and is only available as a suspension, best administered three times a day. Although the potential clinical advantages and disadvantages of these azoles are recognized, there have been no head-to-head studies directly comparing these two agents. Hence, the superiority of one antifungal agent over the other for prophylactic use is still to be demonstrated in appropriate randomized controlled trials. Likewise, little is known about the pharmacoeconomics of using these agents prophylactically. Data from cost-effectiveness studies comparing these two azoles will guide their use.

The current study sought to undertake a cost–benefit analysis of voriconazole versus posaconazole for prophylaxis in AML patients.

Materials and methods

Perspective
The economic modelling adopted the perspective of the Australian hospital system. The analysis included direct medical costs only. Indirect medical costs related to other underlying diseases were not included because the interest here revolved around the costs of prophylactic antifungals only. Indirect non-medical costs were also not included because patients’ social and employment data were not available. Because of the clinical nature of the cohort data, this study did not consider any intangible costs.

Model structure
A decision analytical model was constructed to capture downstream consequences of prophylaxis in patients with AML (Figure 1).

The decision model included 10 possible treatment pathways which depended on whether or not patients discontinued the initial prophylaxis and, if applicable, the reason for discontinuation. Prophylactic antifungal therapy commenced at the start of the induction stage of AML chemotherapy (i.e. 1 month in duration, starting with the onset of chemotherapy). Patients with AML receiving voriconazole or posaconazole at the start of prophylaxis were initially assigned to one of two pathways depending on whether or not they were tolerant of the drug.

Discontinuation due to intolerance was ascribed to either side effects or inability to consume oral medication. Patients were switched to any other licensed antifungal prophylactic agents, and were followed until the end of the induction chemotherapy stage. After such discontinuation, patients who switched to empirical therapy or targeted therapy (because of proven infection) were analysed as part of the intolerance pathway, and were followed until success or death. Patients who had possible or proven infections after the induction stage finished were not considered.

Patients who did not switch prophylaxis because of intolerance encountered the possibilities of therapeutic success, death, a switch to empirical therapy (because of possible infection) or a switch to targeted therapy (because of proven infection). The patients who switched to empirical or targeted therapy were then followed until success or death.

For initial prophylaxis, success was defined as the absence of initial antifungal discontinuation for the duration of the induction stage.

For patients who received alternative antifungals, success was defined as the absence of IFI with alternative prophylaxis, resolution of fever with empirical therapy or eradication of fungal infections with targeted therapy. Death was that reported before the initial or alternative antifungal therapy was deemed successful. Switching to alternative medication may lead to extension of the duration of the induction stage and delay in subsequent chemotherapy.

Model inputs
The modelling was based on data extracted from a 6 year (June 2003 - June 2009) review of hospital medical records of all AML patients at the Royal Melbourne Hospital (RMH), a major tertiary hospital in Victoria, Australia. At the RMH, AML patients are defined and classified according to the standardized international French-American-British (FAB) classification of acute leukaemia. The study was approved by the human research ethics committee of RMH and Monash University. Informed consent was not required from the study subjects.

At RMH, voriconazole was the first-line antifungal prophylactic agent in AML patients from June 2003 until June 2006, when posaconazole replaced voriconazole as the drug of choice for the same setting. Patients were eligible for inclusion if they had newly diagnosed AML, underwent chemotherapy and received voriconazole or posaconazole as the primary antifungal prophylactic agent. Patients were excluded from analysis if they had any underlying haematological disease other than newly diagnosed AML, use of systemic antifungals within 7 days prior to commencing voriconazole or posaconazole, renal impairment [creatinine level ≥2 times the upper limit of normal (ULN)], liver impairment (any liver enzyme level ≥2 times the ULN), or current or previous history of proven or probable IFI. Comparison of baseline characteristics between the voriconazole and posaconazole patient groups was made with Student’s t-test or Fisher’s exact test using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Cost calculations
Costs were calculated in Australian dollars (AUD) for the financial year 2008/09, and no discounting was performed.

The cost of initial prophylaxis was the cost of a complete course of voriconazole or posaconazole until success or death, or until switching to alternative therapy. The cost of alternative therapy was the cost of a complete course of the alternative agent until success or death. The cost of each treatment outcome was the cost of initial and alternative therapies added to the cost of resources consumed. Regardless of outcome, patients were analysed according to the group that they were initially assigned to.

Medication costs used were the drug wholesale prices paid by Australian public hospitals, as per the Health Purchasing Victoria tender (2007–09). Doses for all medications (except posaconazole) were rounded to the nearest vial size. Patients on posaconazole were considered to share the same posaconazole bottle, as is routine hospital practice in Australia.

Hospitalization costs were obtained from published data for Australian Refined Diagnosis-Related Groups (AR-DRG) (2006/07). Hospitalization costs used were the average direct costs associated with acute leukaemia [including both acute lymphoid leukaemia (ALL) and AML], and included the cost of intensive care management. No hospitalization costs that relate only to AML patients are available. To avoid double counting, hospitalization costs used excluded pharmacy, pathology and imaging costs, as reported in the AR-DRG. Hospitalization costs were inflated to 2008/09 values as per the Australian Consumer Price Index (2009).
All other resource costs involved in the study were obtained from the Australian Medicare Benefits Schedule Book (2009). The cost inputs used in the model are summarized in Table 1.

**Sensitivity analyses**

Variations in the values of key variables and assumptions, related to deterministic and probabilistic data, were analysed to assess the robustness of the study conclusion.

**Alternative scenario**

Throughout the study duration, the way that any particular medication was administered did not change. However, posaconazole was only marketed in Australia for use in June 2006 and, therefore, it was not available as an alternative option after the discontinuation of the initial prophylactic antifungal (i.e. voriconazole) during the period June 2003 – June 2006.

To account for this, sensitivity analyses investigated the scenario of posaconazole being available as alternative to voriconazole, whereby, in cases where initial voriconazole was discontinued because of side effects, patients were switched to posaconazole as an alternative. The alternative posaconazole was assumed to be successful and was given for the remainder of the chemotherapy induction stage.

In addition, because data on the use of voriconazole and posaconazole were based on different chronological periods, another alternative scenario analysed was the matching of posaconazole patients with patients receiving voriconazole according to potential confounding factors, which were determined using the expert opinion of two clinicians with clinical expertise in systemic fungal therapy and specialist knowledge in oncology, haematology and infectious diseases.

**One-way sensitivity analyses**

The potential impact of any variations in costs on the study outcome was investigated. This included prices of antifungals, cost of hospital stay and the use of screening and monitoring tests. The effects of the voriconazole dosage form as alternative therapy as well as the duration of hospitalization were also evaluated. Key variables, and the ranges over which they were varied, are shown in Table 2.

**Probabilistic sensitivity analyses**

Uncertainty analysis, by means of Monte Carlo simulation, was performed via @Risk-5.5 (Palisade Corporation, NY, USA). Monte Carlo refers to a method whereby multiple model simulations are run, each time sampling from pre-defined uncertainty ranges of input values. The current probabilistic sensitivity analysis, defined by a triangular type of distribution, was performed with an assumed uncertainty range of 0%–100% associated with the probability of prophylaxis discontinuation due to possible infection, and with an uncertainty of ±5% for all other outcome probabilities in the model. The current uncertainty analysis was based on 10000 model simulations. Corresponding costs were calculated, and a distribution of ‘cost savings’ was obtained. The clinical outcomes that affected the overall therapeutic cost the most were also determined.

**Results**

**Clinical outcomes**

Eligibility criteria were met by 94 patients, 38 of whom were initially given posaconazole and 56 were initially given...
voriconazole. At baseline, the voriconazole and posaconazole groups were only significantly different in terms of the AML grade ‘M3’. All other baseline demographic characteristics were not significantly different between the two groups (Table 3).

The duration of initial prophylaxis was almost similar in the two groups: the mean duration was 18 days [median 19 (range 1–47)] with voriconazole and 19 days [median 20 (range 1–42)] with posaconazole. The mean duration on alternative medication was also about similar in the two groups: 28 days [median 9 (range 1–172)] with voriconazole and 26 days [median 12 (range 2–48)] with posaconazole.

The group of patients starting with posaconazole was associated with fewer possible IFIs and intolerance to side effects and to oral consumption of medication, while the voriconazole group was associated with fewer proven IFIs. The clinical outcomes and their probabilities are summarized in Table 4.

IFIs were only experienced by patients in the posaconazole group (n=2). In addition, the only IFI-related death in the study was reported for a patient in the posaconazole group.

For the patients who experienced proven IFIs in the posaconazole group, one patient, who did not discontinue therapy because of intolerance, was diagnosed with a mixed infection with *Scedosporium apiospermum* and *Aspergillus* species, not

### Table 1. Resource costs

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit</th>
<th>Unit cost (AUS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>200 mg iv vial</td>
<td>190.84</td>
</tr>
<tr>
<td></td>
<td>200 mg oral tablet</td>
<td>45.62</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>105 mL oral suspension</td>
<td>669.50</td>
</tr>
<tr>
<td>LAmB</td>
<td>50 mg iv vial</td>
<td>295.00</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50 mg iv vial</td>
<td>700.00</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200 mg oral capsule</td>
<td>2.61</td>
</tr>
<tr>
<td></td>
<td>200 mg iv vial</td>
<td>19.90</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>500 mg iv vial</td>
<td>5.45</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>250 mg oral tablet</td>
<td>1.19</td>
</tr>
<tr>
<td>Chest X-ray scan</td>
<td>one test</td>
<td>35.35</td>
</tr>
<tr>
<td>CT scan</td>
<td>one test</td>
<td>295.00</td>
</tr>
<tr>
<td>Ultrasound scan</td>
<td>one test</td>
<td>111.30</td>
</tr>
<tr>
<td>MRI scan</td>
<td>one test</td>
<td>358.40</td>
</tr>
<tr>
<td>Non-blood culture</td>
<td>one or more tests (one culture)</td>
<td>34.00</td>
</tr>
<tr>
<td>Blood culture</td>
<td>one test (one culture)</td>
<td>30.95</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>one test</td>
<td>207.70</td>
</tr>
<tr>
<td>PCR</td>
<td>one test</td>
<td>30.00</td>
</tr>
<tr>
<td>Mcs</td>
<td>one test</td>
<td>49.00</td>
</tr>
<tr>
<td>Histology</td>
<td>one test</td>
<td>72.00</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>one test</td>
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</tr>
<tr>
<td>Renal function test</td>
<td>one test</td>
<td>146.30</td>
</tr>
<tr>
<td>Liver function test</td>
<td>one test</td>
<td>17.80</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Inpatient per day</td>
<td>610.00</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; Mcs, microbial culture and sensitivity.

### Table 2. Variation range for variables in sensitivity analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole cost/vial, AUS</td>
<td>190.64</td>
<td>0.00</td>
<td>381.68</td>
</tr>
<tr>
<td>Voriconazole cost/tablet, AUS</td>
<td>45.62</td>
<td>0.00</td>
<td>91.24</td>
</tr>
<tr>
<td>Posaconazole cost/vial, AUS</td>
<td>669.50</td>
<td>0.00</td>
<td>1339.00</td>
</tr>
<tr>
<td>LAmB cost/vials, AUS</td>
<td>295.00</td>
<td>0.00</td>
<td>590.00</td>
</tr>
<tr>
<td>Caspofungin cost/vial, AUS</td>
<td>700.00</td>
<td>0.00</td>
<td>1400.00</td>
</tr>
<tr>
<td>Fluconazole cost/tablet, AUS</td>
<td>2.61</td>
<td>0.00</td>
<td>5.20</td>
</tr>
<tr>
<td>Fluconazole cost/vial, AUS</td>
<td>19.99</td>
<td>0.00</td>
<td>39.80</td>
</tr>
<tr>
<td>Terbinafine cost/tablet, AUS</td>
<td>1.19</td>
<td>0.00</td>
<td>4.00</td>
</tr>
<tr>
<td>Hospitalization cost/day, AUS</td>
<td>610.00</td>
<td>0.00</td>
<td>1220</td>
</tr>
<tr>
<td>Duration of therapy in voriconazole group, days</td>
<td>46</td>
<td>31</td>
<td>66</td>
</tr>
<tr>
<td>Duration of therapy in posaconazole group, days</td>
<td>45</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>Dosage form of voriconazole given as alternative (oral/iv)</td>
<td>1:1</td>
<td>0:1</td>
<td>1:0</td>
</tr>
<tr>
<td>Counting for the costs of monitoring, pathology and imaging tests</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

v voriconazole. At baseline, the voriconazole and posaconazole groups were only significantly different in terms of the AML grade ‘M3’. All other baseline demographic characteristics were not significantly different between the two groups (Table 3).

The duration of initial prophylaxis was almost similar in the two groups: the mean duration was 18 days [median 19 (range 1–47)] with voriconazole and 19 days [median 20 (range 1–42)] with posaconazole. The mean duration on alternative medication was also about similar in the two groups: 28 days [median 9 (range 1–172)] with voriconazole and 26 days [median 12 (range 2–48)] with posaconazole.

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IFIs were only experienced by patients in the posaconazole group (n=2). In addition, the only IFI-related death in the study was reported for a patient in the posaconazole group. For the patients who experienced proven IFIs in the posaconazole group, one patient, who did not discontinue therapy because of intolerance, was diagnosed with a mixed infection with *Scedosporium apiospermum* and *Aspergillus* species, not
Study clinical outcome | Probability in voriconazole arm (%) (n=56) | Probability in posaconazole arm (%) (n=38)
--- | --- | ---
No discontinuations due to intolerance | 64.29 (n=36) | 71.05 (n=27)
  therapeutic success | 69.44 (n=25) | 88.89 (n=24)
  death | 8.33 (n=3)<sup>a</sup> | 0.00 (n=0)
Discontinuation due to proven fungal infection | 0.00 (n=0) | 3.70 (n=1)<sup>b</sup>
  therapeutic success | 0.00 (n=0) | 0.00 (n=0)
  death | 0.00 (n=0) | 100.00 (n=1)<sup>c</sup>
Discontinuation due to possible fungal infection | 22.22 (n=8) | 7.41 (n=2)
  therapeutic success | 62.50 (n=5) | 100.00 (n=2)
  death | 37.50 (n=3)<sup>a</sup> | 0.00 (n=0)
Discontinuation due to intolerance | 35.71 (n=20) | 28.95 (n=11)
  intolerance to side effects | 15.00 (n=3) | 0.00 (n=0)
  therapeutic success | 100.00 (n=3) | 0.00 (n=0)
  death | 0.00 (n=0) | 0.00 (n=0)
Intolerance to oral administration | 85.00 (n=17) | 100.00 (n=11)
  therapeutic success | 100.00 (n=17) | 100.00 (n=11)
  death | 0.00 (n=0) | 0.00 (n=0)

<sup>a</sup>Not related to an invasive fungal infection.
<sup>b</sup>Related to invasive fungal infection.

Further identified, that resulted in death on the day of diagnosis; and a second patient was diagnosed, after discontinuation because of intolerance to oral administration, with Aspergillus species, not further identified, that was treated successfully after 30 days of LAmB therapy and 28 days of oral voriconazole.

The administration of posaconazole was based on thrice-daily oral 200 mg doses in all patients. Voriconazole was administered as twice-daily oral/iv 200 mg doses, whereby 53 patients received oral initial voriconazole prophylaxis and three patients received iv initial voriconazole prophylaxis. Where initial antifungal therapies were discontinued, the alternative therapies included twice-daily oral/iv 200 mg voriconazole, thrice-daily oral 200 mg posaconazole, daily iv 50 mg caspofungin, daily oral/iv 200 mg fluconazole and/or daily oral 250 mg terbinafine, as well as a range of 50–400 mg doses of iv LAmB, administered daily as targeted or empirical therapy, or intermittently for prophylaxis.

### Cost of prophylaxis

Compared with voriconazole, posaconazole had an economic advantage of the order of AUS$17458 per patient (29% difference). The total daily cost of posaconazole was AUS$952 per patient, while for voriconazole it was AUS$1320 per patient. Whereas for voriconazole discontinuation because of intolerance to oral dosing form was the major clinical outcome that most influenced the therapeutic cost, for posaconazole, it was the rate of success among patients who did not discontinue because of intolerance that most influenced the therapy cost. The weighted probability and costs for therapy outcomes are shown in Figure 2. The cost per patient associated with voriconazole and posaconazole as initial medication was higher for voriconazole (AUS$7045 versus AUS$2306, Figure 2). A similar trend was observed with the total cost of alternative therapies (AUS$29728 versus AUS$10203, Figure 2). Similar costs, however, were observed in relation to monitoring, pathology and imaging tests (AUS$3689, AUS$481 and AUS$628, respectively, for voriconazole, and AUS$4673, AUS$708 and AUS$542, respectively, for posaconazole). For hospitalization costs, those associated with voriconazole were higher than those associated with posaconazole (AUS$24191 versus AUS$18708, respectively, per patient).

A higher probability of successful completion of follow-up (i.e. lower probability of death) was associated with the posaconazole group (97.37% versus 89.29%, Table 5). The cost of success per patient in the posaconazole group (AUS$44074) was lower than that for voriconazole (AUS$67617).

### Sensitivity analyses

#### Alternative scenario

The scenario of providing an alternative course of posaconazole to patients with intolerance to voriconazole-related side effects resulted in a negligible reduction in the overall cost difference (AUS$16654 in favour of posaconazole). It is worth mentioning, however, that this scenario resulted in a 37.7% reduction (from AUS$39824 to AUS$24812) in costs associated with discontinuation due to intolerance to side effects with voriconazole.

Regarding the scenario of matching posaconazole patients with voriconazole patients, matching was only undertaken on the basis of age (<60 and ≥60 years), especially as, given the small sample size of the cohort analysed, matching according to a variety of demographic characteristics was not possible.

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Table 4. Outcomes and probabilities as per the medical records review

<table>
<thead>
<tr>
<th>Study clinical outcome</th>
<th>Probability in voriconazole arm (%) (n=56)</th>
<th>Probability in posaconazole arm (%) (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No discontinuations due to intolerance</td>
<td>64.29 (n=36)</td>
<td>71.05 (n=27)</td>
</tr>
<tr>
<td>therapeutic success</td>
<td>69.44 (n=25)</td>
<td>88.89 (n=24)</td>
</tr>
<tr>
<td>death</td>
<td>8.33 (n=3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.00 (n=0)</td>
</tr>
<tr>
<td>Discontinuation due to proven fungal infection</td>
<td>0.00 (n=0)</td>
<td>3.70 (n=1)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>therapeutic success</td>
<td>0.00 (n=0)</td>
<td>0.00 (n=0)</td>
</tr>
<tr>
<td>death</td>
<td>0.00 (n=0)</td>
<td>100.00 (n=1)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Discontinuation due to possible fungal infection</td>
<td>22.22 (n=8)</td>
<td>7.41 (n=2)</td>
</tr>
<tr>
<td>therapeutic success</td>
<td>62.50 (n=5)</td>
<td>100.00 (n=2)</td>
</tr>
<tr>
<td>death</td>
<td>37.50 (n=3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.00 (n=0)</td>
</tr>
<tr>
<td>Discontinuation due to intolerance</td>
<td>35.71 (n=20)</td>
<td>28.95 (n=11)</td>
</tr>
<tr>
<td>intolerance to side effects</td>
<td>15.00 (n=3)</td>
<td>0.00 (n=0)</td>
</tr>
<tr>
<td>therapeutic success</td>
<td>100.00 (n=3)</td>
<td>0.00 (n=0)</td>
</tr>
<tr>
<td>death</td>
<td>0.00 (n=0)</td>
<td>0.00 (n=0)</td>
</tr>
<tr>
<td>Intolerance to oral administration</td>
<td>85.00 (n=17)</td>
<td>100.00 (n=11)</td>
</tr>
<tr>
<td>therapeutic success</td>
<td>100.00 (n=17)</td>
<td>100.00 (n=11)</td>
</tr>
<tr>
<td>death</td>
<td>0.00 (n=0)</td>
<td>0.00 (n=0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Not related to an invasive fungal infection.
<sup>b</sup>Related to invasive fungal infection.
Matching resulted in 18 ‘excess’ patients in the voriconazole group having to be discarded, leaving a total sample of 78 patients. The scenario significantly reduced the cost difference between the two antifungal agents to AU$6369, but still to the advantage of posaconazole.

### Table 5. The proportional cost of prophylactic voriconazole and posaconazole

<table>
<thead>
<tr>
<th>Therapy outcome</th>
<th>Voriconazole</th>
<th></th>
<th>Proportion (%)</th>
<th>Cost (AUS)/patient</th>
<th>Proportional cost (AUS)</th>
<th>Posaconazole</th>
<th></th>
<th>Proportion (%)</th>
<th>Cost (AUS)/patient</th>
<th>Proportional cost (AUS)</th>
</tr>
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<tbody>
<tr>
<td>No discontinuations due to intolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapeutic success</td>
<td>44.64</td>
<td>33919</td>
<td>15142</td>
<td>63.16</td>
<td>33067</td>
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*Individual costs may not add up to total costs because of rounding.*

**Figure 2.** Contribution of different cost components in overall therapy.

One-way sensitivity analyses

The model was insensitive to changes in the acquisition costs of the initial antifungals. The economic advantage of posaconazole changed by a maximum of ±AU$3000 when posaconazole or
oral voriconazole varied between AU$0.00 and a two-fold increase in price. A similar range of variation in the iv voriconazole price resulted in about AU$7000 in the posaconazole cost advantage. Similar variation in the acquisition costs of alternatives LAmB, caspofungin and fluconazole did not affect the overall cost advantage of posaconazole.

The study outcome was also not sensitive to variations in the cost of hospital stay. A daily hospitalization cost of AU$0.00 increased the cost advantage of posaconazole to AU$23 105. A two-fold increase in the hospitalization cost reduced the posaconazole advantage to AU$15 484. A similar outcome was observed with excluding the use of monitoring and screening tests, as well as discontinuation due to possible fungal infections with voriconazole and intolerance with voriconazole.

Figure 3. A tornado diagram of the variables as per their influence on the outcome of the Monte Carlo simulation.

Figure 4. ‘Cost saving’ probability curve of posaconazole.
as with switching all iv doses of the initial and/or alternative voriconazole to oral doses. It must be noted, however, that with switching iv doses of initial voriconazole to oral doses, although the overall economic advantage of posaconazole was only reduced to AU$14047, the cost of initial voriconazole prophylaxis was significantly reduced from AU$7054 to AU$1806.

The result, however, was more sensitive to the duration of therapy. With daily costs of AU$1320 and AU$952 associated with voriconazole and posaconazole, respectively, voriconazole had a cost saving over posaconazole when the total average therapy duration associated with voriconazole decreased from 46 to 31 days, or when the duration of therapy associated with posaconazole increased from 45 to 66 days.

**Probabilistic sensitivity analyses**

The main clinical variables, as per the ranking of their impact on the model outcome in the Monte Carlo simulation, are given in Figure 3. According to the Monte Carlo simulation, the mean cost difference was AU$17159 per patient in favour of posaconazole. Posaconazole had a 91.6% probability of having an economic advantage over voriconazole, with expected cost savings ranging between AU$19313 with voriconazole and AU$55324 with posaconazole. A ‘cost saving’ probability curve is shown in Figure 4.

**Discussion**

This is the first study to investigate the pharmacoconomics of voriconazole versus posaconazole as antifungal prophylaxis. The aim was to assess the direct economic impact of relevant discontinuations that are associated with each drug as primary prophylaxis in patients with AML. Therefore, patients were followed up for the period of the induction stage of the chemotherapy for AML, which is ~1 month. The induction stage is the stage most likely to give an accurate reflection of the effectiveness of these agents, as confounding would be at a minimum. Due to limited diagnostic tools, it is hard to attribute the onset of IFIs occurring during subsequent chemotherapy episodes. IFIs that are detected after the induction stage could actually have been present earlier.

Patient demographics were not significantly different between the voriconazole and posaconazole groups for all baseline characteristics, except for the M3 subtype of AML. Nonetheless, this significant difference in the proportion of M3 class is not expected to be of influence on the outcomes of the study, because the classification of AML is based on the FAB classification, which is, unlike the more recent World Health Organization classification of AML, based solely on differences in morphology descriptions, but not phenotypic and genetic descriptions, which are important in determining prognosis.14,19

From a clinical standpoint, initial therapy with posaconazole demonstrated a lower overall rate of treatment discontinuation and lower mortality. From an economic perspective, initial treatment with posaconazole resulted in a lower cost per success and death prevented.

Death as an endpoint in the current study included both IFI-related and unrelated mortality. This is a recommended outcome to compare between drugs in clinical studies, and is important to at least ensure that a drug is not associated with worse mortality outcome.20

The cost per patient associated with initial prophylaxis was higher for voriconazole as compared with posaconazole. This difference in cost was mainly due to the fact that while posaconazole was only received as an oral formulation, three of the patients on voriconazole received the iv formulation for the 1 month induction stage. This was clearly demonstrated in the one-way sensitivity analysis, whereby the cost of initial voriconazole became less than that for posaconazole when all patients on voriconazole received the oral dosage form of initial voriconazole prophylaxis. The total cost of alternative therapies was also higher with voriconazole as compared with posaconazole. This was expected given that patients receiving posaconazole as initial therapy experienced less overall switching to alternative therapies, which meant that less alternative therapy and, ultimately, cost were consumed. Hospitalization costs associated with the posaconazole group were slightly higher than those associated with voriconazole. This is because, while overall average duration of hospital stay in the posaconazole and voriconazole groups was similar, the duration of administration of high-cost alternative medication was higher in the posaconazole group as compared with the voriconazole group. The impact of this cost advantage with voriconazole, however, was diminished by a superior cost advantage demonstrated by posaconazole, whereby posaconazole was associated with lower total costs of initial and alternative therapies. Consequently, the observed net cost difference was almost totally due to the difference in the costs of antifungal medications. These observations highlight the need for prescribers and other decision makers to consider both drug acquisition costs and secondary costs (i.e. cost of therapy failure), when determining the most appropriate medication for use.

While, for voriconazole, discontinuation because of intolerance to oral dosage form was the major clinical outcome that most influenced the therapeutic cost, for posaconazole, it was the rate of success among patients who did not discontinue because of intolerance that most influenced the therapy cost.

The cost of side effects that did not result in discontinuation was not included in the current study. It was not feasible to provide reliable estimations for the resources consumed in managing such side effects. However, these are usually moderate and do not cause therapy discontinuation, nor are they likely to significantly impact cost estimations. Furthermore, posaconazole has fewer reported side effects than voriconazole,09 therefore, accounting for all side effects associated with the two antifungals would most likely increase the posaconazole economic advantage further.

An ideal economic evaluation would be based on data from a double-blinded randomized clinical trial,21 from which the most robust evidence of efficacy can be drawn. Nonetheless, the current study is based on data that reflected relevant real-life clinical practice. Importantly, sensitivity and uncertainty analyses demonstrated the cost advantage of posaconazole to be robust against large variations in key cost determinants.

The fact that posaconazole was not available as an option for alternative use after voriconazole is a limitation in the current model. However, simulating posaconazole as the sole alternative after intolerance to voriconazole side effects did not alter the study conclusion. Posaconazole and voriconazole have different side effect profiles and, thus, are valid alternatives for one another.
As this was an observational study (no randomization), it was subject to confounding. Therefore, the current study undertook the scenario of matching posaconazole patients with voricon-azole patients according to patient age, deemed to be the demo-
graphic characteristic that may affect the effectiveness of prophylactic antifungal therapies in the AML population. This,
however, did not change the study conclusion. It is important
to emphasize here, however, that regardless of whether match-
ing was performed or not, the baseline demographic character-
istics were not significantly different between the two study
cohorts.

Another limitation in the current model is that the threshold
to discontinue voriconazole prophylaxis because of possible IFIs was possibly lower than that for posaconazole. This is
because the prophylactic use of voriconazole is not supported by
clinical trials and, hence, clinicians were less certain of how
to manage patients who are febrile whilst on voriconazole pro-
phylaxis, whereby voriconazole might have been more likely to
be discontinued. In contrast, posaconazole was introduced
after results from a clinical trial10 on prophylactic posaconazole
were available and demonstrated a low rate of breakthrough
infections. Therefore, there was an element of comfort with
pushing on with posaconazole prophylaxis if patients did not have
signs of IFIs, even if patients were febrile. In addition, in
the period 2006 onward, as compared with previous periods,
higher resolution CT scans were more routinely available for
screening tests. This might have resulted in higher confidence in
screening outcomes; thereby, clinicians might have become
less likely to discontinue prophylaxis if results from the CT scan
were negative, despite the presence of ongoing fever. To
account for this potential limitation, an uncertainty range of
0%–100% was assigned, as part of the probabilistic sensitivity
analysis, to the probability of discontinuation because of possible
IFIs associated with each of voriconazole and posaconazole. This
enabled analysis of the model under the scenario where both
antifungals have similar probability to switch to alternatives
because of possible IFIs. As per the outcomes from the Monte
Carlo simulation, however, posaconazole was still associated
with an average cost saving over voriconazole of the order of
AUS$17159. In addition, the likelihood of posaconazole having a
cost advantage over voriconazole was 90%. The maximum
expected cost saving with posaconazole was higher than that
with voriconazole.

The small sample size in the current study is a limitation.
Therefore, while the results of the current model are compelling,
they warrant validation from other studies.

In conclusion, posaconazole appears to be a more cost-
beneficial option as first-line prophylactic antifungal in AML,
compared with voriconazole. It is associated with a lower rate of
discontinuation and lower direct medical costs. The current
findings support the current use of posaconazole as the standard
care for prophylaxis therapy at the RMH and elsewhere.

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Transparency declarations
M. S. serves on the advisory boards of Pfizer and Schering Plough.
A. G. serves on the advisory board of Schering Plough. All other
authors: none to declare.

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