Cost analysis of voriconazole versus liposomal amphotericin B for primary therapy of invasive aspergillosis among haematological patients in Spain

Marina De Salas-Cansado,[1] María Echave,[1†] Mei Xue,[2] Claudie Charbonneau,[3] Andoni Barrueta[4]

[1]Health Economics and Outcomes Research Department, Pfizer Spain, Madrid, Spain; [2]Pharmerit International, Bethesda, MD, USA; [3]Health Economics and Outcomes Research Department, Pfizer International Operations, Paris, France; [4]Medical Unit, Pfizer Spain, Madrid, Spain

[†]Current affiliation: Pharmacoeconomics and Outcomes Research Iberia, Madrid, Spain

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INTRODUCTION

- Voriconazole (Vfend®, Pfizer Inc) and liposomal amphotericin B (Ambisome®, Gilead Sciences) are licensed for the treatment of invasive aspergillosis (IA), a leading cause of morbidity and mortality in immunocompromised patients which is associated with increased healthcare costs.
- Controlling healthcare budgets is an important priority for all healthcare systems. The Third European Conference on Infections in Leukemia[1] and the Spanish Society of Infectious Diseases and Clinical Microbiology[2] provide recommendations for specific therapies and disease-management strategies in Spain.

OBJECTIVE

- To evaluate the pharmacoeconomics of voriconazole versus liposomal amphotericin B as first-line therapies for IA in patients with haematological malignancy and prolonged neutropenia, or undergoing bone marrow or haematopoietic stem cell transplantation (BMT/HSCT), from a Spanish hospital perspective.

METHODS

Study design

- The study population consisted of patients with haematological malignancy and prolonged neutropenia, or undergoing BMT/HSCT.
- Eligible patients met the criteria for proven or probable IA defined in the key randomised clinical trials of voriconazole[3] and liposomal amphotericin B.[4]
- The model time horizon was the 30-day inpatient follow-up period based on the mean length of stay (LOS) for BMT patients with IA and haematological malignancy in a US claims database analysis.[5]
- To estimate the potential therapy costs of voriconazole versus liposomal amphotericin B, a decision analytic model was developed (Figure 1). Each pathway in the model was defined by the probability of an event occurring and the costs associated with each clinical outcome.

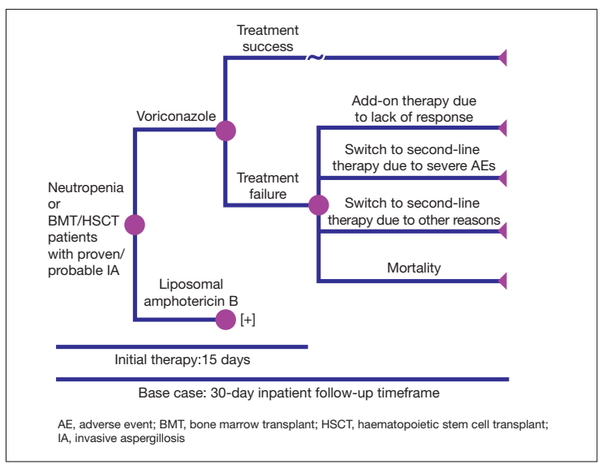

Figure 1. Decision analytic model

- Outcome measures were the total hospital costs (drug and hospitalisation costs) associated with each therapy in 2012 Euros (€).
- Outcome probabilities and cost inputs were derived from the published literature, clinical trials and local database costs.[6,7]

Key model assumptions

Treatment pathway

- In the base-case scenario, patients who failed first-line therapy were assumed to undergo a single switch between comparator drugs or the other drug was added as a second-line therapy.
- Base-case evaluation included only drug-management costs and additional hospitalisation costs due to severe adverse events (AEs) associated with first- and second-line therapies.
- The first-line drugs, voriconazole and liposomal amphotericin B, were only used in an inpatient setting (mean LOS: 30 days). Second-line therapies could be used in both inpatient and outpatient settings.
- First-line length of therapy (LOT) was 7 days of intravenous (IV) voriconazole followed by 8 days of oral voriconazole and 15 days of IV liposomal amphotericin B.
- Second-line LOT was 7 days of IV voriconazole followed by 8 days of oral voriconazole and 15 days of IV liposomal amphotericin B or caspofungin.
- After the initial success of IV voriconazole, oral voriconazole could be used as a first-line therapy, and could also be used as a second-line add-on or switch-to therapy.
- If the comparator drug was added as second-line combination therapy due to lack of response with the first-line monotherapy, the first-line drug (voriconazole or liposomal amphotericin B) was continued as IV therapy (liposomal amphotericin B) or as a combination of IV and oral therapy (voriconazole) for the same duration as the add-on drug.
- It was assumed that the efficacy of second-line therapy was 100% to simplify the model and maintain a short-term horizon. Thus, the cost analysis allowed for two lines of treatment after which the infection was assumed to be resolved.

Hospital length of stay

- Hospital LOS was not included in the cost calculation as it was assumed to be similar across the different therapies. Based on a previously published study that assessed additional resource utilisation associated with AEs, an additional 2.2 days of hospital stay was applied to both treatment arms in the base-case scenario to reflect the impact of severe AEs.[8]

Drug dosage

- Drug dosages were based on patients having an average weight of 70 kg as defined in the key randomised clinical trials of voriconazole[3] and liposomal amphotericin B.[4]
- Voriconazole was administered intravenously at doses of 6 mg/kg twice daily (Day 1) and 4 mg/kg twice daily (Day 2+), and orally at a dose of 200 mg twice daily. IV liposomal amphotericin B was administered at a dose of 3 mg/kg once daily.
- It was assumed that there was no vial wastage during use.

Safety

- Severe AEs associated with first- and second-line therapies included nephrotoxicity and hypokalaemia.[3,4] Although the effects of infusion-related reactions (e.g. visual disturbances, chest pain, back pain) were reported to be significantly different between the two treatment arms, it was assumed that the impact would be captured by the pathway of treatment failure/switch due to AEs, and that any additional costs incurred would be 2.2 days of hospital stay.

Clinical input

- The clinical efficacy and safety data used were based on the default drug dosages and were obtained from the key randomised clinical trials of voriconazole[3] and liposomal amphotericin B[4] (Table 1).

Table 1. Efficacy and safety input data

%	Treatment success	Add-on	Severe AEs/ switch due to severe AEs	Switch (due to other reason)	AE rate
Voriconazole[3]	52.8	19.2	13.4	9.0	13.4
Liposomal amphotericin B[4]	50.0	8.7	20.0	16.0	20.0

AE, adverse event

- The probability of adding on another antifungal drug due to lack of response was calculated as 1 minus the switch rate to second-line therapy.

Costs of medical resource and drug acquisition

- Hospitalisation and outpatient IV administration costs were based on economic research on the treatment of IA in Spain (Table 2).[7]

Table 2. Inpatient and outpatient costs in Spain

	Description	Price (2012 €)
Inpatient	Hospitalisation cost per day	566.52
Outpatient	IV administration cost per unit	34.90

IV, intravenous

- Drug acquisition costs were provided in 2012 € and derived from the Bot Plus database (Table 3).[6]

Table 3. Drug acquisition costs

	Dosage	Unit price (per vial or tablet, 2012 €)
Voriconazole	200 mg IV Oral tablet 200 mg	133.32 35.68
Liposomal amphotericin B	50 mg IV	130.06
Caspofungin	70 mg IV 50 mg IV	570.81 448.76

IV, intravenous

RESULTS

- Based on clinical success rates of 52.8% (voriconazole) and 50% (liposomal amphotericin B), and a LOT of 7 days for IV voriconazole plus 8 days of oral voriconazole and 15 days for IV liposomal amphotericin B, voriconazole had a lower total treatment cost than liposomal amphotericin B (€8,032 vs €10,515) (Figure 2).

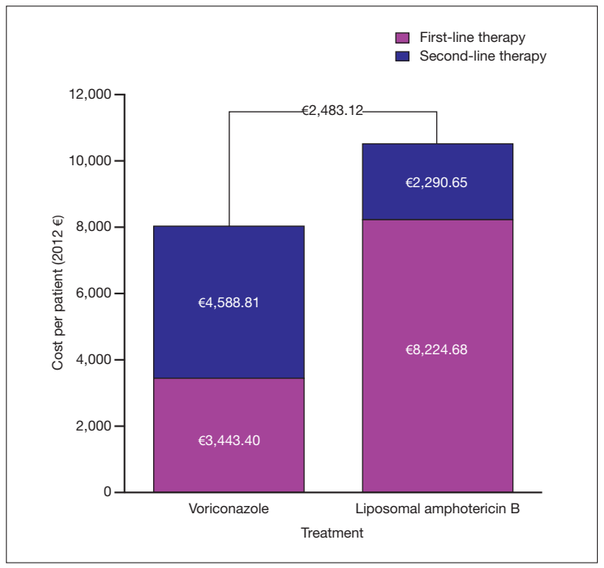

Figure 2. Cost comparison in base-case scenario

- Assuming the same efficacy of 50% for both first-line therapies, voriconazole maintained a lower total treatment cost compared with liposomal amphotericin B (€8,425 vs €10,515) (Figure 3).

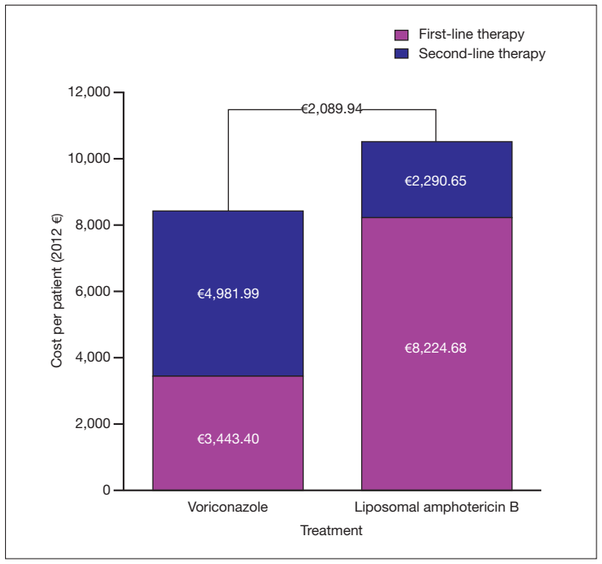

Figure 3. Cost comparison assuming equal efficacy

- Cost savings were primarily attributed to the lower drug costs and shorter IV LOT of voriconazole.
- The results were not sensitive to drug price or daily hospital costs, as demonstrated by sensitivity analyses.

CONCLUSIONS

- The findings from this study, together with the previously reported results from randomised clinical trials, suggest that voriconazole is likely to be cost-saving compared with liposomal amphotericin B for the treatment of IA in Spain, and is a better treatment option from a clinical, safety and economic perspective.
- Study limitations include:
  - Use of clinical trial data, which may not be representative of the general population
  - The assumption of 100% efficacy with second-line therapy. However, this assumption was required to prevent extrapolation of the time horizon beyond 30 days and was considered acceptable by clinical experts as no large trials evaluating efficacy data for second-line therapies have been conducted in this patient population.
- Studies using observational real-world data are required to confirm these findings for patients with IA in Spain.

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