Expert Opinion

Pharmacoeconomics of voriconazole

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Importance of the field: The recent increase in the use of antineoplastic and immune suppressive agents and the use of broad-spectrum antibiotics, prosthetic interventions, organ transplants and more aggressive surgery have been related to a greater prevalence of invasive fungal infections (IFI). Over the past few years, several new antifungal therapies have become available for these patients. Pharmacoeconomic data can play a useful role in comparing the relative benefits of treatment.

Areas covered in this review: This review summarizes all the available evidence regarding the pharmacoeconomics of voriconazole. A systematic review of pharmacoeconomic analyses through a non-restricted literature search was conducted (until May 2009).

What the reader will gain: The reader will gain a greater understanding of the pharmacoeconomics role of voriconazole.

Take home message: The majority of economic analyses have shown that voriconazole is a more cost-effective alternative in the treatment of invasive fungal infections than the antifungal drugs with which it was compared.

Keywords: antifungal drugs, invasive fungal infections, pharmacoeconomics, voriconazole

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1. Introduction

Over the last 20 years, an increase in the frequency and severity of invasive fungal infections (IFI) has been observed as a result of advances in the management of cancer, transplants and autoimmune diseases [1,2]. These infections, mainly caused by *Candida* and *Aspergillus* spp., imply an elevated rate of morbidity-mortality, with a mortality rate in high-risk patients of approximately 40 – 50% for candidiasis [2,3] and 80 – 100% in the case of aspergillosis [4,5]. Patients with IFI also consume a considerable amount of health resources, mainly due to the length of their hospital stay, when compared with patients who are not affected by these infections [6-9].

1.1 Treatment options and unmet medical needs

Antifungal agents can be classified into four strategic categories: prophylaxis (to prevent fungal infections in patients at risk who have no signs or symptoms of fungal infection), pre-emptive or presumptive (to treat asymptomatic patients at high risk who have preliminary evidence for the presence of an early fungal infection), empirical (to treat patients at risk who have signs and/or symptoms – usually febrile neutropenia or persistent fever – due to an infection of unclear aetiology) and definite (to treat patients with fungal infection that is confirmed).

A number of antifungal drugs are available for treating IFIs, such as lipid formulations of amphotericin B, azoles and echinocandins [4,5], each which has advantages and limitations in clinical practice. For example, amphotericin B deoxycholate shows high *in-vitro* activity against multiple fungal species, although it also presents important limitations due to its toxicity profile, mostly affecting the kidney [10-14].

New lipid formulations of amphotericin have been introduced to address these toxicities. The percentage of renal toxicity is reduced with these

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Article highlights.

- Invasive fungal infections are costly to treat. The largest cost component in the treatment of invasive fungal infections is extended hospital stay.
- Cost-effectiveness models show that voriconazole treatment of invasive aspergillosis results in improved patient outcomes and is more cost-effective than amphotericin B when evaluated in multiple health systems.
- Cost-effectiveness models also indicate that voriconazole versus amphotericin B for the treatment of invasive aspergillosis results in cost savings in Spain and Switzerland, and may be either cost-saving or cost-neutral in the US.
- Voriconazole versus liposomal amphotericin B for the treatment of invasive aspergillosis is cost-effective and cost-saving in the Netherlands, Spain and the UK.
- Voriconazole versus caspofungin treatment of aspergillosis or candidiasis is cost-effective in Spain and in Belgium.

This box summarizes key points contained in the article.

formulations –reaching 12% in the case of liposomal amphotericin B, 32% with amphotericin B in a lipid complex, and 41% in the case of colloidal dispersion amphotericin B – in comparison with the 44% observed with amphotericin B deoxycholate [15]. However, none has demonstrated greater efficacy in comparison with the original molecule. Additionally, amphotericin B and its derivatives must be administered exclusively intravenously (IV).

As a class, the azoles are active against a variety of pathogens, itraconazole is available as a capsule, solution and IV forms and is the most potent of the early azoles, although the effectiveness of this agent can be limited by a reduced rate of bioavailability and it is associated with drug interactions [16]. Fluconazole is available in oral (capsules and suspension) and IV forms, and is active against several of the yeasts that are most commonly encountered in immunocompromised patients; however, it is not indicated for aspergillosis [2-4,17]. Posaconazole is a triazole antifungal drug indicated for the treatment of refractory IFIs and for prophylaxis of IFIs in patients who are at high risk of developing these infections due to being severely immunocompromised. This antifungal has been compared with fluconazole or itraconazole in clinical trials [18-20]. Posaconazole is available as an oral suspension and each dose should be administered during or immediately after a meal, to enhance the oral absorption and to ensure adequate exposure.

Since the approval of caspofungin for treating candidiasis in 2002, two new antifungal agents, anidulafungin and micafungin, have appeared as new members of the candin class. However, although they present good antifungal activity, they still cannot currently be considered as a first choice for treating all IFIs [21] and the IV-only availability limits their use outside of the hospital setting. Voriconazole is a synthetic triazole derivative of fluconazole, with a wide spectrum of activity, that has demonstrated to be more effective and better tolerated than conventional amphotericin B in invasive aspergillosis and as effective as conventional amphotericin B followed by fluconazole in non-neutropenic patients with candidaemia.

Voriconazole is available in oral and IV forms with a high bioavailability (96%), which makes its use easier in switch therapy from the intravenous to oral route. The oral formulation allows for reducing the duration of the hospital stay, given that it favours hospital discharge, contributing to a reduction in hospital costs [3,22]. The information about the optimal duration of parenteral administration for switching voriconazole from intravenous to oral route is limited. A comparative study between voriconazole and liposomal amphotericin in patients with febrile neutropenia showed a mean duration of parenteral voriconazole of 5.5 ± 4.1 days before switching to oral route [23].

In the US, IV and/or oral voriconazole formulations are recommended in adults for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, disseminated infections caused by *Candida* spp., oesophageal candidiasis and in patients with scedosporiosis and fusariosis who are refractory to or intolerant of other antifungal therapy [3]. In Europe, IV and/or oral voriconazole formulations are recommended in adults and paediatric patients of at least 2 years of age for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* spp. infections, scedosporiosis and fusariosis [3]. Recent guidelines identify voriconazole as first-line therapy for treatment of invasive aspergillosis infection [24] and as an alternative treatment for patients with invasive *Candida* infections [21].

1.2 Economic impact of invasive fungal infections

The economic impact of IFIs and their treatment has been reviewed in a systematic fashion in previously published works [25-27]. The direct costs that can be attributed to invasive fungal infections are substantial. Fungal infections are rarely the patient's primary reason for hospitalization but can dramatically increase overall medical care costs in addition to the costs incurred due to treatment for the primary condition. Direct costs of invasive fungal infections include inpatient and outpatient costs, such as increased length of stay (LOS) in the hospital, nursing care, home care and antifungal medication costs. Substantial hidden costs are also a factor. These include costs related to the treatment of adverse events associated with antifungal therapy and costs incurred due to the delay in starting antifungal therapy. By far the largest cost drivers to treat invasive fungal infections are costs related to hospitalization. For aspergillosis, the high incidence of renal toxicity associated with polyene-based therapies also contributes significantly to the costs of treatment [6].

The direct costs that can be attributed to *Candida* infections are considerable. These infections are rarely the primary reason for hospitalization but they considerably increase health costs attributable to the base sickness that was the reason for the hospital entry, resulting in an extension of the hospital stay associated with a colonization or infection, with additional direct costs estimated at €8126 and €15,803 per episode, respectively [6,8,28-37].

Scarce information is available on the economic burden of invasive aspergillosis. A case-control study carried out in the US in 1998 estimated that the cost derived from this fungal infection rose to US$72,792. Aspergillosis produced an increase of $36,867 in costs per patient, in comparison with patients who presented a similar base condition but who did not develop the infection [6,7]. This difference was related with a greater duration of the hospital stay in patients affected by this IFI [6,9,31,38].

The failure of the first-line treatment of IFIs is not infrequent and is associated with considerable costs [6]. A recent study evaluated the frequency and costs of the failure of fluconazole as first-line treatment through a clinical and economical database of 500 hospitals in the US [39]. Of a total of 7,170 patients diagnosed with IFI in the form of *Candida* spp. who had received fluconazole IV as first-line treatment, 21% resulted in treatment failure, which meant that they needed a second antifungal medication as a rescue therapy. The total average cost of secondary therapy for each patient was US$76,329, almost double the cost corresponding to patients treated only with fluconazole (US$38,980). In patients with failure, the hospital stay was 75% greater (32 vs 18 days) and more than double in the ICU (15 vs 7 days) in comparison with patients treated only with fluconazole. The average duration of mechanical ventilation and the cost of drug treatments was also greater in patients in whom the fluconazole therapy failed [6,39].

Amphotericin B deoxycholate is a polyenic antifungal drug prescribed to patients with life-threatening fungal infections, a point of reference in systemic antifungal therapy since its introduction in the mid-1950s [6]. As previously noted, the systemic use of amphotericin B has been associated with elevated rates of renal toxicity [40,41], which increases the risk of mortality, and after acute renal failure, an average increase of 8.2 days in hospital stays has been described, and an average cost increase of up to US$29,823 [6,12,42].

2. A review of pharmacoeconomic analyses

2.1 Review objective

Although clinicians now have more effective and safe treatment options, evidence confirming the pharmacoeconomic benefits of newer treatment options is scarce [43]. In their 2005 review, Johnson *et al.* [26] emphasized the importance of considering all costs in any pharmacoeconomic analysis, not just drug acquisition costs. This is largely a function of the difficulties of performing and evaluating such studies.

Voriconazole is the only antifungal to have demonstrated superior efficacy and survival in a clinical study in invasive aspergillosis. The efficacy of voriconazole in invasive aspergillosis is based on the results of the Global Comparative Aspergillosis (GCA) Study [44]. Definitions of 'proven' and 'probable' cases were based on clinical, laboratory, and radiologic findings (per EORTC and MSG criteria that were in usage at the time of the trial). Aspergillosis was proven in 46% of the patients randomized to voriconazole and in 31% of the patients randomized to amphotericin B, whereas the remaining patients had a diagnosis of probable aspergillosis. None of the patients has a diagnosis of possible invasive aspergillosis. The clinical superiority and the availability of both an intravenous formulation and a 100% bioequivalent oral formulation underlies, at least in part, the shorter length of overall hospital and intensive care unit (ICU) stay, compared with that of other antifungal treatments [11,45]. Voriconazole is also well-tolerated and is not associated with a high incidence of nephrotoxicity.

Given the demonstrated clinical benefit of voriconazole, its ability to reduce hospital length of stay and its relative lack of renal toxicity, the main objective of this review was to summarize all the available evidence regarding the pharmacoeconomics of voriconazole, as well as how to revise the economic studies in which it was compared with other available alternatives.

2.2 Studies selection

A bibliographical search without restrictions was done in Medline and Embase for voriconazole as a free term, and also with the following search terms: "Voriconazole" [substance name] AND "Cost and Cost Analysis" [Mesh]; "Voriconazole" [substance name] AND "Cost-Benefit Analysis" [Mesh]; "Voriconazole" [substance name] AND economics; "Voriconazole" [substance name] AND cost-effectiveness. The search was also increased to include databases from the following sources: Library Cochrane Plus, DIMDI Health Technology Assessment databases, NHS Economic Evaluation Database (Centre for Reviews and Dissemination), Canadian Agency for Drugs and Technologies in Health, CEA Registry, Medscape, and the medical journals *Value in Health* and *Health Technology Assessment*. Finally, the bibliographical references from all original articles obtained were revised. The bibliographical search was carried out in May of 2009.

Economic analyses on voriconazole were selected, obtained from the bibliographical revision, and the different possible analysis types (costs, cost-consequence, minimization of costs, cost-effectiveness, cost-utility and cost-benefit), the type of disease management (prophylaxis, documented or empiric therapy of fungal infections) and the type of fungal infection (candidiasis, aspergillosis, others) were distinguished.

In total, 1880 references were revised. From the 35 references initially obtained, 26 different economic analyses of

voriconazole were identified [11,46-70], of which 16 were cost-effectiveness analyses, 3 cost-consequences analyses, 4 were cost and/or resources use analyses, and lastly, 3 were cost-minimization analyses.

3. Economic analyses

The economic analyses of voriconazole were carried out, taking health systems from 13 countries as a reference.

3.1 Treatment of invasive aspergillosis

Eighteen pharmaeconomic studies are available in which the efficiency of voriconazole was analyzed for treating suspected or confirmed invasive aspergillosis (**Table 1**) [11,46-63]. The majority of the studies were cost-effectiveness analyses [46-52,54-58,61], designed as decision analysis models [46-61,63], including four Markov models (with probabilistic analyses) [52-54,57]. The Wingard *et al*. study [11] was a trial-based economic analysis using data from the Global Clinical Aspergillosis Study, a randomized, multinational clinical trial performed on 277 patients with a suspected or confirmed diagnosis of invasive aspergillosis. This study demonstrated significantly improved outcomes in patients treated with voriconazole compared with those treated with conventional amphotericin B (fewer number of days of IV therapy and fewer days in the ICU) [11]. Finally, a non-interventional and non-comparative study published by Van Campenhout *et al*. [62], was designed to gather the clinical response and direct costs of treatment of invasive aspergillosis with voriconazole (oral, IV) in real-world practice in a prospective fashion. This analysis demonstrates that the results provided in the voriconazole arm of the health-economic model were valid estimates with regard to real-world outcomes [47].

The studies mainly had a hospital perspective (ten), followed by public health system perspective (six). Twelve studies were carried out in European countries, five in North America, and two in South America.

The majority of the studies compared the efficiency of voriconazole with amphotericin B deoxycholate [11,46-53,55-58,61,62]. Two studies also compared voriconazole with liposomal amphotericin B [54,59], and two European studies [60,63] compared it with caspofungin.

The main efficiency end-points measured in the majority of the studies were the cost per life-year saved, cost per additional survivor, or cost per additional patient successfully treated with voriconazole versus amphotericin B. In this respect, the majority of the studies [46,49-52,54-56,58,59,61] concluded that voriconazole was the dominant option; in other words, the most effective treatment with the fewest associated costs, both in comparison with amphotericin B deoxycholate and iposomal amphotericin B. In the studies in which voriconazole was not the dominant option, the cost per life-year saved oscillated between €361 (hospital perspective in Germany) [57] and €16,863 (patients with a body weight inferior to 40 kg, in Belgium) [47]. In an analysis of cost minimization carried out in Spain [60], a cost saving of €1,132 per patient treated with voriconazole in place of caspofungin was observed.

With regard to the design of the models, it should be noted that the majority were of a deterministic type (non-Markov models), which is reasonable when considering that the therapeutic response and survival in invasive aspergillosis generally happens 12 weeks after beginning treatment [11,62].

3.2 Prophylaxis and empirical antifungal strategy in oncohaematological high-risk patients

Seven studies of pharmacoeconomics are available in which the efficiency of voriconazole in prophylaxis or in empirical treatment of oncohaematological patients (generally with febrile neutropenia) with a high risk of IFI or with a suspected or confirmed infection was analyzed (**Table 2**) [64-70]. The majority of the studies were non-interventional and retrospective [64-68]. With the exception of the Riedel *et al*. study [66], which was carried out on the prophylaxis of fungal infection, the remaining studies included empirically treated patients with suspected or proven fungal infection. All studies were done from a hospital perspective.

Voriconazole was the dominant treatment in comparison with caspofungin, liposomal amphotericin B and amphotericin B lipid complex in one cost-effective study carried out in Spain [68]. A decision analytic model investigated the health economic impact of using voriconazole and liposomal amphotericin B for febrile neutropenia in Australia [60]. The authors concluded that liposomal amphotericin B was associated with cost savings relative to voriconazole.

In studies carried out in the US, it was established that sequential therapy from intravenous voriconazole or amphotericin B lipid complex to oral voriconazole therapy may produce considerable hospital savings [64], that savings per patient treated with voriconazole versus conventional amphotericin B may reach US$5641 [65] and that prophylaxis with voriconazole significantly reduces renal dysfunctions, along with costs, in comparison with conventional amphotericin B [66,67].

3.3 Treatment of candidaemia

Only one pharmacoeconomic analysis of voriconazole on candidaemia has been identified [71]. This cost-effective analysis, performed in Canada, was based on a decision-analytical model in which voriconazole and a regimen of conventional amphotericin B followed by fluconazole were compared in the treatment of non-neutropenic patients diagnosed with candidaemia. According to the model's results, the total incremental cost per patient treated with voriconazole was Can$1121. However, with voriconazole, the hospitalization rate was reduced with savings of Can$3115 per patient. At the same time, a greater survival rate (64.5 vs 58.2%) and less toxicity

Table 1. Pharmacoeconomics of voriconazole: treatment of invasive aspergillosis.

Study author, year [ref.] country	Study type	Study design/time horizon/perspective	Antifungal medications	Type of fungal infection/therapy/ patient	Efficiency variable	Results (Voriconazole vs control)
Calabró, 2003 [46] Brazil	Cost-effectiveness	Decision-analytic model/12 weeks/ hospital	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy	Cost per life-year gained of treating with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡
Marbaix, 2003 [47] Belgium	Cost-effectiveness	Decision-analytic model/12 weeks/PHS	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy	Cost per life-year gained of treating with voriconazole versus amphotericin B	Patient >40 kg (mean: 65 kg): €6085 Patient <40 kg (mean: 35 kg): €16,863
Soto, 2003 [48] Spain	Cost-effectiveness	Decision-analytic model/12 months/ hospital	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy/ immune-deprived patient	Additional cost per patient successfully treated with voriconazole versus amphotericin B	€25,266
Rotstein, 2004 [49] Canada	Cost-effectiveness	Decision-analytic model/12 weeks/PHS	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy	Additional cost per patient successfully treated and cost per life-year gained with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡
Garbino, 2005 [50] Switzerland	Cost-effectiveness	Decision-analytic model/12 weeks/ hospital	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy	Cost per life-year gained of treating with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡
Grau, 2005 [51] Spain	Cost-effectiveness	Decision-analytic model/12 weeks/ hospital	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy	Additional cost per patient successfully treated with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡
Jansen, 2005 [52] The Netherlands	Cost-effectiveness	Markov-Probabilistic analysis/life time/ hospital	Voriconazole Amphotericin B* Itraconazole	Proven or suspected infection/primary therapy	Additional cost per patient successfully treated and cost per life-year gained with voriconazole versus amphotericin B	Vs amphotericin B: dominant Vs itraconazole: €7800
Lewis, 2005 [53] USA	Cost analysis drug acquisition	Markov model/12 week/hospital	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy	Cost differences between voriconazole and amphotericin B	Cost saving with voriconazole, per patient: US$961
Mesrobian, 2005 [54] United Kingdom	Cost-effectiveness	Markov-Probabilistic analysis/life time/PHS	Voriconazole Liposomal Amphotericin B	Proven or suspected infection/primary therapy	Additional cost per patient successfully treated and cost per life-year gained with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡
Wenzel, 2005 [55] USA	Cost-effectiveness	Decision-analytic model/12 weeks/PHS	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy	Additional cost per patient successfully treated and cost per life-year gained with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡
Aiello, 2006 [56] Argentina	Cost-effectiveness	Decision-analytic model/12 weeks/PHS	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy/ immune-deprived patient	Additional cost per patient successfully treated with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡

*Conventional Amphotericin B deoxycholate.

‡A treatment is dominates another when it is more efficient, with less costs than the other.

€: Euro; $: US dollar; CT: Thoracic computer scan; PHS: Public Health System; USA: United States of America.

Table 1. Pharmacoeconomics of voriconazole: treatment of invasive aspergillosis (continued).

Study author, year [ref.] country	Study type	Study design/time horizon/perspective	Antifungal medications	Type of fungal infection/therapy/ patient	Efficiency variable	Results (Voriconazole vs control)
Jansen, 2006 [57] Germany	Cost-effectiveness	Markov-Probabilistic analysis/life time/ Societal & hospital	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy/ immune-deprived patient	Cost per life-year gained of treating with voriconazole versus amphotericin B	Societal: €3242 Hospital: €361
Ravasio, 2006 [58] Italy	Cost-effectiveness	Decision-analytic model/12 weeks/PHS	Voriconazole Amphotericin B*	Proven or suspected infection/primary therapy/ immune-deprived patient	Cost per life-year gained of treating with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡
Ament, 2007 [59] The Netherlands	Cost-effectiveness	Decision-analytic model/life time/ hospital	Voriconazole Amphotericin B* Liposomal Amphotericin B	Proven or probable infection/primary therapy/ haemato-poietic stem cell transplant	Cost per life-year gained of treating with voriconazole versus amphotericin B	Voriconazole is the dominant treatment‡ With caspofungin as a 3rd treatment: €107,000
Domínguez, 2007 [60] Spain	Cost-minimization	Deterministic model/ 20.9 days/hospital	Voriconazole Caspofungin	Proven or probable infection/primary therapy	Costs saving per episode with voriconazole versus amphotericin B	€1132 Robust results for any duration and to bodyweight <103.42 kg
Greene, 2007 [61] USA	Cost-effectiveness	Decision-analytic model-Monte Carlo/12 weeks/societal	Voriconazole Amphotericin B*	Invasive pulmonary aspergillosis	Cost per additional survivor with voriconazole versus amphotericin B	Halo sign at thoracic CT scan (baseline) Yes: voriconazole is the dominant treatment‡ No: US$8321
Wingard, 2007 [11] USA	Resource use & cost	Clinical trial/12 weeks/ hospital	Voriconazole (n = 143) Amphotericin B* (n = 131)	Proven or probable infection/primary therapy	Total hospital days Total intensive care unit days Total costs	27.8 vs 27.7 (p = 0.97) 5.6 vs 8.1 (p = 0.11) US$78,860 vs US$83,857 (p = 0.51)
Van Campenhout, 2008 [62] Belgium	Resource use & cost	Non-interventional prospective study, real-world practice/12 weeks/hospital	Voriconazole (n = 116)	Proven or probable infection/primary therapy	Average total cost Average fungal infection related cost	€19,674 €12,376 Model predicted costs = €21,298
Salleslag, 2009 [63] Belgium	Cost-minimization	Deterministic model & Observational study/ EORTC study/PHS	Voriconazole Caspofungin	First line treatment of invasive aspergillosis	Weighted cost per episode of fungal infection (voriconazole IV followed by oral voriconazole and intravenous caspofungin only)	The incremental saving with voriconazole treatment was £1661 per patient

*Conventional Amphotericin B deoxycholate.

‡A treatment is dominates another when it is more efficient, with less costs than the other.

€: Euro; $: US dollar; CT: Thoracic computer scan; PHS: Public Health System; USA: United States of America.

Table 2. Pharmacoeconomics of voriconazole: prophylaxis and empirical antifungal strategy in oncohaematological patients with a high risk of IFI.

Study author, year [ref.] country	Study type	Study design/time horizon/perspective	Antifungal medications	Type of fungal infection/patient	Efficiency variable	Results (Voriconazole vs control)
Arnold, 2004 [64] USA	Costs study	Non-interventional retrospective study/8 months/hospital	Treatment change with voriconazole or amphotericin B Lipid complex IV a PO voriconazole (n = 42)	Suspected infection/ febrile neutropenic patients	Costs saving due to changing voriconazole IV to PO	The IV-PO Voriconazole switch strategy saved 475,462 US$ (42 patients)
Collins, 2007 [65] USA	Cost-minimization	Decision-analytic model-Monte Carlo & Retrospective chart review/1 year/hospital	Voriconazole (n = 32) Amphotericin B* (n = 31)	Suspected infection/ febrile neutropenic patients	Costs saving per patient treated with voriconazole versus amphotericin B	US$5641
Riedel, 2007 [66] USA	Cost-consequences	Non-interventional retrospective cohort study/1 year/hospital	Voriconazole or fluconazole (n = 321) Amphotericin B* (n = 259)	Prophylaxis of fungal infections/febrile neutropenic patients	Aspergillus breakthrough incidence Mild/moderate renal dysfunctions Severe renal dysfunctions Mean total hospital costs	0.6 vs 1.9% (p = 0.19) 5.3 vs 24.7% ($p <$ 0.0001) 4.4 vs 13.5% (p <0.001) 53,257 US$ vs 44,129 US $ (p = 0.014)
Shehab, 2007 [67] USA	Cost-consequences	Retrospective chart review/1 year/hospital	Voriconazole (n = 32) Liposomal amphotericin B (n = 26)	Suspected infection/ febrile neutropenic patients	Breakthrough invasive infection Elevated serum creatinine levels Mean drug cost per episode	12 vs 11% (p >0.999) 3 vs 27% (p = 0.017) 5,217 US$ vs 6,379 US$
Romá, 2008 [68] Spain	Cost-effectiveness	Non-interventional retrospective study/10.8 days/hospital	Voriconazole (n = 6) Caspofungin (n = 25) Amphotericin B lipid complex (n = 25) Liposomal amphotericin B (n = 53)	Suspected infection/ febrile neutropenic patients	Cost per additional complete or partial response with Voriconazole versus comparators	Voriconazole is the dominant treatment in comparison to the others compared‡
Slobbe, 2008 [69] The Netherlands	Cost-consequences	Cohort study/ maximum 6 months/ hospital	Voriconazole (n = 73)	Proven or probable invasive aspergillosis/ myelogenous leukemia–myelodysplastic syndrome	Invasive aspergillosis (IA) related costs increase, compared with patients without invasive aspergillosis	Possible IA: US$8360 Probable IA: US$15,280 (p <0.001)
Al-Badriyeh, 2009 [70] Australia	Cost-effectiveness	Decision-analytic model-Monte Carlo & Randomized clinical trial/7 days beyond the end of therapy/ hospital	Voriconazole (n = 415) Liposomal amphotericin B (n = 422)	Suspected infection/ febrile neutropenic patients	Cost per death prevented/ successful treatment gained with voriconazole versus amphotericin B	Liposomal amphotericin B is the dominant treatment‡

*Conventional Amphotericin B deoxycholate.

‡A treatment is dominates another when it is more efficient, with less costs than the other.

€: Euro; $: US dollar; IA: Invasive aspergillosis; IFI: Invasive fungal infection; IV: Intravenous; PHS: Public Health System; PO: oral; USA: United States of America.

(52.5 vs 64.5%) were observed with voriconazole. The cost for each additional surviving patient on day 98 and of avoiding a toxicity case with voriconazole was Can$17,739 and Can $9298, respectively. The probabilistic sensitivity analysis confirmed the study's robustness, observing greater survival and fewer costs (dominance) with voriconazole in 88 and 49% of simulations carried out, respectively.

4. Conclusions

The last 20 years have seen an increase in the frequency and severity of invasive fungal infections (IFI) [1,2]. These infections are difficult to treat, are seen mainly in high-risk populations, and entail an elevated morbidity-mortality rate with elevated associated costs [5,7,26]. In fact, antifungal treatments imply greater expense in anti-infectives for many hospital centres [26]. For this reason, it is necessary to have new antifungal treatments that offer a greater activity spectrum with assumable effective costs per additional unit for national health systems.

Voriconazole is an efficient option for treating invasive aspergillosis and candidaemia in non-neutropenic patients, serious invasive fluconazole-resistant *Candida* spp, and other less frequent fungal infections produced by *Fusarium* and *Scedosporium* spp [3].

In this systematic revision, 26 pharmacoeconomic studies on voriconazole were identified. The following conclusions were drawn from these studies:

1. *Treatment of invasive aspergillosis*: voriconazole was the dominant option in the majority of studies [46,49-52,54-56, 58,59,61]; that is to say, the most effective treatment at the lowest associated cost, in comparison with both amphotericin B deoxycholate and liposomal amphotericin B. In the studies in which voriconazole was not the dominant option, the cost per life-year saved oscillated between €361 (hospital perspective in Germany) [57] and €16,863 (patients with a body weight <40 kg in Belgium) [47]. Despite non-dominance status, voriconazole was a cost-effective option due to the cost per life-year saved was below the European threshold of cost-effectiveness (between €30,000 and £30,000) [72,73]. In a cost-minimization analysis carried out in Spain [60], a cost saving of €1132 was observed per patient treated with voriconazole in place of caspofungin.

2. *Prophylaxis and empirical antifungal strategy in oncohaematological high-risk patients*: voriconazole was the dominant option in comparison with caspofungin, liposomal amphotericin B and amphotericin B lipid complex in one cost-effectiveness study carried out in Spain [68]. Voriconazole was dominated by liposomal amphotericin B in one empirical model performed in Australia [70]. In the studies carried out in the US, the sequential therapy from intravenous voriconazole or amphotericin B lipid complex to oral voriconazole treatment produced considerable hospital savings [64], with savings per patient treated with voriconazole versus conventional amphotericin B of US$5641 [65]; it was also established that prophylaxis with voriconazole significantly reduces renal dysfunction and costs in comparison with conventional amphotericin B [66,67].

3. *Treatment of candidaemia*: in a cost-effectiveness analysis carried out in Canada [71] in which voriconazole was compared with a regimen of conventional amphotericin B followed by fluconazole in treating non-neutropenic patients diagnosed with candidaemia, the total incremental cost per patient treated with voriconazole was Can$1121. However, with voriconazole, the hospitalization rate was reduced (with savings of Can$3115 per patient), a greater survival rate with voriconazole was observed (64.5 vs 58.2%) and there was less toxicity (52.5 vs 64.5%).

5. Expert opinion

Diagnosis of IFI is increasing, in particular in neutropenic haematological patients, immunosuppressed patients, in critical patients and in those subjected to aggressive surgical interventions. The beginning of an IFI may pass by unnoticed, which means that the introduction of diagnostic procedures that can help to exclude or confirm its presence is important. The early administration of an adequate antifungal treatment is essential, as delaying this therapy has been related to an increase in mortality in patients with IFI. A recent study [74] demonstrated that initiation of antifungal treatment on the basis of the identification of a halo sign by chest CT is associated with a significantly better response to treatment and improved survival of invasive pulmonary aspergillosis.

Few studies have specifically estimated the economic consequences of invasive aspergillosis but the associated financial burden is consistently high [55]. Increased length of hospital stay is the key component driving the cost of invasive aspergillosis, accounting for 47% of total increased costs [7]. In terms of hospital stay, ICU bed days are the most expensive, costing up to 3.6 times more than a non-ICU bed stay [55]. Reducing length of ICU stay can improve cost-effectiveness [7].

When the economic impact of antifungal treatment is analyzed, many factors besides its price of acquisition should be considered; these additional costs are generally the cost-drivers, for example: the length of stay in the hospital and in the intensive care unit, complications of the sickness, the development of resistances and the need for rescue treatment. Just as with other medications, with an elevated price, it is erroneous to consider the clinical use of voriconazole based only on the cost of acquisition variable.

The economic impact of *Aspergillus* and *Candida* spp. infections is mainly due to the prolonged length of stay in hospital, the need to implement second-line therapies after the failure of first-line treatments and the toxicity of some treatment alternatives, such as is the case with amphotericin B deoxycholate [6] and the majority of its formulations associated with lipids.

To date, voriconazole is the only antifungal to have demonstrated to improve survival in a clinical trial in invasive fungal infection. In their 2006 review article on economic evaluations of antifungal agents, Moeremans and Annemans [27] concluded that voriconazole 'is the treatment of choice' for invasive aspergillosis. Voriconazole is particularly attractive from a pharmacoeconomic point of view because of the possibility of switching from the intravenous to the oral route with voriconazole, and its elevated therapeutic efficacy in treatment of IFIs. Multiple pharmacoeconomic studies have been conducted to evaluate the cost-effectiveness of voriconazole compared to other therapeutic options in the treatment of IFI. The majority of these evaluations have shown that voriconazole is a cost-effective alternative in treating IFIs in comparison with amphotericin B (both conventional and lipid formulations) and caspofungin. No information is available from pharmacoeconomic studies of voriconazole with anidulafungin, micafungin or posaconazole, a new azole utilized in prophylaxis of IFI in neutropenic patients [19,20]. In the majority of analyses, voriconazole was either the dominant treatment (more efficacy and with fewer associated costs) or had a cost per life-year saved assumable by national health systems, in agreement with generally accepted cost-effectiveness thresholds [75].

Despite the proven cost-effectiveness results, other data support the economic value of voriconazole. In the economic analysis of the Wingard *et al*. study [11], patients treated initially with voriconazole required fewer days in the ICU than those receiving conventional amphotericin B. Surviving patients who were treated with voriconazole spent more days out of hospital than those treated with amphotericin B. The relevance of these data is that patients not only survived longer with voriconazole, but they survived longer out of the hospital without additional resource utilization.

At the time of selecting an antifungal treatment, the probability of success of different therapeutic options should be considered in order to reduce morbidity-mortality in the most efficient fashion for national health systems. Voriconazole can play an important role in reducing both the mortality and the cost burden of invasive fungal infections across a range of patients including those with transplants or haematologic malignancies. Early appropriate treatment of invasive fungal infections may be essential to optimize outcomes.

Future pharmacoeconomic analyses comparing the efficiency of antifungal treatments should comply with methodological recommendations from International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [76].

Declaration of interest

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