Pharmacoeconomic evaluation of isavuconazole, posaconazole and voriconazole in the treatment of invasive fungal infection: initial therapy prior to pathogen differential diagnosis in China

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Abstract

Background

Invasive fungal infections (IFIs) is associated with high mortality and a substantial economic burden. For high-risk patients, fever drive or diagnostic drive therapy is usually initiated prior to the differential diagnosis of the pathogen. This study evaluated the cost-effectiveness of isavuconazole, posaconazole, versus voriconazole in the treatment of invasive fungal infections from the perspective of the Chinese healthcare system, informing healthcare decision-making and resource allocation.

Methods

A decision analytic model was constructed using TreeAge Pro 2011 software to evaluate the cost-effectiveness of the entire disease course. We assumed that the prevalence of mucormycosis in the patients entering the model was 7.8%. Efficacy, cost, adverse events, and other data included in the model were mainly derived from clinical studies, published literature, and publicly available databases. The primary outcomes of the model output were total cost, quality-adjusted life years (QALYs), life years (Lys), and incremental cost-effectiveness ratio (ICER). The willing-to-pay (WTP) threshold was defined as one to three times China's GDP per capita in 2022. One-way sensitivity analysis and probability sensitivity analysis were used to determine the robustness of the model. At the same time, the cost-effectiveness of three triazole antifungal agents under a broader range of mucormycosis prevalence, when voriconazole was covered by medical insurance reimbursement, and after the price reduction of posaconazole was discussed.

Results

Base-case analysis showed that isavuconazole had greater efficacy (+ 0.38 LYs and + 0.31 QALYs) than voriconazole; ICER was $15,702.46 /QALY, well below the WTP threshold ($38,223 /QALY). However, posaconazole did not provide a significant economic advantage over voriconazole (ICER $64,466.57 /QALY). One-way sensitivity analysis found that ICER was highly sensitive to the mortality of patients with invasive aspergillus infection. In the probabilistic sensitivity analysis, when the WTP threshold was $38223 /QALY, the probability of isavuconazole being cost-effective was 72.9%. The scenario analysis results indicated that posaconazole would become cost-effective when the price was reduced by 15% or the prevalence of mucormycosis was 14%.

Conclusions

Isavuconazole represents a cost-effective initial option for treating IFIs in high-risk patients prior to the differential diagnosis of pathogens. It will also be economical when a 15% reduction in posaconazole cost is achieved.

Introduction

Invasive fungal infections (IFIs) are opportunistic fungal infections that frequently occur in immunocompromised patients, such as those with hematological malignancies, hematopoietic stem cell

transplantation, and solid organ transplantation. The most common fungal pathogens are *Candida*, *Aspergillus*, and *Mucorales* species [1]. Although advancements in modern medical technology have vastly improved such patients' survival rates and survival time, it has also increased the incidence of IFI [2]. The prevalence of invasive *aspergillus* (IA) varies between 0.94% and 14% among China's immunocompromised individuals [3]. In Europe, approximately 60,000 cases of IA occur annually, whereas estimates suggest that over 160,000 cases of IA arise each year in China [4]. IFI imposes a heavy burden on patients and healthcare systems. A retrospective study of invasive pulmonary aspergillosis (IPA) found higher rates of mechanical ventilation (43.3% vs. 5%), longer hospital stays (45.8 days vs. 18.4 days), and increased mortality rates (43.3% vs. 11.4%) in IPA cases relative to non-IPA patients [5]. Mucormycosis, another IFI, also has s significant economic impact on society and individuals due to its lengthy treatment duration, high cost, and limited safe and effective drug options. According to a Chinese study, the mortality rate of mucormycosis exceeds 40%, and the economic burden is 3 to 10 times the country’s annual disposable income per capita [6].

Identification of IA and mucormycosis on time is challenging due to their similar clinical and radiological manifestations, with co-infections further complicating the differential diagnosis [7, 8]. Treatment of IFIs is typically initiated based on patient risk factors and clinical and radiological signs before the identification of the causative agent. As a result, a significant proportion of mucormycosis cases are initially misdiagnosed as IA.

Voriconazole is the recommended primary treatment agent for IA by the Infectious Diseases Society of America (IDSA), the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) guidelines [9, 10]. However, liver dysfunction is a common adverse event. And clinical use is limited due to its inhibition of cytochrome P450 isoenzymes and the presence of sulfobutylether-beta-cyclodextrin in the intravenous formulation. Recently, a phase 3, randomized, controlled, non-inferiority trial evaluated the efficacy and safety of posaconazole for treating IA [11]. Given its effectiveness, it was approved by the United States Food and Drug Administration in June 2021 for treating IA. Isavuconazole is another antifungal drug used as a primary or alternative treatment agent for IA [9, 10]. Compared to voriconazole, isavuconazole has similar efficacy but significantly lower rates of drug-related adverse events such as hepatotoxicity and visual impairment (42% vs. 60%) [12]. The rate of permanent discontinuation due to drug-related adverse events is also lower for isavuconazole than for voriconazole (8% vs. 14%) [12]. Notably, in addition to their anti-*aspergillus* activity, both posaconazole and isavuconazole have shown activity against *mucorales*, whereas voriconazole has not. Consequently, posaconazole and isavuconazole are recommended as first-line treatments for mucormycosis by the global guideline for the diagnosis and management of mucormycosis published by the ECMM [13].

Voriconazole has been the standard treatment for IA for a considerable period. Nonetheless, with the advent of isavuconazole and posaconazole, more options are now available for the clinical treatment of IA. Hence, it is imperative to determine the most cost-effective treatment options to conserve medical resources and reduce the financial burden on patients. Several studies have shown that isavuconazole is a cost-effective treatment for IA or suspected IA compared to voriconazole in the United States and some European countries [14–17]. However, there has yet to be a report on the cost-effectiveness of isavuconazole and posaconazole

versus voriconazole in China. Therefore, an economic model was developed to explore the cost-effectiveness of using voriconazole, isavuconazole, and posaconazole to treat adults with suspected IFIs when the differential diagnosis between IA and mucormycosis is uncertain at the start of treatment.

Methods

Model structure

A decision analytic model (Fig. 1) was adopted from a healthcare system perspective to evaluate the cost-effectiveness of isavuconazole, posaconazole, and voriconazole for treating IFIs. The model was based on the published literature [14, 15, 17] and used TreeAge Pro 2011 (TreeAge Software Inc., Williamstown, MA, USA), incorporating China-specific costs and resource utilization.

Assuming 1,000 patients with a suspected IFI entered the model, antifungal therapy was initiated before obtaining pathogen information. Patients were assigned to the following treatment sequences: isavuconazole, posaconazole, and voriconazole. Only 50% of patients had their pathogens identified, with *aspergillus* accounting for 92.2% of the cases and *mucorales* accounting for 7.8%. Given the absence of domestic data, the pathogen detection rate was referenced from previous studies [14, 17]. Depending on clinical responsiveness, drug tolerance, and other factors, patients could switch to second-line treatment with liposomal amphotericin B (L-AmB). As voriconazole had no activity against *mucorales*, patients initially treated with voriconazole switched to L-AmB therapy if *mucorales* were identified during treatment. Otherwise, voriconazole therapy was maintained until the patient's demise. The sequential regimen consisted of oral triazoles. Two additional triazoles, other than the initial one, were administrated orally at a 50%/50% ratio. However, for isavuconazole (posaconazole) -treated patients with mucormycosis, only oral posaconazole (isavuconazole) sequential L-AmB was allowed.

Model inputs and data sources

Clinical data

The proportion of switching to second-line treatment and all-cause mortality were derived from several large clinical studies [11, 12, 18] and literature [19, 20]. Since there were no head-to-head clinical studies between posaconazole and isavuconazole, in vitro drug sensitivity tests showed that both drugs had similar good activity against *mucorales* [21], it was assumed that the data of isavuconazole were also applicable to posaconazole for mucormycosis.

Treatment regimen and duration

Patients entering the model were assumed to have normal liver and kidney function or not require dose adjustment. Of all patients, 75% received intravenous therapy initially and then switched to oral treatment, while 25% received oral medicine at the outset [14, 15, 17]. The daily loading and maintenance doses of isavuconazole, posaconazole, and voriconazole were 600 mg/200 mg, 600 mg/300 mg, and 800 mg/400 mg, respectively, whether administrated orally or intravenously. The dose of L-AmB was administrated at 5

mg/kg, and the mean body weight (60 kg) of Chinese patients with hematologic malignancies or hematopoietic stem cell transplantation was used to calculate the total daily dose of L-AmB [22, 23].

The treatment duration in the model was 67 days (intravenous 9 days) for invasive *aspergillus* (IA) [11] and 149 days (intravenous 15.5 days) for mucormycosis [18]. Referring to the published literature, isavuconazole, posaconazole, and voriconazole were thought to have the same course of treatment [14, 15, 17]. On average, patients who did not respond to first-line therapy changed their regimen on day 21 because most no-responders switched treatment between day 1 to 42 [12, 18]. However, patients treated with voriconazole who were later diagnosed with mucormycosis changed their regimen on day 11 [24]; those who did not receive a diagnosis of mucormycosis continued to be treated as IA for 67 days (intravenous 9 days). After the failure of first-line treatment, L-AmB took 14.5 days to treat IA [25] and 27.2 days to treat mucormycosis based on previous literature [18].

The average length of hospital stay (LOS) for first-line treatment of IA and mucormycosis was 19.7 days [12] and 19.3 days [18], respectively. Due to a lack of data for second-line treatment, we hypothesized an extended LOS to (19.7 + 21) and (27.2 + 21) days for treatment of IA and mucormycosis, respectively, to meet the required course of treatment and the necessary LOS. Clinical experts also endorsed this hypothesis.

Costs

The unit costs of isavuconazole (Cresemba®), posaconazole (Noxafil®), and voriconazole (Vfend®) were available from a tertiary care general hospital with 2,000 beds. Furthermore, Fengkesong® was the commonly used L-AmB in Chinese hospitals, so we adopted its price. The model also incorporated additional resources utilized beyond the cost of antifungal drugs, such as the costs of laboratory testing, microbiological detection, galactomannan antigen determination, imaging examination, hospitalization cost (cost for bed utilization, nursing fees, etc.), and outpatient follow-up cost. Considering the pharmacokinetics advantages of isavuconazole, the actual situation of Chinese hospitals, and the recommendations of the 2017 ESCMID-ECMM-ERS guideline [10], therapeutic drug monitoring was only conducted for posaconazole and voriconazole. Severe hepatotoxicity was considered the only adverse event that required intensive therapy and affected the cost. The incidence of severe hepatotoxicity was obtained from phase 3 clinical trials [11, 12] and publicly available databases. An artificial liver support molecular adsorbent recirculating system will be used to treat liver failure, and the cost was a one-time fee obtained from a study in China [26].

Utility and life expectancy

Since the key clinical outcomes of the model were derived from several clinical studies mainly targeting acute myeloid leukemia patients [12, 18], and the underlying disease will impact the quality of life and life expectancy for survivors of IFI, a lifetime horizon was chosen to capture the long-term effects and costs of the three compared drugs. A quality of life utility value of 0.82 [27], a life expectancy of 17 years [28], and a discount rate of 3% were applied to discount the costs and health impacts. All input data for the decision-tree model were shown in Table 1.

Table 1
Input data used for the decision-tree model

Parameter	Isavuconazole	Posaconazole	Voriconazole	2nd-line treatment *
Epidemiology inputs				
Prevalence of Invasive aspergillosis	92.2%			
Prevalence of Mucormycosis	7.8% [14, 17]			
Clinical inputs				
Proportion switching to 2nd-line treatment #				
Invasive aspergillosis	47.7% [12]	42.7% [11]	45.3%/38.3%	-
Mucormycosis	35.1% [18]	35.1%	100.0%	-
All-cause mortality				
Invasive aspergillosis	20.0% [12]	19.0% [11]	23.0%/19.0%	65.0%
Mucormycosis	43.2% [18]	43.2%	100.0%	82.9%
Incidence of severe hepatotoxicity	1.2% [12]	3.1% [11]	2.8%	-
Duration of treatment (days)				
Invasive aspergillosis	67 (IV: 9.0) [11]			14.5 [25]
Mucormycosis	149 (IV: 15.5) [18]		-	27.2 [18]
Duration prior to switching 2nd-line therapy (days)	21 (IV: 9.0) [12, 18], except voriconazole for mucormycosis: 11 (IV: 9.0) [24]			
Length of hospital stay (days)				
Invasive aspergillosis	19.7 [12]			19.7 + 21
Mucormycosis	19.3 [18]		27.2 + 11	27.2 + 21
Days from therapy to death (days)				
Invasive aspergillosis	37			-
Mucormycosis	28			-
Economic inputs				
Unit of drug costs ($)				
IV	336.26	282.32	138.29	18.75

Parameter	Isavuconazole	Posaconazole	Voriconazole	2nd-line treatment *
Epidemiology inputs				
Oral	89.95	39.62	39.00	-
Cost of treatment other than drugs ($)				
Single laboratory test cost	102.67			
Single microbiological detection cost	86.18			
Single GM test	22.29			
Single imaging examination cost	29.72			
Other hospitalization costs per day	21.99			
Single outpatient follow-up cost	3.71			
Therapeutic drug monitoring	22.29			
The cost of DILI's treatment	3982.17			
Utility (quality of life)	0.82			

* Liposomal amphotericin B is 2-line treatment drug. # The proportion switching to 2nd-line treatment was calculated by the numbers of patients who discontinued 1st-line treatment minus the number of patients who died during treatment. Abbreviations: IV, intravenous; GM, galactomannan; DILI, drug-induced liver injury.

Cost-effectiveness outcomes and model analysis

The model calculated quality-adjusted life years (QALYs), life years (LYs), and costs in each sequence. The incremental cost-effectiveness ratios (ICER) were represented by the ratio of cost to QALY. ICERs were compared to the willingness-to-pay (WTP) threshold of 3 times China's GDP per capita in 2022 (3×$12741) to assess cost-effectiveness.

In order to evaluate the robustness of the model, one-way sensitivity analysis was performed to examine the impact of varying the parameter on ICER. The following parameters were modified within a certain range: cost parameters, utility parameters, and duration of treatment were varied by ± 25% of the base-case values; probability parameters were varied by ± 10% of the base-case values. The upper and lower bounds of parameters within the range of 0 to 1 were restricted within their respective boundaries. The tornado diagrams displayed which parameters were the key drivers of the results.

Probabilistic sensitivity analysis (PSA) using 10,000 Monte Carlo iterations were performed to account for uncertainty in the model inputs and estimate the likelihood of different outcomes. Probability and utility parameters (bounded by 0 and 1) were assigned a beta distribution, while costs and treatment duration (due to positive values and bounded at 0) were assigned a gamma distribution. The standard error for some parameters was assumed to equal 10–25% of the mean because of lacking information on their variability.

The results of PSA were presented by the cost-effectiveness acceptability curve, which showed the probability of compared drugs being cost-effective over a range of WTP threshold.

Scenario analysis were used to examine the results of the model under different scenarios or hypothetical situations. Given the absence of domestic data of *mucorales*, the impact of this parameter on ICER was tested by using a higher (14%) and a lower (2%) pathogen detection rate, respectively. As a classic old drug, the cost of voriconazole has been covered by health insurance payment in China, but the other two drugs are not. Eligible patients pay only a minimal account for voriconazole. Therefore, the cost-effectiveness of the three drugs in this patient population was evaluated. Finally, considering the situation of price decreases after the loss of exclusivity, we assessed the influence of the dynamics of drug price on results.

Results

Base-case analysis

The outcomes and costs over a lifetime horizon with isavuconazole, posaconazole, and voriconazole were shown in Table 2. The ICERs were calculated to voriconazole, which was regarded as the standard antifungal therapy. Isavuconazole demonstrated greater efficacy (+ 0.38 LYs and + 0.31 QALYs) than voriconazole, albeit at a higher cost (+$4,857.71). An ICER of $15,702.46 for each extra QALY obtained was just only 23% higher than China's GDP per capita in 2022.

Table 2
Base case cost-effectiveness results

Parameters	Isavuconazole			Voriconazole			Incremental value
	IA	IM	Combined	IA	IM	Combined	
Cost ($)	20,794.19	1,814.21	22,608.39	16,285.18	1,465.50	17,750.68	**4,857.71**
LYs	9.24	0.05	9.29	8.91	0.01	8.91	**0.38**
QALYs	7.58	0.04	7.62	7.30	0.01	7.31	**0.31**
ICER ($/QALY)							**15,702.46**
Parameters	**Posaconazole**			**Voriconazole**			**Incremental value**
	IA	IM	Combined	IA	IM	Combined	
Cost ($)	17,159.57	1,443.36	18,602.93	15,025.51	1,465.50	16,491.01	**2,111.92**
LYs	9.35	0.05	9.40	9.35	0.01	9.36	**0.04**
QALYs	7.67	0.04	7.71	7.67	0.01	7.68	**0.03**
ICER ($/QALY)							**64,466.57**

Abbreviations: IA, invasive aspergillosis; IM, invasive mucormycosis; LYs, life years; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

In contrast, posaconazole did not provide a significant cost-effectiveness advantage over voriconazole. The treatment cost of posaconazole was higher (+$2,111.92), but it only had a slight therapeutic advantage (+ 0.04 LYs and + 0.03 QALYs). It resulted in an ICER of $64,466.57 per additional QALY gained, which was well over 3 times GDP per capita.

One-way sensitivity analysis

In the one-way sensitivity analysis, a total of 35 parameters were tested, and the 12 parameters that greatly impacted the model results were presented in Fig. 2. It was found that ICER was most sensitive to the change of mortality in voriconazole-treated and isavuconazole-treated patients with IA in the model of isavuconazole. In addition, changes in other parameters (parameters of the unit price of oral or intravenous isavuconazole, LY, QALY, etc.) did not result in an ICER above the $21,000 threshold. In the model of posaconazole, negative ICERs on the graph indicated a dominance of posaconazole over voriconazole. The reversal of results occurred when mortality decreased by 5% for posaconazole-treated with IA or increased by 5% for voriconazole-treated with IA.

Probabilistic sensitivity analysis

The PSA results revealed that the probability of voriconazole being cost-effective at a lower WTP threshold was higher than isavuconazole (Fig. 3). Nevertheless, beyond the WTP threshold of $15,289 per QALY, the probability of isavuconazole was more cost-effective than voriconazole. Especially, isavuconazole was the

optimal antifungal regimen in 61.6%, 72.9% and 80.3% of simulations at the $22,934, $38,223 and $76,446 threshold, respectively.

Scenario analysis

The results of scenario analysis were outlined in Table 3. If the health insurance paid the voriconazole cost, ICER might increase to $27,705.55, but isavuconazole still had an advantage. The higher (14%) or lower (2%) detection rate of *mucorales* also did not affect the results of the base-case model. Scenario analysis considering price decreases after the loss of exclusivity revealed that posaconazole began to show a cost-effectiveness advantage when the unit price decreased by 15%. Once it fell to 30%, it would become a dominant strategy.

Table 3
Scenario analysis results

Scenario	Δ Cost ($)	Δ LY	Δ QALY	ICER ($/QALY)
BC: Isavuconazole - Voriconazole	**4,857.71**	**0.38**	**0.31**	**15,702.46**
Payment of voriconazole by the health insurance	8,588.72	0.38	0.31	27,705.55
The prevalence of mucormycosis is 2%	4,882.06	0.39	0.32	15,256.44
The prevalence of mucormycosis is 14%	4831.68	0.43	0.35	13,804.80
BC: Posaconazole - Voriconazole	**2,111.92**	**0.04**	**0.03**	**64,466.57**
Posaconazole after 15% price reduction	1143.91	0.04	0.03	38,130.33
Posaconazole after 30% price reduction	175.91	0.04	0.03	5,863.67
The prevalence of mucormycosis is 14%	1950.82	0.13	0.11	17,734.73
Abbreviations: BC, base case value; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.				

Discussion

This study was the first investigation into the cost-effectiveness of three triazole antifungal agents for treating IFIs. It informed healthcare decision-making and resource allocation to improve patients' outcomes and medical efficiency.

Early definitive diagnosis and early initiation of antifungal therapy are essential for effectively managing IFIs. Immunocompromised patients, particularly those with hematologic malignancies after chemotherapy, are at significantly increased risk of developing IFIs, even when no microbiological culture results are available [29]. Initial antifungal therapy is paramount due to several factors, including the difficulty in clinically distinguishing between invasive aspergillosis (IA) and mucormycosis, which present with similar clinical presentations; the rapid and aggressive disease progression with a high mortality rate [20, 30] ; and the lack of antifungal activity of voriconazole against *mucorales*. Delayed antifungal treatment significantly

increases the mortality rate [31, 32]. Therefore, choosing a cost-effective treatment option is crucial for optimal patient management.

Our base-case analysis indicates that compared to voriconazole, isavuconazole is a cost-effective option for suspected IFIs, while posaconazole is not. This finding is attributable to the favorable outcomes of isavuconazole not only against *aspergillus*, but also *mucorales* [18]. Although isavuconazole carries a high drug cost, its lower expenses in laboratory analysis (TDM), adverse events, and other treatment-related costs offset the high drug cost. On the other hand, posaconazole is effective against mucormycosis [33], but its drug cost is higher than that of voriconazole. Additionally, the costs associated with disease treatment do not differ significantly between posaconazole and voriconazole, further contributing to the disadvantage of posaconazole in terms of the total cost.

The one-way sensitivity analysis revealed the robustness of our findings. Consistent with previous studies in European countries, the model was highly sensitive to the mortality rate of patients with IA. [14, 15, 17]. The model also demonstrated that the prices of isavuconazole and posaconazole impacted its sensitivity, which was unsurprising. These brand drugs have not been on the Chinese market for long and are expensive under patent protection. However, once their patents expire, the entry of generic drugs into the market will likely lower their cost. Subsequent price reductions could affect the cost-effectiveness of these drugs differently. To explore this possibility, we performed a scenario analysis, and the result showed that a mere 15% decrease in the price of posaconazole could lead to a pharmacoeconomic advantage.

There were several advantages of our model. For example, the model was constructed based on the complete process of treating IFIs in high-risk patients, which included empirical therapy prior to pathogen differential diagnosis and targeted therapy after identification, thereby highly replicating the real-world diagnostic and therapeutic processes. The model also allowed for transitions between different treatment regimens by capturing the impact of various treatment choices through detailed data, including the proportion of oral and intravenous medications selected, various oral sequential therapy plans, and the cost of outpatient follow-up for antifungal treatment. This abundance of information could help healthcare professionals consider a comprehensive range of factors when making treatment decisions.

Despite these strengths, our study has several limitations. Firstly, as with many modeling studies, the quality of available data limited the model inputs. The mortality in the model came from patients with hematologic malignancies and hematopoietic stem cell transplantation, which restricted the generalization of our results to other patient cohorts at different IFIs risks. Additionally, due to the lack of epidemiological data on mucormycosis in high-risk patients with IFIs in China, we relied on European data [14, 17]. To address this issue, we simulated a broader range (2%-14%) of mucormycosis prevalence in the scenario analysis. The results showed that when the incidence was 14%, the ICER decreased to $17734.73 /QALY, below the WTP threshold ($38223 /QALY). Compared with voriconazole, posaconazole became more cost-effective. Secondly, since the absence of relevant studies exploring the impact of IFIs on quality of life, our research did not set utility parameters based on this aspect. Finally, our study did not consider the drug-drug interactions and the direct or indirect costs associated with such interactions. It may underestimate the superiority of isavuconazole because of its lower frequency of drug-drug interactions [34].

Conclusion

Patients with a high risk of suspected IFIs should be treated with antifungal therapy as soon as possible. When making treatment decisions, healthcare professionals should take into account the possibility and incidence of mucormycosis, as well as the effectiveness and safety of triazole antifungal drugs. Our results suggested that isavuconazole represented a cost-effective initial option for treating IFIs in high-risk patients prior to the differential diagnosis of pathogens. It would also be economical when a 15% reduction in posaconazole cost was achieved.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

All authors contributed to the study's conception and design. XS and QX developed the model and analyzed the data. GH and XL performed the literature search and interpreted the results. XS and GH wrote the initial draft. QL critically reviewed and revised the manuscript.

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Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

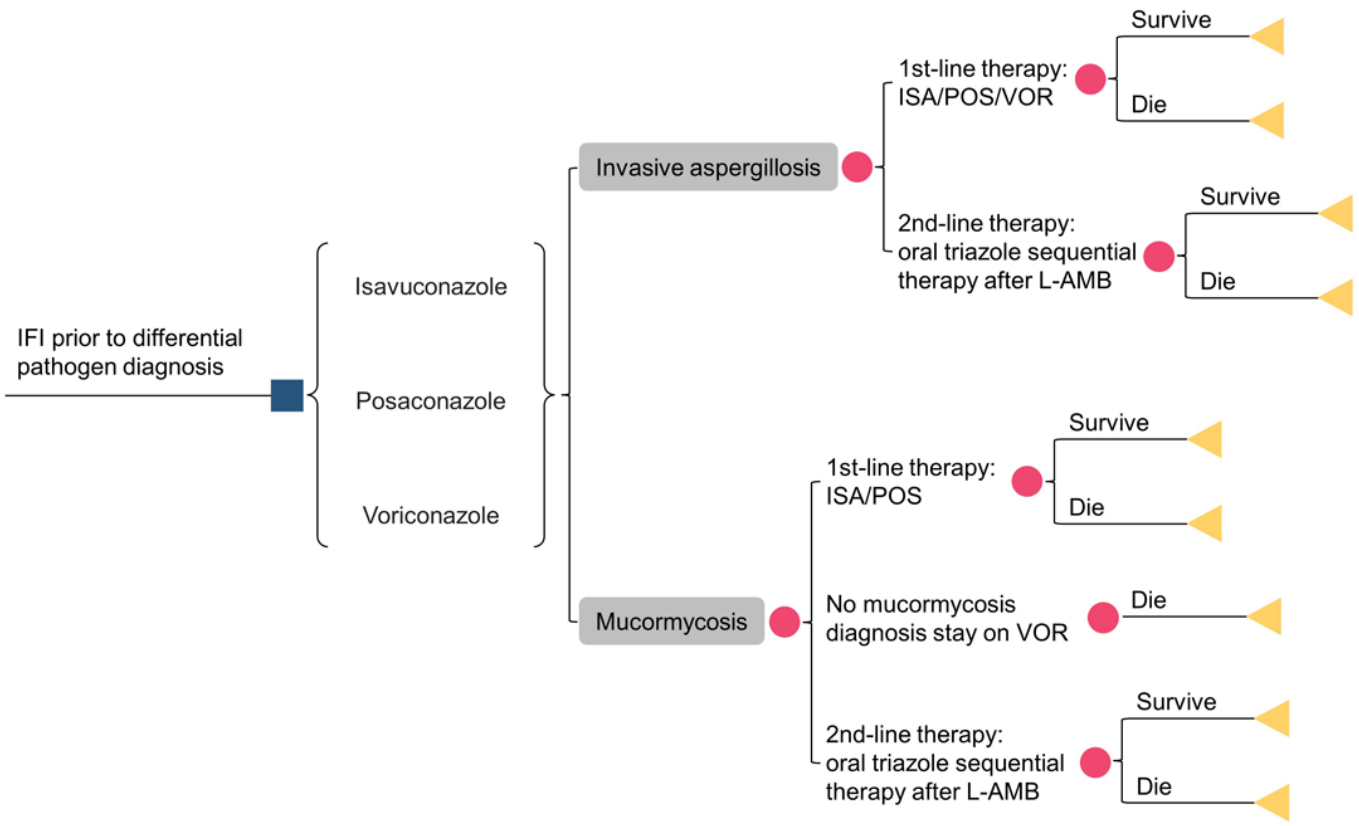

Figure 1

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Figure 2

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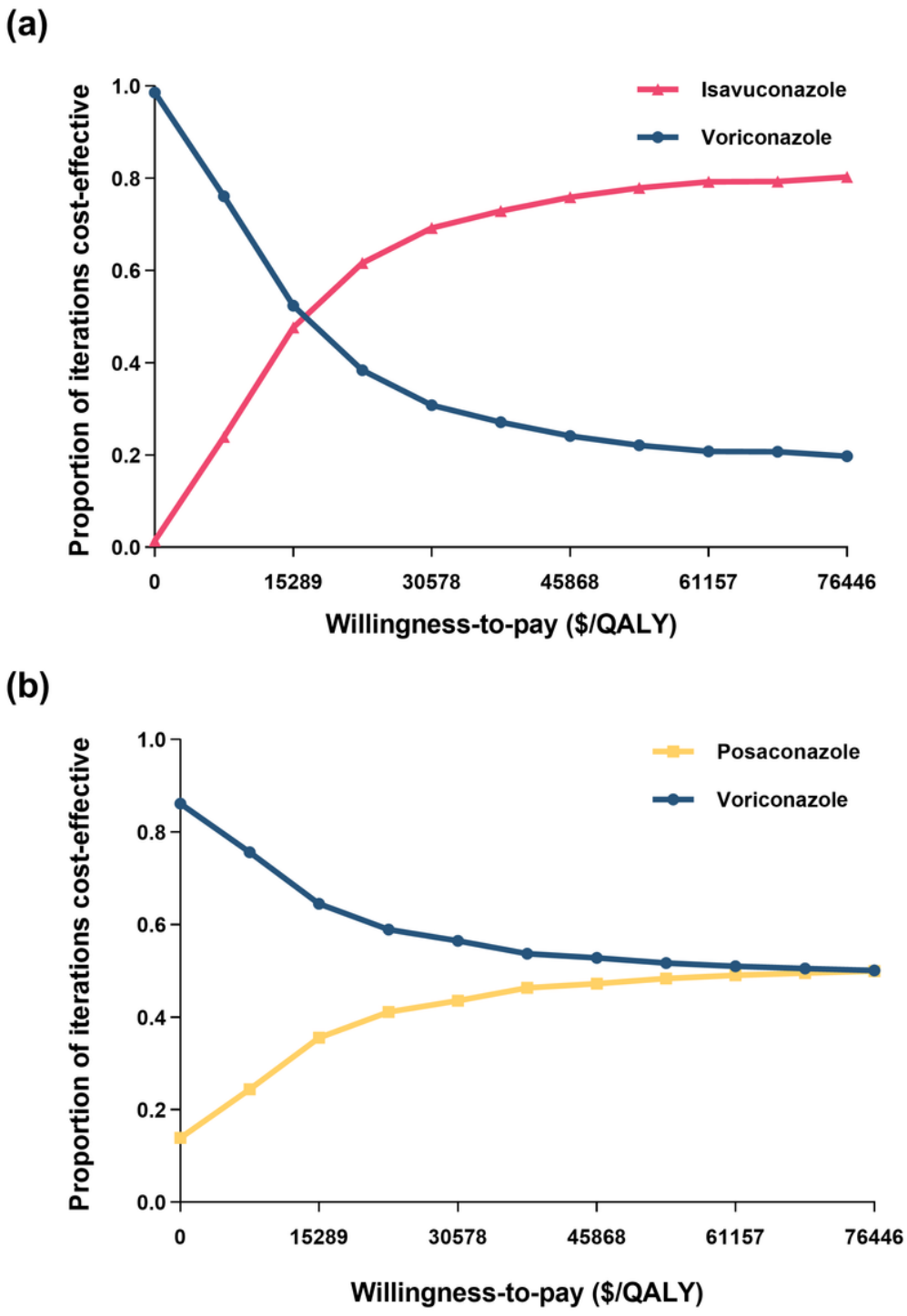

Figure 3

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