

COST-EFFECTIVENESS ANALYSIS OF ISAVUCONAZOLE FOR THE TREATMENT OF INVASIVE ASPERGILLOSIS IN THE CZECH REPUBLIC

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BACKGROUND

Achieving a prompt pathogen confirmation in invasive fungal infections (IFIs) can be extremely difficult, particularly in the case of a differential diagnosis between invasive aspergillosis (IA) and mucormycosis. As a result, the treatment of IFIs is commonly initiated on the basis of patient risk factors and clinical and radiological signs, before the causal pathogen has been confirmed.¹ Nevertheless, IA and mucormycosis may be associated with mortality approaching 100% if untreated or if effective treatment is delayed.²⁻⁴

Prompt administration of appropriate antifungal therapy plays, therefore, a vital role to avoid poor outcomes. However, in the absence of differential diagnosis between IA and mucormycosis, this can be a challenge, unless the initial treatment covers both pathogens. The results of the SECURE⁵ and VITAL⁶ studies indicate that isavuconazole is appropriate, as it is active against both *Aspergillus* and *Mucorales* species. Consequently, it may offer not only clinical but also economic benefit relative to treatments without *Mucorales* coverage, such as voriconazole.

OBJECTIVE

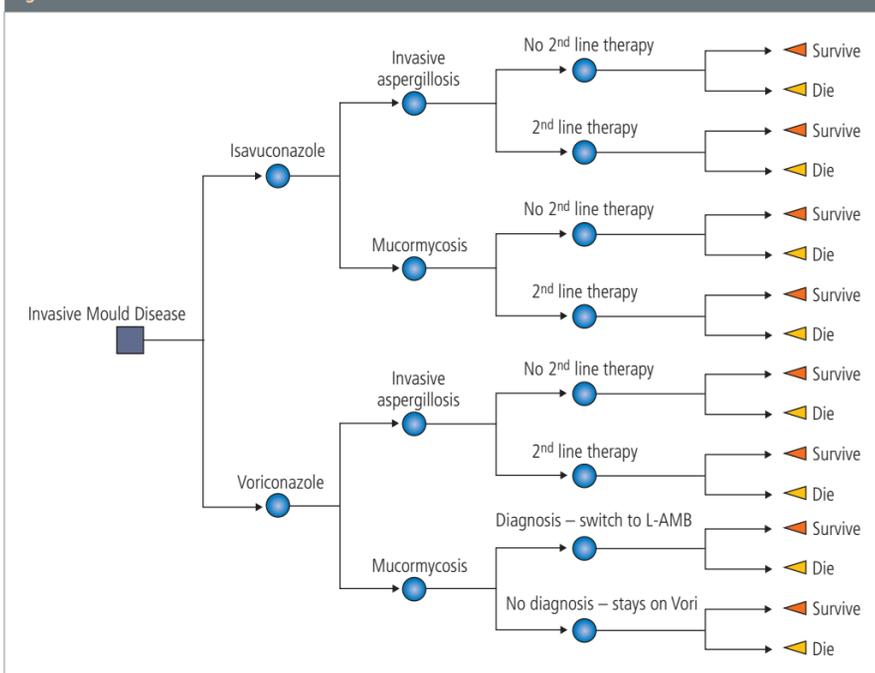
- The main objective was to assess the cost-effectiveness of isavuconazole for the treatment of presumed invasive aspergillosis (IA) in Czech adult patients when, at the point of treatment initiation, a differential diagnosis between IA and mucormycosis has not been achieved.
- Isavuconazole was compared to the standard of care (SoC, i.e. voriconazole) which is ineffective against mucormycosis.

METHODS

A decision tree model (DT) was created to assess the cost-effectiveness. The DT was broken down in branches representing the presence of either IA or mucormycosis. Figure 1 illustrates its structure and Table 1 outlines its settings. The examined patient population was composed of individuals presumed of having IA, with a certain percentage actually having mucormycosis. For IA, tree branches for both treatment strategies replicated the SECURE⁵ study. The isavuconazole-mucormycosis branch replicated the VITAL⁶ as well as the SECURE⁵ study (Table 2, Table 3). In this group, it was assumed that pathogen information did not alter the patient pathway. On the other hand, patients with mucormycosis receiving voriconazole were assumed to be receiving treatment as per IA (if no pathogen information becomes available) or to switch to liposomal amphotericin-B (if pathogen information becomes available). Finally, patients not responding to initial treatment underwent second-line treatment with liposomal amphotericin-B in both arms.

The model projects quality-adjusted life-years (QALYs) and costs from healthcare payers' perspective. Table 4 presents drug costs, that were based on list prices and reimbursement tariffs as of 02/2018. The results were extrapolated to a lifetime horizon using the average life expectancy⁷ and quality of life⁸ relevant to the underlying health condition of patients treated for invasive mould disease – i.e. acute myeloid leukaemia (Table 5). Costs, as well as outcomes, were discounted by 3%. One-way sensitivity analysis (OWSA) accompanied by scenario analysis (SA) explored the impact of all considered variables and several assumptions on the base-case result. Probabilistic sensitivity analysis (PSA) using 1,000 iterations was performed using an implicit willingness-to-pay (WTP) threshold equal to 3-times GDP per capita, i.e. approx. €47,000/QALY, in the Czech Republic. Table 6 summarizes the PSA settings.

Figure 1. Decision-tree model structure



RESULTS

- Isavuconazole compared to voriconazole yields over a lifetime horizon additional 0.30 QALYs (7.80 vs. 7.50) at the additional total cost of €3,011 (€18,373 vs. €15,362) (Table 7).
- The incremental cost-effectiveness ratio thus equals €10,090 per QALY gained.
- In the case of QALYs, the difference between the two comparators was mainly due to the differing effects of the two treatments in patients with mucormycosis.
- The probability of isavuconazole to be cost-effective is 80.4% at the WTP threshold, as shown in Figure 2.
- OWSA and SA confirmed the robustness of the base-case result. The tornado diagram in Figure 3 shows that the most influential were changes in mortality and costs.

Table 1. Summary of the model settings

Perspective	Healthcare payer's (public health insurance)
Analysis type and model type	Cost-utility analysis, Decision-tree model
Software	Microsoft Excel 2013
Time horizon	Life-time
Discount rate	3% for costs and outcomes
Patient population	Patients presumed of having IA, with a certain percentage actually having mucormycosis
Assessed intervention	Isavuconazole
Comparator	Voriconazole
Outcomes	Quality-adjusted life-years (QALYs)
Sensitivity analysis	Probabilistic, one-way and scenario analysis

Table 2. Percentage of patients switching to 2nd line treatment

Invasive mould disease	Treatment	2 nd line %
IA	Isavuconazole	47.67%
	Voriconazole	47.67%
Mucormycosis	Isavuconazole	33.33%
	Voriconazole	100.00%

Table 3. Death rate

Invasive mould disease	Treatment	Death rate %
IA	Isavuconazole	29.07%
	Voriconazole	29.07%
	L-AMB + posaconazole	29.07%
Mucormycosis	Isavuconazole	42.86%
	Delayed therapy - Abelcet	82.86%
	Untreated	96.20%

Figure 2. Incremental cost-effectiveness scatter plot

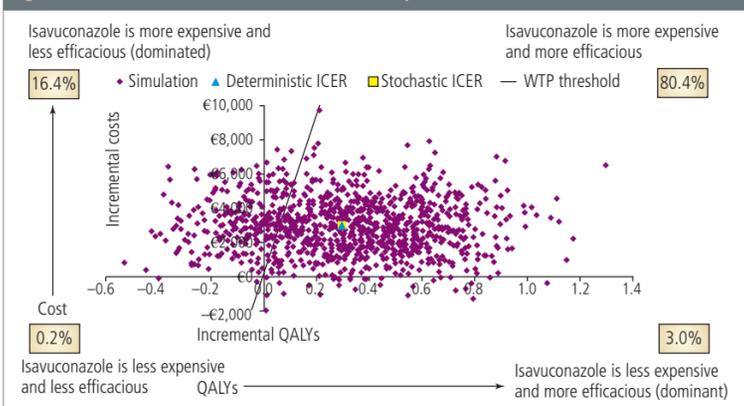


Table 4. Drug costs

Invasive aspergillosis			Mucormycosis		
Isavuconazole	Cost per long treatment course*	€9,386	Isavuconazole	Cost per long treatment course	€24,001
	Cost per short treatment course**	€4,822		Cost per short treatment course	€6,151
Voriconazole	Cost per long treatment course	€5,952	Voriconazole	Cost per course of voriconazole	€2,535
	Cost per short treatment course	€3,108		Cost per course of voriconazole – no pathogen information assumption	€4,596
2 nd line treatment	Cost of 2 nd line treatment	€8,982	2 nd line treatment	Cost of 2 nd line treatment	€21,402

*long treatment = without switching

**short treatment = length of treatment prior to switching to 2nd line treatment

Table 5. Utility value, life expectancy

Utility value ⁸	0.82
Life expectancy ⁷	17 years
Discounted life expectancy (3%)	13.56 years
Total QALY	11.12 QALY (13.56*0.82)

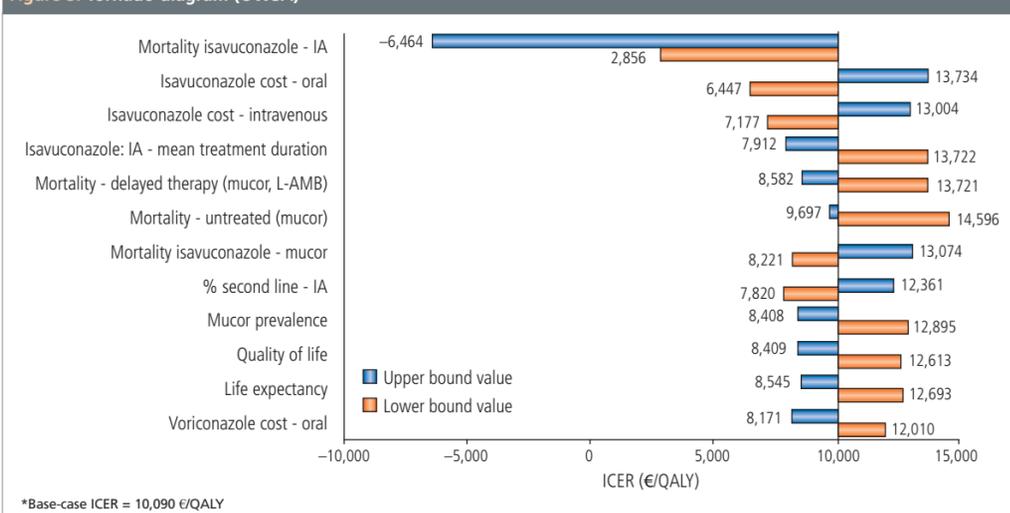
Table 6. PSA settings

Parameter	Distribution
Rates: 2 nd line treatment and death	Beta
Utilities	Beta
Costs	Gamma

Table 7. The results of cost-effectiveness analysis

		Costs					QALY
		Drug costs	Hospitalisation	Adverse events	Monitoring	Total	
Isavuconazole	IA	€10,832	€5,403	€195	€164	€16,594	7.43
	Mucor	€1,448	€293	€10	€29	€1,780	0.37
	Total	€12,280	€5,696	€205	€192	€18,373	7.80
Voriconazole	IA	€8,368	€5,403	€275	€181	€14,227	7.43
	Mucor	€820	€297	€13	€5.0	€1,135	0.07
	Total	€9,188	€5,700	€288	€186	€15,362	7.50
Increment					€3,011	0.30	
ICER		€10,090 / QALY					

Figure 3. Tornado diagram (OWSA)



*Base-case ICER = 10,090 €/QALY

CONCLUSIONS

The analysis demonstrates that prompt administration of effective antifungal therapy may prolong life when an invasive fungal disease is suspected. Isavuconazole has broad coverage and may, therefore, be appropriate as well as cost-effective in the case when the final diagnosis is not yet available.

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