RESEARCH ARTICLE

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The cost of treating mucormycosis with isavuconazole compared with standard therapy in the UK

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Aim: Mucormycosis is a fungal infection associated with high mortality. Until recently, the only licensed treatments were amphotericin B (AMB) formulations. Isavuconazole (ISAV) is a new mucormycosis treatment. A UK-based economic model explored treatment costs with ISAV versus liposomal AMB followed by posaconazole. **Materials & methods:** As a matched case–control analysis showed similar efficacy for ISAV and AMB, a cost-minimization approach was taken. Direct costs – drug acquisition, monitoring and administration, and hospitalization costs – were estimated from the National Health Service perspective. **Results:** Per-patient costs for ISAV and liposomal AMB + posaconazole were UK£26,810 and UK£41,855, respectively, with savings primarily driven by drug acquisition and hospitalization costs. **Conclusion:** ISAV may reduce costs compared with standard mucormycosis therapy.

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Mucormycosis is a rapidly progressive and life-threatening invasive fungal disease [1,2]. Although rare – affecting around 0.06–0.16 people per 10,000 globally each year [3–5] – the threat of mucormycosis is growing, as the size of the at-risk population, comprising mainly immunocompromised and critically ill patients, is increasing [6]. Mortality rates for mucormycosis of 17–66% have been reported in recent studies [1–2,6–10]; however, these can rise to over 90% in cases of disseminated infection [11].

The cost of treating patients with mucormycosis is considerable, with total costs more than threefold higher for mucormycosis patients compared with matched controls at high risk of mucormycosis infection [7]. The contribution of antifungal drugs toward total treatment costs is substantial [12,13]; one evaluation reported antifungal costs of UK£17,752 for hematology patients with proven/probable invasive fungal infections in 2010 [12]. Surgical debridement and adverse events (AEs) management can also add to total treatment costs and increase the duration of hospital stays [14,15].

Until recently, the only licensed antifungal therapies for mucormycosis were amphotericin B (AMB) formulations, with liposomal AMB (L-AMB) currently the standard of care in Europe [14]. However, L-AMB carries a considerable risk of renal toxicity [16,17], which has been linked with dose reductions and discontinuations [17,18]. It is also not available as an oral formulation [16] and,

KEYWORDS

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- healthcare • invasive fungal infection
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- liposomal amphotericin B
- mucormycosis
- posaconazole

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if outpatient maintenance therapy is required, an off-label step-down to oral posaconazole (POSA) has been suggested [19]. However, there is no evidence from prospective clinical trials to support the use of POSA in mucormycosis [20], and switches in drug class, such as this, carry the risk of treatment failure or disease progression.

Isavuconazole (ISAV) is a broad-spectrum, triazole antifungal [21], indicated in the EU in adults for the treatment of mucormycosis in patients for whom AMB is inappropriate, and for invasive aspergillosis [22]. ISAV's efficacy in the primary treatment of mucormycosis was comparable with that of AMB ± POSA in a matched case–control analysis of ISAV-treated patients with proven/probable mucormycosis from the global, Phase III, single-arm VITAL study with AMB (mainly L-AMB) ± POSA-treated patients from the FungiScope™ global registry database of emerging fungal infections (day 42 crude all-cause mortality 33% of 21 ISAV patients vs 39% of 33 AMB patients) [23]. ISAV has also been shown to be well tolerated compared with voriconazole, the standard of care therapy for invasive aspergillosis [24].

To evaluate the impact of ISAV with respect to healthcare resource use, a health-economic model was developed to estimate the per-patient cost of treating mucormycosis in the UK with ISAV alone compared with L-AMB followed by maintenance POSA.

Materials & methods

• Model structure & key assumptions

A cost-minimization approach was chosen to model the per-patient cost of mucormycosis treatment with ISAV compared with a regimen of L-AMB followed by maintenance therapy with POSA. As the matched case–control analysis of the VITAL study and FungiScope registry demonstrated no significant difference in day 42 all-cause mortality between ISAV and AMB ± POSA in the primary treatment of mucormycosis [23], ISAV and L-AMB + POSA were assumed to have equivalent efficacy and only differences in costs between the treatments were considered in the model. Treatment modalities for ISAV and L-AMB were assumed to be as per the regimens described in the matched case–control analysis.

The model was developed from the perspective of the UK National Health Service, and evaluated direct treatment costs incurred by treating patients with mucormycosis. Total

costs comprised drug acquisition, intravenous (iv.) drug preparation and administration, monitoring, and hospitalization costs (Figure 1).

The model time horizon was from onset to completion of mucormycosis treatment, at either resolution of the Mucorales infection or death. Costs were calculated in 2016 UK£, with source values adjusted using a UK consumer price index where necessary [25].

• Model parameters

Drug acquisition

Drug acquisition costs included only the cost of ISAV, L-AMB and POSA. Dosing for ISAV was calculated in accordance with its Summary of Product Characteristics (SmPC; 2 × 100 mg oral capsules per day or 1 × 200 mg vial per day, loading dose on day 1 and 2 of 600 mg [3 × 200 mg]) [22]. As POSA is not indicated for mucormycosis, the doses recommended in its SmPC for the treatment of refractory invasive fungal infections [26] were used in the model (3 × 100 mg oral tablets per day, loading dose on day 1 of 600 mg [2 × 300 mg]). The model considered the costs of the tablet form and not the oral suspension (which was received by the FungiScope cohort), as this is now recommended owing to higher bioavailability [21,22]. For L-AMB, a daily dose of 5 mg/kg was assumed, based on the median dose of L-AMB received by the FungiScope cohort [23] and as recommended in European clinical guidelines [14]. L-AMB dosing requirements were calculated using the patient weight distribution from the mucormycosis primary therapy population of the VITAL study (mean 75.9 kg, SD 19.9 kg).

In the VITAL study, 14.3% of mucormycosis patients who received ISAV as primary therapy were initiated on oral therapy; this proportion was therefore also assumed in the model. Treatment durations for ISAV (15.5 days iv. therapy followed by 133.5 days oral therapy; patients initiated on oral therapy received 0 days iv. and 149.0 days oral therapy) and L-AMB (27.2 days iv. therapy) were derived from the means of the mucormycosis primary therapy population of the VITAL study and the AMB-treated cohort of the FungiScope registry, respectively. As too few FungiScope patients received POSA to ensure an adequate sample size for the treatment duration ($n = 12$), a conservative assumption was made that the duration of POSA would be set to equal the mean total duration of ISAV treatment

Figure 1. Model structure.

[†]Including loading dose as applicable.

ISAV: Isavuconazole; iv.: Intravenous; L-AMB: Liposomal amphotericin B; POSA: Posaconazole.

in the VITAL study minus the mean duration of iv. AMB treatment in the FungiScope cohort. Drug acquisition costs for L-AMB and POSA were taken from the British National Formulary [27], while the unit cost of ISAV was taken from the Monthly Index of Medical Specialities [28] (Table 1).

Monitoring & administration

The costs of performing urinalysis, serum creatinine tests and liver-function tests were included in the model (Table 1). Based on the AEs and precautions listed in each product's SmPC, it was assumed that patients treated with L-AMB + POSA would require weekly monitoring with all three tests and patients treated with ISAV would have fortnightly liver-function testing only.

Therapeutic drug monitoring (Table 1) was assumed to be required twice over the course of treatment for L-AMB + POSA, based on British Society for Medical Mycology recommendations to perform therapeutic drug monitoring in patients receiving POSA [33]. Therapeutic drug monitoring is not a standard recommendation for ISAV [22], and was therefore not included for the ISAV arm of the model.

iv. administration costs (Table 1) were based on an administration time of 5 min and 51 s published elsewhere [31], and nursing salaries

as reported by the Personal Social Services Research Unit [32].

Hospitalizations

Hospitalization costs (Table 1) were estimated by multiplying the duration of hospital stay by the daily cost of a hematology ward bed [12], as hematology patients were considered to be representative of the patient group that is at risk of mucormycosis [6,34]. For ISAV, the length of hospital stay was set to 19.3 days – the mean duration of initial hospitalization of patients who received ISAV as primary therapy in VITAL. For L-AMB + POSA, patients were assumed to remain hospitalized for the duration of iv. therapy (27.2 days).

• Scenario analyses

Scenario analyses were performed to test uncertainty in the model parameters. The base-case analysis assumed that most ISAV patients started on iv. therapy. However, as both the iv. and oral formulations of ISAV can be given as initial therapy, and given the potentially large cost-impact if the proportion of patients on either formulation were to be changed, two scenario analyses were performed in which this composition was altered. In the first, 100% of ISAV patients started on oral therapy and in the second, 100% started on iv., before moving to oral therapy as appropriate.

Table 1. Acquisition costs.

Cost factor	Unit cost (£)
Drugs: [†]	
– ISAV (200 mg vial)	297.84
– ISAV (14-pack of 100 mg tablets)	599.28
– L-AMB (50 mg vial)	82.19
– POSA (24-pack of 100 mg tablets)	595.96
Urinalysis, serum creatinine test, liver function test [‡]	0.83
Therapeutic drug monitoring [§]	58.51
iv. administration [¶]	3.53
Hospital bed day [#]	523.33

[†]Based on British National Formulary [27] and Monthly Index of Medical Specialities list prices [28].
[‡]Based on Scottish health service costs for clinical chemistry tests [29].
[§]Based on the price listed by the Mycology Reference Centre, Manchester [30].
[¶]Based on an administration time of 5 min and 51 s published elsewhere [31], and nursing salaries as reported by the Personal Social Services Research Unit [32].
[#]Based on the daily cost of a hematology ward bed [12].
 ISAV: Isavuconazole; iv.: Intravenous; L-AMB: Liposomal amphotericin B; mg: Milligram; POSA: Posaconazole.

A further scenario analysis was performed, in which the duration of L-AMB + POSA treatment was varied. The base-case analysis assumed an L-AMB duration equal to the mean duration of AMB received in the FungiScope cohort. The duration of POSA was calculated by taking this from the mean duration of ISAV in the VITAL primary therapy population. In the scenario analysis, the L-AMB and POSA durations were set to the mean duration of AMB and POSA administered to the subset of FungiScope patients who received AMB followed by POSA ($n = 12$; 25.3 days L-AMB; 200.4 days POSA).

Finally, although the base-case analysis was undertaken in the primary treatment setting, ISAV is indicated when AMB is inappropriate. To estimate the cost of ISAV treatment in this indication, and to determine whether costs would change across patient populations, two additional analyses were performed. The first used the mean duration of therapy for VITAL patients with disease refractory to prior antifungal treatment ($n = 11$, 91% of whom received prior AMB; 22.8 days iv. therapy, 94.2 days oral therapy) and the second used the mean duration of therapy of patients intolerant to prior treatment ($n = 5$, 60% of whom received prior AMB; 17.3 days iv. therapy, 80.1 days oral therapy). The results of these analyses were compared with the cost of ISAV treatment in the primary setting. For these analyses, comparisons with L-AMB + POSA were not considered suitable, given L-AMB's primary-treatment indication.

Results

• Base case

In the base-case analysis, the total per-patient cost of mucormycosis treatment was UK£26,810 with ISAV versus UK£41,855 with L-AMB + POSA (**Table 2 & Figure 2**). This represents a saving of 36% with ISAV relative to L-AMB + POSA. Savings were primarily driven by lower iv. drug acquisition costs for ISAV than for L-AMB (UK£4978 vs UK£18,189) in addition to lower hospitalization costs (UK£10,100 vs UK£14,235). The combined cost of monitoring and administration was also lower with ISAV than with L-AMB + POSA (UK£64 vs UK£269).

• Scenario analyses

Several scenario analyses were performed. In the first two, the proportion of ISAV patients initiated on iv. or oral therapy was varied. When 100% of ISAV patients started on oral therapy, total per-patient costs were UK£18,592 less with ISAV than with L-AMB + POSA, and when 100% of ISAV patients started on iv. therapy, per-patient costs were UK£14,813 less than with L-AMB + POSA (**Figure 3**).

In another scenario analysis, the treatment durations for L-AMB + POSA were set to the means derived from the subset of FungiScope patients who received AMB + POSA. Here, ISAV was UK£19,633 less costly per patient than the comparator combination (**Figure 4**).

In the final scenario analyses, the duration of ISAV treatment was taken from that of VITAL study patients unsuitable for AMB treatment.

Table 2. Results of base-case cost-minimization analysis.

Cost source	ISAV		L-AMB + POSA		(L-AMB + POSA) – (ISAV)
	Resource use	Cost (£)	Resource use	Cost (£)	Savings £ (% change)
iv. drug	15.5 days [†]	4978	27.2 days	18,189	13,210 (73)
Oral drug	133.5 days [†]	11,668	121.8 days	9163	-2504 (-27)
Total drug acquisition	149.0 days	16,646	149.0 days	27,352	10,706 (39)
Hospitalization	19.3 days	10,100	27.2 days	14,235	4134 (29)
Monitoring and administration	11.6 tests [‡]	64	68.9 tests [‡]	269	204 (76)
Total costs		26,810		41,855	15,045 (36)

[†]Patients initiated on oral therapy received 0.0 days iv. and 149.0 days oral therapy.

[‡]ISAV patients underwent 11.6 liver-function tests; L-AMB + POSA patients underwent 2.0 instances of therapeutic drug monitoring plus 22.3 of each of the following: urinalysis, serum creatinine tests and liver-function tests.

ISAV: Isavuconazole; iv.: Intravenous; L-AMB: Liposomal amphotericin B; POSA: Posaconazole.

When the treatment duration of patients with refractory disease was used, total per-patient costs for ISAV were UK£25,425, compared with UK£26,810 in the base-case analysis (**Figure 5**). When the duration of ISAV treatment was taken from VITAL study patients intolerant to prior antifungal treatment, total per-patient costs for ISAV were UK£22,727.

Discussion

A health-economic model was developed to compare the per-patient costs of treating mucormycosis with ISAV compared with L-AMB followed by oral maintenance POSA in the UK. The model estimated that use of ISAV as therapy against mucormycosis is likely to lead

to substantial cost savings relative to L-AMB + POSA, primarily attributable to lower drug acquisition costs for ISAV compared with L-AMB, as well as lower hospitalization costs for the ISAV regimen.

Several scenario analyses were performed. When the proportion of ISAV patients starting on iv. or oral therapy was varied, ISAV remained cost saving relative to L-AMB + POSA. Similarly, when the duration of L-AMB + POSA treatment was altered to reflect the duration of treatment in the subset of FungiScope patients who received AMB followed by POSA, ISAV remained cost saving. When the duration of ISAV treatment was changed to that observed with refractory or intolerant patients in the VITAL study, total treatment costs were

Figure 2. Results of base-case cost-minimization analysis.

ISAV: Isavuconazole; L-AMB: Liposomal amphotericin B; POSA: Posaconazole.

Figure 3. Results of scenario analyses: variation in proportion of isavuconazole patients starting on oral or iv. therapy.
 ISAV: Isavuconazole; iv.: Intravenous; L-AMB: Liposomal amphotericin B; POSA: Posaconazole.

similar to those for ISAV in the primary therapy setting, suggesting that ISAV treatment costs are likely to remain stable across different populations.

Given the rarity of mucormycosis, few studies have examined the cost of treatment; this is the first to evaluate the cost of mucormycosis treatment with ISAV. However, the key underlying assumption of the cost-minimization analysis – that of equal efficacy between ISAV and AMB – can be verified by comparison of outcomes in the VITAL study with those of historical studies of AMB-treated control populations. Three studies have been identified that can be considered similar in design to VITAL, as they included at least 20 patients treated with AMB-based regimens (majority L-AMB) and measured response to treatment according to accepted definitions from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [35]. All of these studies reported similar rates of complete or partial overall response to AMB therapy at the end of treatment (ranging from 32 to 42% [8,18,36]) to those seen with ISAV in the VITAL study, in both the overall VITAL mucormycosis population (31%), and the subset receiving primary therapy (32%) [23] (Table 3).

In the three historical control studies, the daily doses of AMB administered were generally higher than the median dose of L-AMB in the FungiScope cohort, which was used for the model (Lanternier *et al.* 10 mg/kg [18], Shoham *et al.* 3–14 mg/kg [36], Xhaard *et al.* not reported [8], FungiScope cohort 5 mg/kg [23]). Therefore, the modeled savings with ISAV relative to L-AMB + POSA described here may be considered conservative estimates.

A limited number of studies have investigated the cost of treating mucormycosis using AMB. Ibrahim *et al.* modeled data from a retrospective study to estimate the annual in-hospital cost of mucormycosis to the US healthcare system at US\$97,743. They found that the average drug costs associated with AMB formulations amounted to US\$14,085 (2007) – equivalent to ~UK£7,201 – per patient [13]. When compared with the cost of iv. L-AMB generated by our model (UK£18,189), this value seems low. However, the Ibrahim study analyzed the cost of various AMB formulations, whereas the model presented here considered only the recommended formulation, L-AMB [14]. In addition to drug costs, Ibrahim *et al.* found the average duration of hospitalization to be 35 days. This is greater than the length of stay for L-AMB used in the current model and suggests that estimates of

hospitalization costs for L-AMB in the model may be conservative.

The model has several limitations. In the case of a rare disease like mucormycosis, where the availability of data is low, creating an accurate model is particularly challenging, and indirect evidence and assumptions must be used more frequently than is desirable. In addition, as the input values were based on a small number of patients (21 primary therapy patients from VITAL for ISAV and 33 from the FungiScope registry for L-AMB + POSA), the current model did not include sensitivity analyses; any results derived under these conditions would not be meaningful. A head-to-head trial between ISAV and L-AMB + POSA, reporting both clinical and resource use outcomes, would be preferable; however, the feasibility of conducting such a trial in a rare disease is low [37]. Future experience with ISAV in clinical practice will be useful to corroborate many of the assumptions made in the current model and will provide data with respect to cost–effectiveness in the real-world setting.

In addition to excluding the effect of AEs on patient utility, the current model did not evaluate their cost impact. The available AE data for ISAV and L-AMB were considered too different to make a robust comparison. Given that AE rates would have been sourced from separate

trials and that the types of AEs commonly associated ISAV and L-AMB are very different in nature [16,22], a standardized method of comparison would be very challenging to develop.

The model did not include several in-hospital costs likely to be incurred during mucormycosis treatment, namely the costs of surgery, imaging, or any additional treatments. For instance, non-mucormycosis-active antifungals, such as voriconazole or fluconazole, may be given prior to the modeled treatments, before confirmation of diagnosis and administration of targeted treatment. Although these costs could vary between ISAV and L-AMB + POSA, with a large potential impact on the total cost of mucormycosis treatment, they were not included in the model, as there is no evidence to suggest a difference in the need for surgery or prior treatment between ISAV and L-AMB. Had these costs been included, total costs would have likely risen by the same amount for each comparator. It should also be noted that use of ISAV or L-AMB early in the course of treatment may reduce costs associated with the inappropriate use of narrower-spectrum antifungals that lack activity in mucormycosis.

A further point is that cost-minimization modeling permits only a narrow scope of outcomes to be presented and limits the comparisons that can be made between treatments with respect to their economic impacts. Although,

Figure 4. Results of scenario analysis: variation in duration of liposomal amphotericin B + posaconazole treatment based on FungiScope™ cohort.

ISAV: Isavuconazole; L-AMB: Liposomal amphotericin B; POSA: Posaconazole.

Figure 5. Results of scenario analyses: variation in isavuconazole treatment duration based on primary, refractory and intolerant patients in VITAL. ISAV: Isavuconazole.

for the current analysis, this approach was considered appropriate, a cost–utility approach, for example, would have allowed for a more rounded health–economic evaluation, including patient utility. As more data become available, more sophisticated analyses may be performed. Finally, it should be noted that the applicability of our model is limited to the current UK perspective; any extrapolation of the results to other countries or time periods should be made with caution. Differences in healthcare systems, approaches to treating mucormycosis

and changes in unit costs over time will affect treatment costs. Tied to this point, our analysis is limited by the fact that a global patient population was used to inform efficacy comparisons for the UK model. Efficacy outcomes and treatment regimens may have differed if a strictly UK-based population had been used, which could have affected resource use and costs.

Conclusion

Mucormycosis is a life-threatening fungal infection, with few treatment options. The

Table 3. Overall response to treatment in VITAL and historical amphotericin B -treated controls at end of treatment.					
Overall response to treatment (%)	Study population				
	Shoham <i>et al.</i> [36] n = 28	Xhaard <i>et al.</i> [8] n = 24	Lanternier <i>et al.</i> [18] n = 33	VITAL, all mucormycosis patients n/n = 35/37 [†]	VITAL, primary therapy mucormycosis patients n/n = 19/21 [†]
Complete response	32 complete + partial	29	18	14	16
Partial response		13	18	17	16
Stable disease	11	58 stable + progression	12	29	32
Disease progression	57		52	40	37

[†]Two patients were receiving treatment at the time of database lock and had no end-of-treatment assessment.

current standard of care, L-AMB, has been used for many years for the treatment of mucormycosis but has limitations, for example, it carries a risk of renal toxicity and is only available as an iv.-administered formulation. ISAV is a recently licensed treatment for mucormycosis in adults for whom AMB is inappropriate. ISAV has comparable efficacy to AMB, an acceptable safety profile, and is available in both iv. and oral formulations. Results from the current model suggest that the use of ISAV can potentially reduce the cost of treating patients with mucormycosis compared with a regimen of L-AMB followed by oral POSA. ISAV may prove to be a cost-effective option for the treatment of mucormycosis; however, further health-economic evaluations are needed to confirm this.

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EXECUTIVE SUMMARY

- Mucormycosis is a rapidly progressive fungal infection, with a high risk of mortality, which affects mainly immunocompromised and critically ill people.
- The cost of treating patients with mucormycosis is substantial, largely owing to the prolonged use of high-cost antifungals.
- Liposomal amphotericin B (L-AMB) – the standard treatment for mucormycosis in the UK – carries a risk of renal toxicity and is only available as an intravenous-administered formulation.
- Isavuconazole (ISAV) is a new treatment for mucormycosis in adults for whom AMB is inappropriate.
- A cost-minimization model was developed from the perspective of the UK National Health Service to explore the per-patient cost (drug acquisition, monitoring and administration, and hospitalization costs) of treating mucormycosis with ISAV versus L-AMB followed by posaconazole (POSA).
- Total per-patient treatment costs were estimated to be UK£26,810 with ISAV versus UK£41,855 with L-AMB + POSA.
- Savings were primarily driven by lower drug acquisition costs with ISAV relative to L-AMB, alongside lower hospitalization costs, since the iv.-to-oral switch occurred earlier for ISAV patients than for those who received LAMB + POSA.
- ISAV consistently remained cost saving across various scenario analyses designed to test the model parameters with most uncertainty.
- ISAV appears to be a cost-effective option for the treatment of mucormycosis; however, further health-economic evaluations are warranted.

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• of interest; •• of considerable interest

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