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The cost of treating invasive mould disease caused by *Aspergillus* and other filamentous fungi with isavuconazole compared with liposomal amphotericin B followed by posaconazole in the United Kingdom

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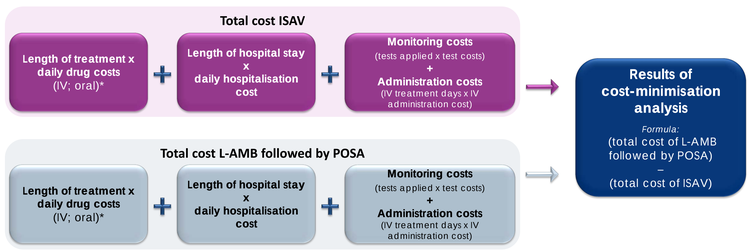
Introduction and Purpose

- Invasive mould diseases (IMDs) – severe infections caused by *Aspergillus* species and other filamentous fungi, such as Mucorales – typically affect immunocompromised individuals and can be associated with high mortality[1,2] and treatment costs[3–6].
- Differentiation between IMD types can be challenging[7] – treatment is commonly started before a differential diagnosis is made (*Aspergillus* vs Mucorales) and, in many cases, a definitive diagnosis may never be achieved[8].
- In the absence of a differential diagnosis, where coverage for both *Aspergillus* and Mucorales is required, the options for first-line antifungal treatment were historically limited to intravenous (IV) liposomal amphotericin B (L-AMB)[9]. A step down to oral posaconazole (POSA) is possible, although it is only indicated for salvage therapy[10].
- Isavuconazole (ISAV) is a recently approved IV and oral, broad-spectrum triazole antifungal, which has activity against both *Aspergillus* and Mucorales[11].
- ISAV has comparable efficacy to L-AMB in the treatment of invasive aspergillosis, as demonstrated in a mixed-treatment comparison (MTC) meta-analysis[12], which included the phase 3, double-blind SECURE study for ISAV[13] and two studies of L-AMB[14,15].
- ISAV also has comparable efficacy to L-AMB in the treatment of mucormycosis, as demonstrated in a case-control analysis between the phase 3 VITAL study and the FungiScope™ registry[16].
- A health-economic model was developed to explore the per-patient cost to the United Kingdom (UK) National Health Service (NHS) of treating adults requiring primary therapy for IMD with ISAV alone, compared with L-AMB → POSA.

Methods

- As ISAV and L-AMB have comparable efficacy, the model took a cost-minimisation approach (Figure 1).
- The time horizon was until end of treatment at resolution of infection, or death.

Figure 1 Model structure



*Including loading dose as applicable; see Figure 2

Key assumptions

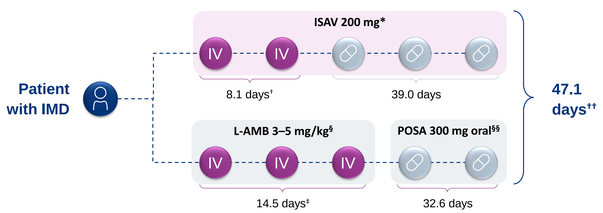
- No differences in clinical outcomes between treatment arms.
- Treatment regimens as in clinical studies (ISAV: SECURE/VITAL[13,16,17], L-AMB: MTC studies – Leenders et al.[14], Cornely et al.[15]).
- Patients initiated on L-AMB received oral step-down therapy with POSA tablets.

Model parameters

Drug acquisition

- Antifungal drug administration regimens are presented in Figure 2.
- Based on data from invasive aspergillosis patients in the VITAL study, 25% of ISAV patients were assumed to start on oral therapy[18]. The remainder started on IV therapy, before moving to oral therapy.
- It was assumed that 100% of L-AMB → POSA patients received IV L-AMB before stepping down to oral POSA.
- UK list prices were used for all drugs:
  - L-AMB: £82.19 per 50 mg vial[19].
  - POSA: £596.96 per 24-pack of 100 mg tablets[19].
  - ISAV: £599.28 per 14-pack of 100 mg capsules and £297.84 per 200 mg vial[20].
- Any drug wastage incurred through the need for weight-based dosing of L-AMB – which is only available in 50 mg vials that should not be stored for future administration once partially used[9] – was included in the total drug volume.

Figure 2 Drug regimens



*If initiating treatment, loading dose on day 1 and 2 of 600 mg (3 x 200 mg)[11]; †Based on mean ISAV duration in SECURE intention-to-treat population. 25% of ISAV patients assumed to start on oral therapy and receive 0.0 days IV and 47.1 days oral therapy[17]; ††Total treatment duration in both arms assumed to be equal to mean total duration of ISAV in SECURE study[17]; §50% of L-AMB patients received 3 mg/kg, 50% received 5 mg/kg. Dose based on range recommended in Infectious Diseases Society of America guidelines[21] and doses received by L-AMB patients in MTC studies[14,15], applied according to the weight distribution in SECURE study (mean 68.6 kg, standard deviation 16.4 kg) and dose; §§Dose for refractory invasive fungal infections used. Loading dose on day 1 of 600 mg (2 x 300 mg); ‡Based on median L-AMB duration in Leenders *et al.*[14]

Monitoring and administration

- The costs of performing urinalysis, serum creatinine tests, magnesium tests, and liver function tests were included at £1.00 per test, based on the 2014–15 NHS reference cost for Clinical Biochemistry[22], adjusted for inflation[23]. Based on adverse events and precautions listed in Summaries of Product Characteristics[9–11], patients treated with L-AMB → POSA were assumed to require urinalysis, serum creatinine tests, and liver function tests 7 times over the treatment course, plus 6 magnesium tests, while ISAV patients required 7 liver function tests.
- Therapeutic drug monitoring was included at £58.51 per sample, based on the price listed by the Mycology Reference Centre, Manchester[24]. Monitoring was included twice over the treatment course for L-AMB → POSA , in line with clinical guidelines[25], and once for ISAV.
- Administration costs of £18.08 and £6.03 were applied per IV administration of L-AMB and ISAV, respectively. These were calculated by multiplying administration times of 30 and 10 minutes, respectively, based on expert opinion, by the cost per working hour for a Band 5 hospital nurse (£36), as reported by the Personal Social Services Research Unit[26]. Costs were adjusted for inflation[23].

Hospitalisations

- Daily hospital costs of £477.66 were calculated as a weighted average of the 2014–15 NHS reference costs for elective and non-elective bed days for Malignant Disorders of Lymphatic or Haematological Systems[22], adjusted for inflation[23]. The rate for haematological and lymphatic disorders was selected as these patients were considered to be representative of the group that is at risk of IMD[1].
- The daily cost was multiplied by the mean duration of hospitalisation in the SECURE study (19.0 days) for ISAV. The duration of hospitalisation for L-AMB → POSA was assumed to be the same as for ISAV.

Scenario analyses

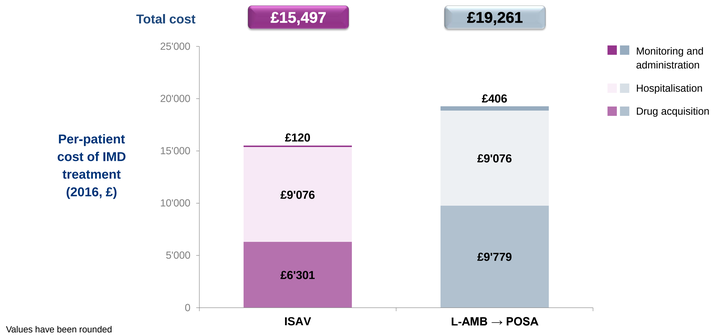
- The following scenario analyses were performed to test uncertainty in the model parameters:
  - All ISAV patients were initiated on IV therapy, and moved to oral therapy in line with the timings in the base case and, in an alternative scenario, all ISAV patients received oral therapy only.
  - As the recommended dose of L-AMB for IMD treatment can vary between 3 and 5 mg/kg[21], two further scenario analyses were performed, in which the dose of L-AMB was set to 3 mg/kg and 5 mg/kg, in turn.

Results

Base case

- Total per-patient IMD treatment costs were estimated to be 20% lower with ISAV than with L-AMB → POSA (£15,497 vs £19,261; Figure 3 and Table 1).
- Drug acquisition costs were the greatest driver of savings, due to a lower daily drug cost for ISAV than for L-AMB, combined with a shorter duration of IV therapy.
- Monitoring and administration costs were also lower with ISAV than with L-AMB → POSA.

Figure 3 Base case per-patient cost of invasive mould disease treatment



Values have been rounded

Table 1: Base case per-patient cost of invasive mould disease treatment

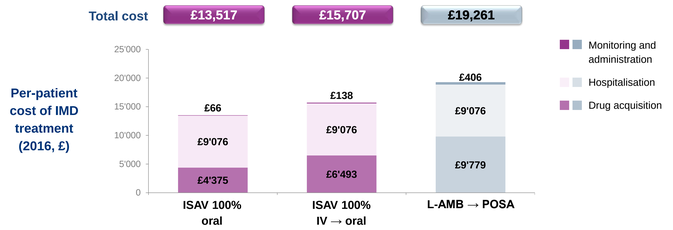
Cost source	ISAV resource use	ISAV, £	L-AMB → POSA resource use	L-AMB → POSA, £	[L-AMB → POSA] - [ISAV] £ (% change)
IV drug	*8.1 days*	*2,703*	*14.5 days*	*7,271*	*4,569 (63)*
Oral drug	*39.0 days*	*3,598*	*32.6 days*	*2,507*	*-1,091 (-43)*
Total drug acquisition	47.1 days	6,301	47.1 days	9,779	3,478 (36)
Hospitalisation	19.0 days	9,076	19.0 days	9,076	0 (0)
Monitoring and administration	8 tests, IV drug preparation	120	29 tests, IV drug preparation	406	286 (70)
Total cost		**15,497**		**19,261**	**3,764 (20)**

Values have been rounded

Scenario analyses

- When 100% of ISAV patients were initiated on either oral or IV therapy, ISAV remained cost saving relative to L-AMB → POSA (Figure 4).
- Total per-patient savings were £5,744 (30%) and £3,554 (18%) when 100% of ISAV patients were initiated on oral and IV therapy, respectively.

Figure 4: Results of scenario analysis: variation in proportion of ISAV patients initiated on oral or IV therapy



- When L-AMB doses of 3 mg/kg and 5 mg/kg were used, ISAV remained cost saving relative to L-AMB → POSA (Figure 5).
- Total per-patient savings with ISAV were £2,202 (12%) and £5,225 (25%) when L-AMB doses of 3 mg/kg and 5 mg/kg were used, respectively.

Figure 5: Results of scenario analysis: variation in L-AMB dose

Conclusions

- In this study:
  - Treatment of IMD with isavuconazole in the UK would be associated with cost savings relative to liposomal amphotericin B followed by posaconazole, regardless of whether patients started treatment with the IV or oral formulation of isavuconazole, or when the dose of liposomal amphotericin B was varied between 3 mg/kg and 5 mg/kg.
- While isavuconazole appears to be a cost-effective option for the treatment of IMD, further evaluations in other healthcare settings are warranted.

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Disclosures

This study was sponsored by Basilea Pharmaceutica International Ltd., Basel, Switzerland. Emma Bagshaw and Michael Blackney are employees of Covance Market Access, which was contracted by Basilea to provide support for this poster. Jan Posthumus, Christopher Longshaw, and Daniel Kuessner are employees of Basilea and hold stock options with Basilea. David Enoch and Paul Micallef-Eynaud have no conflicts they wish to disclose.

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