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Matched-paired analysis of patients treated for invasive mucormycosis: standard treatment versus posaconazole new formulations (MoveOn)

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Background: First-line antifungal treatment for invasive mucormycosis (IM) consists of liposomal amphotericin B. Salvage treatment options are limited and often based on posaconazole oral suspension. With the approval of posaconazole new formulations, patients could benefit from improved pharmacokinetics, safety and tolerability.

Objectives: Our aim was to assess the effectiveness of posaconazole new formulations for IM treatment.

Methods: We performed a case-matched analysis with proven or probable IM patients from the FungiScope® Registry. First-line posaconazole new formulations (1st-POS*new*) and first-line amphotericin B plus posaconazole new formulations (1st-AMB+POS*new*) cases were matched with first-line amphotericin B-based (1st-AMB) treatment controls. Salvage posaconazole new formulations (SAL-POS*new*) cases were matched with salvage posaconazole oral suspension (SAL-POS*susp*) controls. Each case was matched with up to three controls (based on severity, haematological/oncological malignancy, surgery and/or renal dysfunction).

Results: Five patients receiving 1st-POS*new*, 18 receiving 1st-AMB+POS*new* and 22 receiving SAL-POS*new* were identified. By day 42, a favourable response was reported for 80.0% (*n*=4/5) of patients receiving 1st-POS*new*, for 27.8% (*n*=5/18) receiving 1st-AMB+POS*new* and for 50.0% (*n*=11/22) receiving SAL-POS*new*. Day 42 all-cause mortality of patients receiving posaconazole new formulations was lower compared with controls [20.0% (*n*=1/5) in 1st-POS*new* versus 53.3% (*n*=8/15) in 1st-AMB; 33.3% (*n*=6/18) in 1st-AMB+POS*new* versus 52.0% (*n*=26/50) in 1st-AMB; and 0.0% (*n*=0/22) in SAL-POS*new* versus 4.4% (*n*=2/45) in SAL-POS*susp*].

Conclusions: Posaconazole new formulations were effective in terms of treatment response and associated mortality of IM. While posaconazole new formulations may be an alternative for treatment of IM, the limited sample size of our study calls for a cautious interpretation of these observations.

Introduction

Invasive mucormycosis (IM) is an emerging invasive fungal disease (IFD) with a considerable incidence in patients with haematological/oncological malignancies.[1,2] Compared with *Aspergillus* spp., however, Mucorales remain an unusual cause of IFD, being the causative pathogen of 8% of IFD in high-risk haematological/oncological patients, with a cumulative incidence of 0.29%.[3,4] Antifungal treatment, surgical debridement and correction of predisposing underlying conditions are crucial in the treatment of IM.[5,6] Despite this multimodal approach, reported mortality rates reach 91%.[1,2,7] We hypothesized that the optimal use of the available antifungal armamentarium may reduce mortality and improve patient outcome.

European medical guidelines advocate amphotericin B (AMB)-based drugs as first-line treatment.[5] However, their utilization is restricted by significant nephrotoxicity, even when liposomal formulations are employed.[8–12] Along with the most recent triazole, isavuconazole, posaconazole is another antifungal with *in vitro* activity against Mucorales.[13,14] To date, use of posaconazole for treating IM has been mainly restricted to salvage treatment,[10,15–17] although there are case reports of patients treated with posaconazole new formulations (POS*new*) as first-line treatment.[18] The availability of posaconazole new formulations as delayed-release tablets and intravenous infusion may enable improved treatment of IM, as these two formulations facilitate increased and stable plasma concentrations.[19] Previous studies demonstrated the benefits of posaconazole new formulations concerning pharmacokinetics, safety and tolerability.[20–24]

Here, we present the results of a retrospective matched-paired analysis of patients treated for IM, comparing standard treatments with posaconazole new formulations.

Patients and methods

Setting

Proven and probable cases of IM were identified from FungiScope®[25,26] (www.ClinicalTrials.gov, NCT 01731353), according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria (Figure 1).[27] FungiScope® (www.fungiscope.net) is a worldwide university-based registry aiming to improve knowledge on different aspects of emerging IFD, including clinical manifestations, epidemiology and antifungal treatment. Data are collected via a web-based questionnaire hosted at www.clinicalsurveys.net, and, after documentation, an infectious diseases specialist validates each case with regard to coherence and completeness. Ethics approval from the University of Cologne, Germany was obtained for FungiScope® (Study ID: 05-102).

Definitions

Primary treatment

Primary treatment was defined as treatment of patients with an acute IM [onset <14 days before first administration of posaconazole new formulations (1st-POS*new*) or amphotericin B (1st-AMB) for at least four consecutive days]. Patients receiving another treatment active against Mucorales (i.e. isavuconazole or itraconazole)[28,29] for >4 days within 7 days prior to the first posaconazole new formulations or amphotericin B administration were excluded.

Together with the previous criteria, any patient who received >3 days of treatment with posaconazole new formulations combined with amphotericin B (1st-AMB+POS*new*) was compared with a patient treated with 1st-AMB alone, in an independent analysis.

Salvage treatment

Salvage treatment was defined as treatment of patients refractory or intolerant to the initial treatment, based on the opinion of the treating physician entering the data. Initial treatment included treatment with antifungals active against Mucorales other than posaconazole administered for at least 7 days with an onset <14 days after IM diagnosis. Patients receiving salvage treatment with posaconazole new formulations (SAL-POS*new*) were compared with patients treated with standard posaconazole oral suspension (SAL-POS*susp*).

Day zero

Day zero was defined as the day when the patient was initiated in the respective treatment group active against IM (1st-AMB, 1st-POS*new*, 1st-AMB+POS*new*, SAL-POS*new* or SAL-POS*susp*).

Response to treatment

Response to antifungal treatment was determined according to pre-established criteria,[30,31] with four categories: complete response and partial response, grouped into 'favourable response'; and stable disease and progression, grouped into 'unfavourable response' (Table S1, available as Supplementary data at *JAC* Online).

Case matching procedure

Severe disease, defined as CNS involvement and/or disseminated disease[2,9] (involvement of two or more non-contiguous organs or pathogen isolation from blood), presence of an underlying haematological/oncological condition and renal dysfunction, defined as a glomerular filtration rate (GFR) <90 mL/min at antifungal treatment initiation,[5,16] were considered underlying conditions for an unfavourable response to treatment of IM.[2,7,8,15] Surgery, defined as resection or debridement of the infected site within 14 days prior to or after diagnosis of IM, has been shown to reduce mortality.[1,2,5,13] Based on these considerations, matching factors in first-line treatment analyses included: (i) severe disease; (ii) surgery; (iii) renal dysfunction; and (iv) haematological/oncological malignancy. In the salvage treatment analysis, renal dysfunction was excluded as a matching factor.

Case–control matching was performed using the computing environment R (R Development Core Team, version 3.4.3, Vienna, Austria). A control patient could be matched only once. Patients in the 1st-POS*new* and the 1st-AMB+POS*new* groups were matched with up to three controls receiving 1st-AMB separately. This matching procedure was also performed in SAL-POS*new* patients, who were matched with up to three controls receiving SAL-POS*susp*. When a matching in all the variables was not possible, surgery was ignored.

Statistical analysis

SPSS software was used for the statistical analyses (SPSS, version 25.0, Chicago, IL, USA). Data were summarized employing frequencies and percentages, and median and IQR as appropriate. Categorical data were compared using χ^2 or Fisher's exact test when a cell value was <5. A *P* value $\leq$0.05 was considered statistically significant.

For all-cause mortality endpoints, cumulative and weighted mortality rates were calculated, weights being applied depending on the ratio of controls matched per case. Survival probability was tested using Kaplan–Meier survival plots for each group comparison for day 84 after treatment initiation. Log-rank tests were performed to determine statistically significant differences between groups' survival lines.

Results

In November 2018, a total of 874 cases were extracted from FungiScope® to retrospectively assess the effectiveness of posaconazole new formulations as first-line and salvage treatments in IM. Of these, 439 patients were excluded since their diagnosis was other than IM, 205 additional cases did not meet the inclusion criteria (due to possible mucormycosis, proven or probable mucormycosis diagnosed by PCR, no treatment administration or administration of a different antifungal regimen from that required) and 84 patients remained unmatched (all with standard treatment regimens). Eventually, 79 patients were selected for first-line treatment analyses (5 1st-POS*new* cases matched to 15 1st-AMB controls and 18 1st-AMB+POS*new* cases matched to 50 1st-AMB controls) and 67 for salvage treatment analysis (22 SAL-POS*new* cases matched to 45 SAL-POS*susp* controls) (Figure 1, Tables S2, S3 and S4).

Overall, five adult cases receiving 1st-POS*new* were matched with 15 adult controls receiving 1st-AMB (Figure 1, Table S2), diagnosed between 2015 and 2016. These controls were diagnosed between 2000 and 2017 and included three (20.0%) children/adolescents and 12 (80.0%) adults (Table 1).

Lichtheimia spp. was reported as the causative pathogen in two (40.0%) 1st-POS*new* patients. Additionally, *Rhizomucor* spp. and *Aspergillus* spp. coinfection was described in one (20.0%) patient. The most prevalent pathogens in patients receiving 1st-AMB were *Mucor* spp. in five (33.3%) patients, *Rhizopus* spp. in four (26.7%) patients and *Lichtheimia* spp. in three (20.0%) patients (Table 1, Tables S5 and S6).

Prevalent haematological/oncological malignancy and corticosteroids/immunosuppressive administration, with four (80.0%) patients each, were the most prevalent underlying conditions in the 1st-POS*new* group. Obesity and neutropenia with two (40.0%) patients each were also relevant underlying conditions. A similar distribution was observed in the 1st-AMB group, with 12 (80.0%) patients having a diagnosis of haematological/oncological malignancy. Neutropenia was present in nine (60.0%) patients, and corticosteroids/immunosuppressive administration in eight (53.3%) patients in the 1st-AMB controls.

The lung was the most frequently affected organ in the 1st-POS*new* group concerning three (60.0%) patients. Two (40.0%) patients had non-lung infection, one of which presented with coinfection of the paranasal sinus(es), deep soft tissue, skin and eye(s), and the other with localized deep soft tissue infection. No patient had disseminated IM. In the 1st-AMB group, the majority of the patients had localized infection, with IM affecting the bowel, lung (*n*=4; 26.7% each), deep soft tissue (*n*=3; 20.0%) or paranasal sinuses (*n*=1; 6.7%). Additionally, three (20.0%) patients had two organs affected simultaneously, specifically lung and paranasal sinuses, skin and paranasal sinuses, and skin and deep soft tissues (Table 1, Tables S6 and S7).

Treatment duration was similar between the 1st-POS*new* cases and 1st-AMB controls [median of 26.0 (IQR 9.0–55.0) days versus median of 30.0 (IQR 10.0–45.0) days, respectively]. 1st-POS*new* patients [median of 81.0 (IQR 68.0–184.0) days] were observed for longer than 1st-AMB controls [median of 33.0 (IQR 10.0–45.0) days]. No drug-related adverse effects ascribed to antifungal treatment were reported in 1st-POS*new* patients, whereas one (6.7%) patient in the 1st-AMB group experienced renal dysfunction (Table 2, Table S8).

A day 42 favourable response was observed in four (80.0%) 1st-POS*new* patients, compared with three (20.0%) 1st-AMB controls (Table 3, Table S9). By day 42, one (20.0%) 1st-POS*new* patient had died compared with eight (53.3%) in the 1st-AMB group. Weighted mortality did not differ from crude mortality (Table 4). On day 84 after treatment start, in Kaplan–Meier survival curves, 1st-POS*new* patients exhibited a higher survival probability (80.0%) than did 1st-AMB patients (33.8%), although this did not reach statistical significance (*P*=0.117) (Figure 2a).

In the 18 1st-AMB+POS*new* patients, IM was diagnosed between 2010 and 2018. They were matched with 50 patients receiving 1st-AMB and who were diagnosed between 1997 and 2018 (Figure 1, Table S3). The 1st-AMB+POS*new* group consisted of two (8.0%) children/adolescents and 16 (92.0%) adults, whereas the 1st-AMB control group included six (11.0%) children/adolescents and 44 (89.0%) adults (Table 1).

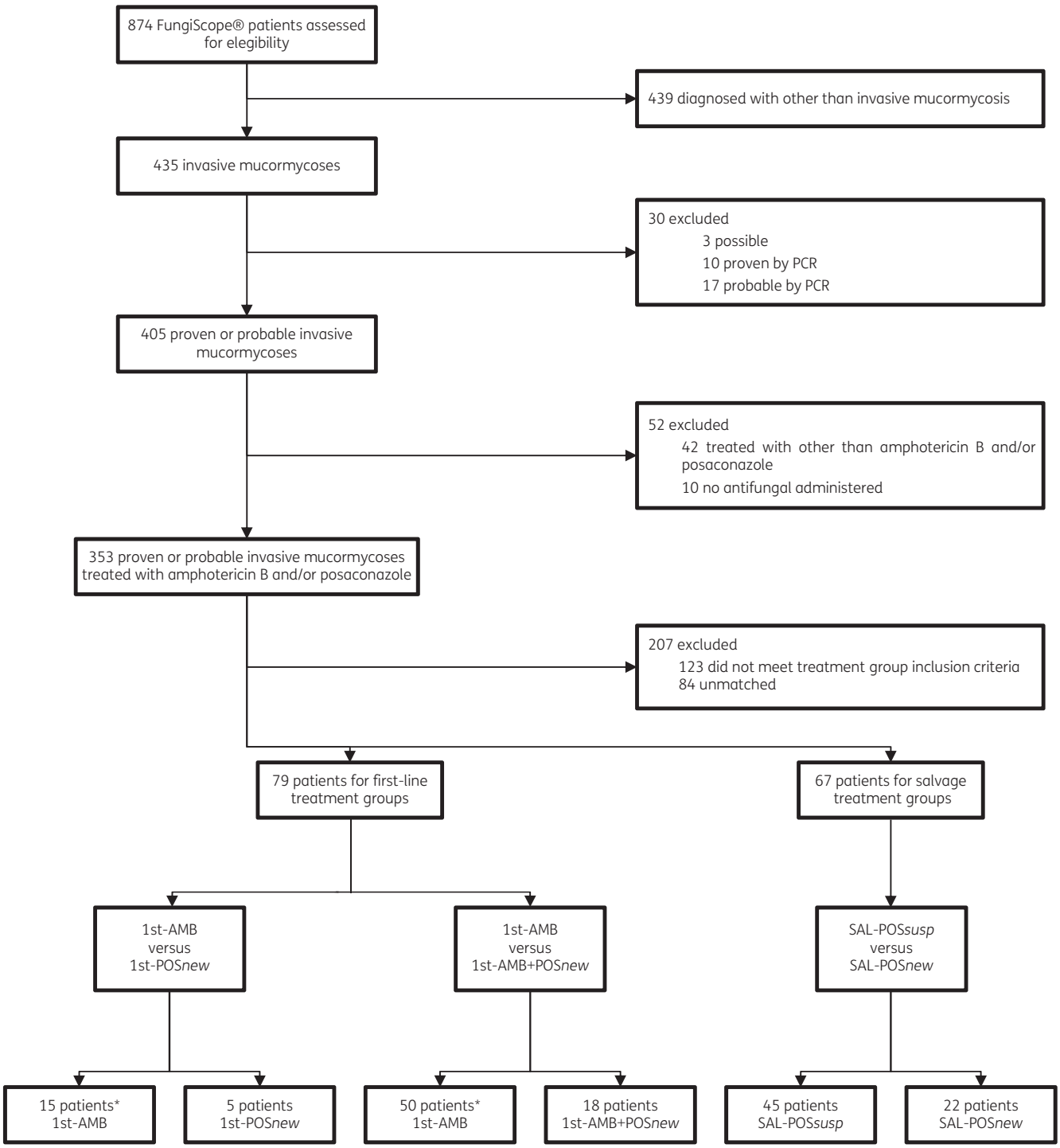

Figure 1. MoveOn enrolment and study flow chart. The asterisks indicate that nine patients treated with 1st-AMB were employed as matched pairs for both 1st-POS*new* and 1st-AMB+POS*new* cases.

Rhizopus spp. were reported as the causative pathogen in 10 (55.6%) patients receiving 1st-AMB+POS*new*, followed by the pathogens *Apophysomyces* spp. in three (16.7%) cases and Mucorales-not otherwise specified (NOS) in two (11.1%) cases. In 1st-AMB patients, the most prevalent causative pathogens were *Mucor* spp. and *Rhizopus* spp., with 15 (30.0%) cases each, followed by *Lichtheimia* spp. in five (10.0%) cases and *Rhizomucor* spp. in four (8.0%). Two (11.1%) 1st-AMB+POS*new* cases had a coinfection (both with *Candida* spp.), as did seven (14.0%) 1st-AMB controls (*Aspergillus* spp., *Candida* spp. and/or *Scedosporium*/*Lomentospora* spp.) (Table 1, Tables S5 and S6).

Table 1. Patient characteristics by group

	1st-AMB (*n*=15)	1st-POS*new* (*n*=5)	1st-AMB (*n*=50)	1st-AMB+POS*new* (*n*=18)	SAL-POS*susp* (*n*=45)	SAL-POS*new* (*n*=22)
Year of infection	2000–17	2015–16	1997–2018	2010–18	2000–18	2008–17
Age at diagnosis						
child/adolescent	3 (20.0)	–	6 (11.0)	2 (8.0)	4 (8.8)	1 (4.5)
0–6 years	–	–	2 (4.0)	1 (5.6)	2 (4.4)	–
7–11 years	1 (6.7)	–	2 (4.0)	–	1 (2.2)	–
12–16 years	2 (13.3)	–	2 (4.0)	1 (5.6)	1 (2.2)	1 (4.5)
adult	12 (80.1)	5 (100.0)	44 (89.0)	16 (92.0)	41 (91.1)	21 (95.4)
17–29 years	1 (6.7)	2 (40.0)	7 (14.0)	1 (5.6)	4 (8.9)	2 (9.1)
30–49 years	3 (20.0)	3 (60.0)	11 (22.0)	7 (38.9)	8 (17.8)	1 (4.5)
50–69 years	7 (46.7)	–	19 (38.0)	6 (33.3)	24 (53.3)	15 (68.2)
≥70 years	1 (6.7)	–	7 (14.0)	2 (11.1)	5 (11.1)	3 (13.6)
Female (%)	5 (33.3)	1 (20.0)	18 (36.0)	7 (38.9)	18 (40.0)	8 (36.4)
Causative pathogen						
Apophysomyces spp.	–	–	2 (4.0)	3 (16.7)	–	–
Cunninghamella spp.	1 (6.7)	–	3 (6.0)	1 (5.6)	1 (2.2)	–
Lichtheimia spp.	3 (20.0)	2 (40.0)	6 (11.0)	–	8 (17.8)	4 (18.2)
Mucor spp.	5 (33.3)	–	15 (30.0)	1 (5.6)	12 (26.7)	5 (22.7)
Rhizomucor spp.	–	1 (20.0)	4 (8.0)	1 (5.6)	1 (2.2)	2 (9.1)
Rhizopus spp.	4 (26.7)	1 (20.0)	15 (30.0)	11 (61.1)	12 (26.7)	9 (40.5)
Saksenaea spp.	–	–	2 (4.0)	–	–	1 (4.5)
Mucorales-NOS[a]	2 (13.3)	1 (20.0)	3 (6.0)	2 (11.1)	11 (24.4)	1 (4.5)
Underlying conditions						
haematological/oncological malignancy	12 (80.0)	4 (80.0)	29 (58.0)	11 (61.1)	30 (66.7)	10 (45.5)
type of malignancy						
acute leukaemia	8 (53.3)	4 (80.0)	17 (34.0)	6 (33.3)	17 (37.8)	6 (27.3)
aplastic anaemia	–	–	1 (2.0)	1 (5.6)	1 (2.2)	–
chronic leukaemia	–	–	5 (10.0)	–	5 (11.1)	1 (4.5)
lymphoma	3 (20.0)	–	3 (6.0)	1 (5.6)	5 (11.1)	1 (4.5)
multiple myeloma	1 (6.7)	–	1 (2.0)	–	–	–
myelodysplastic syndrome	–	–	–	2 (11.1)	2 (4.4)	3 (13.6)
solid tumour[b]	–	–	2 (4.0)	1 (5.6)	2 (4.4)	2 (9.1)
other[c]	–	–	–	–	1 (2.2)	–
treatment for malignancy						
chemotherapy	12 (80.0)	4 (80.0)	28 (56.0)	11 (61.1)	25 (55.6)	7 (31.8)
allogeneic-HSCT	4 (26.7)	2 (40.0)	11 (22.0)	4 (22.2)	6 (13.3)	5 (22.7)
autologous-HSCT	1 (6.7)	–	–	–	1 (2.2)	1 (4.5)
corticosteroids/immunosuppressives	8 (53.3)	4 (80.0)	29 (58.0)	9 (50.0)	18 (40.0)	13 (59.1)
neutropenia	9 (60.0)	2 (40.0)	20 (40.0)	7 (38.9)	15 (33.3)	7 (31.8)
alcoholism	–	–	2 (4.0)	–	1 (2.2)	1 (4.5)
burn	–	–	–	1 (5.6)	–	–
chronic cardiovascular disease	2 (13.3)	–	3 (6.0)	1 (5.6)	–	–
chronic liver disease	–	–	–	–	1 (2.2)	1 (4.5)
chronic lung disease	3 (20.0)	–	3 (6.0)	–	2 (4.4)	3 (13.6)
chronic renal disease	–	–	4 (8.0)	1 (5.6)	1 (2.2)	1 (4.5)
diabetes mellitus	2 (13.3)	1 (20.0)	13 (26.0)	1 (5.6)	9 (20.0)	6 (27.3)
GvHD[d]	1 (6.7)	1 (20.0)	5 (10.0)	2 (11.1)	3 (6.7)	3 (13.6)
major surgery[e]	–	–	–	2 (11.1)	1 (2.2)	3 (13.6)
rheumatic/autoimmune disease	–	–	1 (2.0)	1 (5.6)	–	5 (22.7)
obesity or underweight	2 (13.3)	2 (40.0)	5 (10.0)	3 (16.7)	8 (17.8)	3 (13.6)
solid organ transplantation	–	–	2 (4.0)	1 (5.6)	1 (2.2)	1 (4.5)
trauma	1 (6.7)	–	4 (8.0)	4 (22.2)	3 (6.7)	2 (9.1)
treatment in ICU	1 (6.7)	1 (20.0)	9 (18.0)	5 (27.8)	4 (8.9)	2 (9.1)

Continued

Table 1. *Continued*

	1st-AMB (*n*=15)	1st-POS*new* (*n*=5)	1st-AMB (*n*=50)	1st-AMB+POS*new* (*n*=18)	SAL-POS*susp* (*n*=45)	SAL-POS*new* (*n*=22)
viral pneumonia[f]	1 (6.7)	–	–	–	–	2 (9.1)
other underlying conditions[g]	1 (6.7)	–	3 (6.0)	–	1 (2.2)	3 (13.6)
no risk factor identified	1 (6.7)	1 (20.0)	3 (6.0)	–	–	1 (4.5)
Disease location						
lung only	4 (26.7)	3 (60.0)	11 (22.0)	3 (16.7)	17 (37.8)	6 (27.3)
lung and other organs	1 (6.7)	–	10 (20.0)	3 (16.7)	6 (13.3)	3 (13.6)
non-lung disease	10 (66.7)	2 (40.0)	29 (58.0)	12 (66.7)	22 (48.9)	13 (59.1)
Non-lung disease location						
paranasal sinus(es)	3 (20.0)	1 (20.0)	16 (32.0)	5 (27.8)	14 (31.1)	5 (22.7)
deep soft tissues	4 (26.7)	2 (40.0)	17 (34.0)	9 (50.0)	9 (20.0)	5 (22.7)
CNS	–	–	9 (18.0)	2 (11.1)	7 (15.6)	3 (13.6)
blood	–	–	3 (6.0)	–	–	1 (4.5)
bowel	4 (26.7)	–	6 (12.0)	–	5 (11.1)	2 (9.1)
kidneys	–	–	3 (6.0)	–	1 (2.2)	1 (4.5)
peritoneum	–	–	2 (4.0)	1 (5.6)	–	2 (9.1)
skin	2 (13.3)	1 (20.0)	4 (8.0)	–	2 (4.4)	1 (4.5)
spleen	–	–	2 (4.0)	1 (5.6)	1 (2.2)	1 (4.5)
vessels	–	–	2 (4.0)	–	–	–
bone	–	–	2 (4.0)	1 (5.6)	8 (17.8)	1 (4.5)
eye(s)	–	1 (20.0)	3 (6.0)	2 (11.1)	2 (4.4)	–
liver	–	–	2 (4.0)	1 (5.6)	3 (6.7)	1 (4.5)
other site of infection[h]	–	–	1 (2.0)	–	2 (4.4)	2 (9.1)
disseminated disease[i]	–	–	12 (24.0)	5 (27.8)	8 (17.8)	4 (18.2)

Data are *n* (%). Underlying conditions and affected organs might be superadditive. Abbreviations: 1st-AMB, first-line amphotericin B; 1st-POS*new*, first-line posaconazole new formulations; 1st-AMB+POS*new*, first-line amphotericin B + posaconazole new formulations; SAL-POS*susp*, salvage posaconazole oral suspension; SAL-POS*new*, salvage posaconazole new formulations.
[a]Mucorales-NOS, Mucorales not otherwise specified.
[b]Solid tumour includes gastric adenocarcinoma, neuroblastoma, myelofibrosis and urinary cancer.
[c]Other haematological/oncological malignancy, including Fanconi anaemia.
[d]GvHD, graft-versus-host disease.
[e]Major surgery does not include surgery as antifungal therapy.
[f]Viral pneumonia within 30 days prior to diagnosis of the invasive mucormycosis.
[g]Other underlying conditions includes chronic pancreatitis, dental manipulation, malnutrition, near-drowning in a goose pond, severe peptic ulcer disease, sweet syndrome and titanium plate in right orbital ground.
[h]Other sites of infection included catheter-related bloodstream infection, dura, larynx and trachea, thyroid.
[i]Disseminated invasive mucormycosis is defined as an infection with positive blood culture and/or at least two non-adjacent organs affected.

Haematological/oncological malignancy was the most frequently identified risk factor in both 1st-AMB+POS*new* cases (*n*=11; 61.1%) and 1st-AMB controls (*n*=29; 58.0%). Corticosteroids/immunosuppressive administration (*n*=9; 50.0% in the 1st-AMB+POS*new* group versus *n*=29; 58.0% in the 1st-AMB group) and neutropenia (*n*=7; 38.9% in the 1st-AMB+POS*new* group versus *n*=20; 40.0% in the 1st-AMB group) were other common underlying conditions.

Deep soft tissues were the most prevalently affected site in the 1st-AMB+POS*new* group (*n*=9; 50.0%). Moreover, six (33.3%) patients suffered from IM of the lung, and five (27.8%) of the paranasal sinuses. In the 1st-AMB group, most of the patients had a lung IM [21 (42.0%) patients], involvement of deep soft tissues (*n*=17; 34.0%) or the paranasal sinuses (*n*=16; 32.0%). A total of five (27.8%) 1st-AMB+POS*new* cases suffered from disseminated IM, as did 12 (24.0%) of the 1st-AMB controls (Table 1, Tables S6 and S7).

Patients from the 1st-AMB+POS*new* group received treatment for a median of 15.5 (IQR 8.0–29.0) days, similar to 1st-AMB patients [20.5 (IQR 14.0–46.0) days]. Median time of observation in the 1st-AMB+POS*new* cases [median of 32.0 (IQR 14.0–120.0) days] was longer than in 1st-AMB controls [median of 22.5 (IQR 15.0–62.0) days]. Four (22.2%) patients in the 1st-AMB+POS*new* group reported adverse effects, three (16.7%) due to administration of amphotericin B, two (11.1%) due to posaconazole new formulations and one (5.6%) due to both amphotericin B and posaconazole new formulations. Eight (16.0%) patients in the 1st-AMB control group reported adverse effects (Table 2, Table S8).

A day 42 favourable response was observed in five (27.8%) 1st-AMB+POS*new* patients and in 14 (28.0%) of the 1st-AMB controls

Table 2. Treatment details by group

	1st-AMB (*n*=15)	1st-POS*new* (*n*=5)	1st-AMB (*n*=50)	1st-AMB+POS*new* (*n*=18)	SAL-POS*susp* (*n*=45)	SAL-POS*new* (*n*=22)
Other antifungal treatments						
surgery	8 (53.3)	3 (60.0)	22 (44.0)	8 (44.4)	14 (31.8)	6 (27.3)
iron chelators	–	–	1 (2.0)	2 (11.1)	–	–
G-CSF	–	–	–	1 (5.6)	1 (2.2)	–
Antifungal treatment duration (days)	33.0 (13.0–45.0)	26.0 (9.0–55.0)	20.5 (14.0–46.0)	15.5 (8.0–29.0)	99.0 (43.0–153.0)	76.0 (41.0–135.0)
AMB formulation, *n* (%)[a]						
deoxycholate	–	–	13 (26.0)	4 (22.2)	13 (28.9)	2 (9.1)
lipid complex	3 (20.0)	–	8 (16.0)	5 (27.8)	18 (40.0)	2 (9.1)
liposomal	13 (86.7)	–	34 (68.0)	10 (55.6)	19 (42.0)	19 (86.4)
POS formulation, *n* (%)[a]						
intravenous	–	3 (60.0)	–	8 (44.4)	–	2 (9.1)
suspension	–	–	–	–	45 (100.0)	–
tablet	–	3 (60.0)	–	10 (55.6)	–	22 (100.0)
Days with AMB before salvage treatment	–	–	–	–	23.0 (14.0–32.0)	20.5 (9.0–42.0)
Duration of observation (days)	36.0 (13.0–62.0)	81.0 (68.0–184.0)	22.5 (15.0–62.0)	32.0 (14.0–120.0)	143.0 (76.0–230.0)	102.5 (44.0–159.0)
Drug-related adverse effects, *n* (%)[a]						
no adverse effects	14 (93.3)	5 (100.0)	42 (84.0)	14 (77.8)	39 (86.7)	14 (63.6)
adverse effects	1 (6.7)	–	8 (16.0)	4 (22.2)	6 (13.3)	8 (36.4)
after AMB	1 (6.7)	–	8 (16.0)	3 (16.7)	5 (11.1)	7 (31.8)
electrolyte imbalance	–	–	1 (2.0)	–	2 (4.4)	–
liver dysfunction	–	–	–	–	–	1 (4.5)
renal dysfunction	1 (6.7)	–	7 (14.0)	3 (16.7)	2 (4.4)	4 (18.2)
other[b]	–	–	1 (2.0)	–	1 (2.2)	2 (9.1)
after POS tablets	–	–	–	2 (11.1)	–	1 (4.5)
liver dysfunction	–	–	–	2 (11.1)	–	–
giddiness	–	–	–	–	–	1 (4.5)
after POS suspension	–	–	–	–	1 (2.2)	–
thrombocytopenia	–	–	–	–	1 (2.2)	–

Data are median (IQR) unless otherwise indicated. G-SCF, granulocyte–colony-stimulating factor; AMB, amphotericin B; POS, posaconazole.
[a]Superadditive.
[b]Other adverse effects include exanthema on truncus and limbs, fever and non-stated adverse effects.

(Table 3, Table S9). At day 42, 6 (33.3%) 1st-AMB+POS*new* patients had died, as had 26 (52.0%) in the 1st-AMB group. Mortality analysis showed similar values for both groups on day 42 for crude and weighted mortality (Table 4). On day 84 Kaplan–Meier survival curves, 1st-AMB+POS*new* patients (59.3%) demonstrated a higher survival probability than 1st-AMB patients (33.9%), without reaching statistical significance (P=0.202) (Figure 2b).

SAL-POS*new* was administered in 22 cases, who were matched with 45 controls receiving SAL-POS*susp* (Figure 1, Table S4). SAL-POS*new* cases were diagnosed between 2008 and 2017; 21 (95.4%) patients were adults. SAL-POS*susp* controls were diagnosed between 2000 and 2018; 41 (91.1%) were adults (Table 1).

Rhizopus spp. was reported as the causative pathogen in nine (40.9%) cases receiving SAL-POS*new*. Other SAL-POS*new* patients had IM due to *Mucor* spp. (*n*=5; 22.7%) and *Lichtheimia* spp. (*n*=4; 18.2%). The most frequently observed causative pathogens in the SAL-POS*susp* group were *Mucor* spp. and *Rhizopus* spp. (*n*=12; 26.7% each), Mucorales-NOS (*n*=11; 24.4%) and *Lichtheimia* spp. (*n*=8; 17.8%). Six (27.3%) SAL-POS*new* cases had a coinfection, four (18.2%) with *Aspergillus* spp. and one (4.5%) each with *Candida* spp. and *Cladosporium* spp. Overall, eight (17.8%) SAL-POS*susp* controls presented coinfections, five (11.1%) with *Aspergillus* spp. and one (2.2%) each with *Aspergillus* spp. + *Penicillium* spp., *Candida* spp. and *Paecilomyces* spp. (Table 1, Tables S5 and S6).

Haematological/oncological malignancy (*n*=10; 45.5% SAL-POS*new* cases versus *n*=30; 66.7% SAL-POS*susp* controls) and corticosteroids/immunosuppressive administration (*n*=13; 59.1% SAL-POS*new* cases versus *n*=18; 40.0%) were the most prevalent underlying conditions for patients in the salvage treatment group. Neutropenia was also a relevant risk factor in both groups (*n*=7; 31.8% SAL-POS*new* cases versus *n*=15; 33.3% SAL-POS*susp* controls).

Lung was the most frequently affected organ in both groups, including nine (40.5%) patients in SAL-POS*new* cases and 23

Table 3. Response to treatment by group

	1st-AMB (*n*=15)	1st-POS*new* (*n*=5)	1st-AMB (*n*=50)	1st-AMB+POS*new* (*n*=18)	SAL-POS*susp* (*n*=45)	SAL-POS*new* (*n*=22)
Day 42						
favourable response	3/15 (20.0)	4/5 (80.0)	14/50 (28.0)	5/18 (27.8)	26/45 (57.8)	11/22 (50.0)
complete response	2/15 (13.3)	–	6/50 (12.0)	2/18 (11.1)	12/45 (26.7)	4/22 (18.2)
partial response	1/15 (6.7)	4/5 (80.0)	8/50 (16.0)	3/18 (16.7)	14/45 (31.1)	7/22 (31.8)
unfavourable response	2/15 (13.3)	–	5/50 (10.0)	3/18 (16.7)	16/45 (35.6)	7/22 (31.8)
stable disease	2/15 (13.3)	–	3/50 (6.0)	2/18 (11.1)	9/45 (20.0)	4/22 (18.2)
progression	–	–	2/50 (4.0)	1/18 (5.6)	7/45 (15.6)	3/22 (13.6)
not applicable	8/15 (53.3)	1/5 (20.0)	26/50 (52.0)	6/18 (33.3)	2/45 (4.4)	–
lost to follow-up	2/15 (13.3)	–	5/50 (10.0)	4/18 (22.2)	1/45 (2.2)	4/22 (18.2)
Day 84						
favourable response	2/15 (13.3)	2/5 (40.0)	10/50 (20.0)	6/18 (33.4)	22/45 (48.9)	7/22 (31.8)
complete response	2/15 (13.3)	–	5/50 (10.0)	3/18 (16.7)	8/45 (17.8)	2/22 (9.1)
partial response	–	2/5 (40.0)	5/50 (10.0)	3/18 (16.7)	14/45 (31.1)	5/22 (22.7)
unfavourable response	–	–	–	1/18 (5.6)	11/45 (24.5)	5/22 (22.7)
stable disease	–	–	–	1/18 (5.6)	8/45 (17.8)	3/22 (13.6)
progression	–	–	–	–	3/45 (6.7)	2/22 (9.1)
not applicable	9/15 (60.0)	1/5 (20.0)	30/50 (60.0)	7/18 (38.9)	5/45 (11.1)	1/22 (4.5)
lost to follow-up	4/15 (26.7)	2/5 (40.0)	10/50 (20.0)	4/18 (22.2)	7/45 (15.6)	9/22 (40.9)
Final day						
favourable response	6/15 (40.0)	4/5 (80.0)	19/50 (38.0)	9/18 (50.0)	30/45 (66.7)	17/22 (77.2)
complete response	6/15 (40.0)	2/5 (40.0)	18/50 (36.0)	8/18 (44.4)	21/45 (46.7)	16/22 (72.7)
partial response	–	2/5 (40.0)	1/50 (2.0)	1/18 (5.6)	9/45 (20.0)	1/22 (4.5)
unfavourable response	9/15 (60.0)	1/5 (20.0)	31/50 (62.0)	9/18 (50.0)	15/45 (33.3)	5/22 (22.7)
stable disease	2/15 (13.3)	–	3/50 (6.0)	1/18 (5.6)	4/45 (8.9)	2/22 (9.1)
progression	7/15 (46.7)	1/5 (20.0)	28/50 (56.0)	8/18 (44.4)	11/45 (24.4)	3/22 (13.6)

Data are *n/N* (%). Day 0 was considered the day when treatment started. Complete response, resolution of all attributable signs and symptoms of disease, radiological abnormalities (persistence of only a scar or postoperative changes can be equated with a complete radiological response) and mycological evidence of eradication of disease. Partial response, improvement in attributable signs and symptoms of disease, radiological abnormalities (at least 25% reduction in diameter of radiological lesion) and evidence of clearance of cultures or reduction of fungal burden. In cases of radiological stabilization (defined as a 0%–25% reduction in the diameter of the lesion), resolution of all attributable symptoms and signs of fungal disease can be equated with a partial response. Stable disease, minor or no improvement in fungal disease but no evidence of progression, as determined on the basis of a composite of clinical, radiological and mycological criteria or persistent isolation of mould or histological presence of invasive hyphae in infected sites. Progression, evidence of progressive fungal disease based on a composite of clinical, radiological and mycological criteria. Not applicable, patient has already died before the respective timepoint. Lost to follow-up, patient has already been discharged alive before the respective timepoint.

(51.1%) patients in SAL-POS*susp* controls. Seventeen (37.8%) controls presented with localized disease, and, in six (13.3%) cases, an adjacent organ was involved. The number of disseminated cases of IM was similar between SAL-POS*new* cases (*n*=4; 18.2%) and SAL-POS*susp* controls (*n*=8; 17.8%) (Table 1, Tables S6 and S7).

SAL-POS*new* patients received treatment for a median of 76.0 (IQR 41.0–135.0) days, a shorter time than patients in the SAL-POS*susp* group [99.0 (IQR 43.0–153.0) days]. SAL-POS*new* patients' final assessment of treatment response [median of 102.0 (IQR 44.0–159.0) days] was documented earlier than for SAL-POS*susp* controls [median of 143.0 (IQR 76.0–230.0) days]. For eight (36.4%) SAL-POS*new* patients, adverse effects were reported [*n*=7; 31.8% related to amphotericin B use and one (4.5%) to posaconazole new formulations], compared with six (13.3%) SAL-POS*susp* patients [*n*=5; 11.1% related to amphotericin B use and one (2.2%) to posaconazole oral suspension] (Table 2, Table S8).

A day 42 favourable response was observed in 11 (50.0%) SAL-POS*new* patients, and in 26 (57.8%) SAL-POS*susp* controls (Table 3, Table S9). However, all SAL-POS*new* patients were alive at day 42, as compared with 43 (95.6%) patients in the SAL-POS*susp* group. Additionally, four (18.2%) SAL-POS*new* patients were already discharged alive on day 42 compared with one (2.2%) from the SAL-POS*susp* group. Weighted and crude mortality at day 42 were similar for the SAL-POS*new* and the SAL-POS*susp* groups (Table 4). On day 84 Kaplan–Meier survival curves, SAL-POS*new* patients had a higher survival probability (94.4%) than SAL-POS*susp* patients (88.4%), without reaching statistical significance (*P*=0.504) (Figure 2c).

Discussion

Since the legal approval and marketing of posaconazole new formulations, further and improved treatment options have become

Table 4. Mortality by group

	1st-AMB (*n*=15)	1st-POS*new* (*n*=5)	*P*	1st-AMB (*n*=50)	1st-AMB+POS*new* (*n*=18)	*P*	SAL-POS*susp* (*n*=45)	SAL-POS*new* (*n*=22)	*P*
Diagnosis post-mortem	–	–	–	2 (4.0)	–	–	–	–	–
Death attributable to IFI	5 (33.3)	1 (20.0)	–	24 (48.0)	5 (27.8)	–	5 (11.1)	1 (4.5)	–
Autopsy	1 (6.7)	–	–	4 (8.0)	1 (5.6)	–	6 (13.3)	–	–
Day of death	18.0 (7.0–36.0)	109.5 (35.0–184.0)	–	16.5 (8.0–21.0)	17.0 (8.0–46.0)	–	113 (46.0–223.0)	117.5 (68.5–161.5)	–
Crude									
day 42 all-cause mortality	8/15 (53.3) [26.6–78.7]	1/5 (20.0) [0.5–71.6]	0.319	26/50 (52.0) [37.4–66.3]	6/18 (33.3) [13.3–59.0]	0.271	2/45 (4.4) [0.5–15.1]	0/22 (0.0) [0.0–15.4]	1.000
day 84 all-cause mortality	9/15 (60.0) [32.3–83.7]	1/5 (20.0) [5.0–71.6]	0.303	30/50 (60.0) [45.2–73.6]	7/18 (38.9) [17.3–64.3]	0.169	5/45 (11.1) [3.7–24.1]	1/22 (4.5) [0.1–22.8]	0.655
final day all-cause mortality	9/15 (60.0) [32.3–83.7]	2/5 (40.0) [5.3–85.3]	0.617	30/50 (60.0) [45.2–73.6]	9/18 (50.0) [26.0–74.0]	0.580	15/45 (33.3) [20.0–49.0]	4/22 (18.2) [5.2–40.3]	0.255
By matching covariates									
haematological/oncological malignancy	8/15 (53.3)	2/5 (40.0)	–	23/50 (46.0)	7/18 (38.9)	–	11/45 (24.4)	3/22 (13.6)	–
severe disease[a]	–	–	–	11/50 (22.0)	4/18 (22.2)	–	6/45 (13.3)	–	–
surgical treatment[b]	3/15 (20.0)	2/5 (40.0)	–	9/50 (18.0)	3/18 (16.7)	–	6/45 (13.3)	–	–
renal dysfunction[c]	2/15 (13.3)	–	–	11/50 (22.0)	4/18 (22.2)	–	–	–	–
Weighted[d]									
day 42 all-cause mortality	53.3 (38.8–67.9)	20.0 (0.0–40.2)	0.025	51.4 (43.2–59.6)	32.0 (19.1–44.9)	0.018	5.3 (1.2–9.4)	0.0 (0.0–0.0)	1.000
day 84 all-cause mortality	60.0 (45.7–74.3)	20.0 (0.0–40.2)	0.007	58.3 (50.3–66.4)	38.0 (24.5–51.5)	0.013	11.5 (5.6–17.4)	6.7 (0.0–14.0)	0.560
final day all-cause mortality	60.0 (45.7–74.3)	40.0 (15.2–64.8)	0.178	58.3 (50.3–66.4)	50.0 (36.1–63.9)	0.306	35.4 (26.6–44.2)	22.2 (10.1–34.4)	0.108

Data for crude mortality are *n/N* (%) [95% CI]. 95% CI is based on Clopper–Pearson's binomial exact method. *P* values are calculated from Fisher's exact test. Data for weighted mortality are *n* (%) [95% CI]. 95% CI is based on Wald normal approximation method. *P* values are calculated from χ^2 test except for day 84, calculated with Fisher's exact test.

[a]CNS involvement and/or disseminated disease (involvement of more than one non-contiguous organ or pathogen isolated from blood).

[b]Surgical treatment defined as debridement or resection within 14 days since invasive mucormycosis diagnosis at site of infection.

[c]Renal dysfunction was categorized based on a GFR <90 mL/min at antifungal treatment initiation.

[d]Patients were weighted with respect to the ratio of the amount of controls matched to each case.

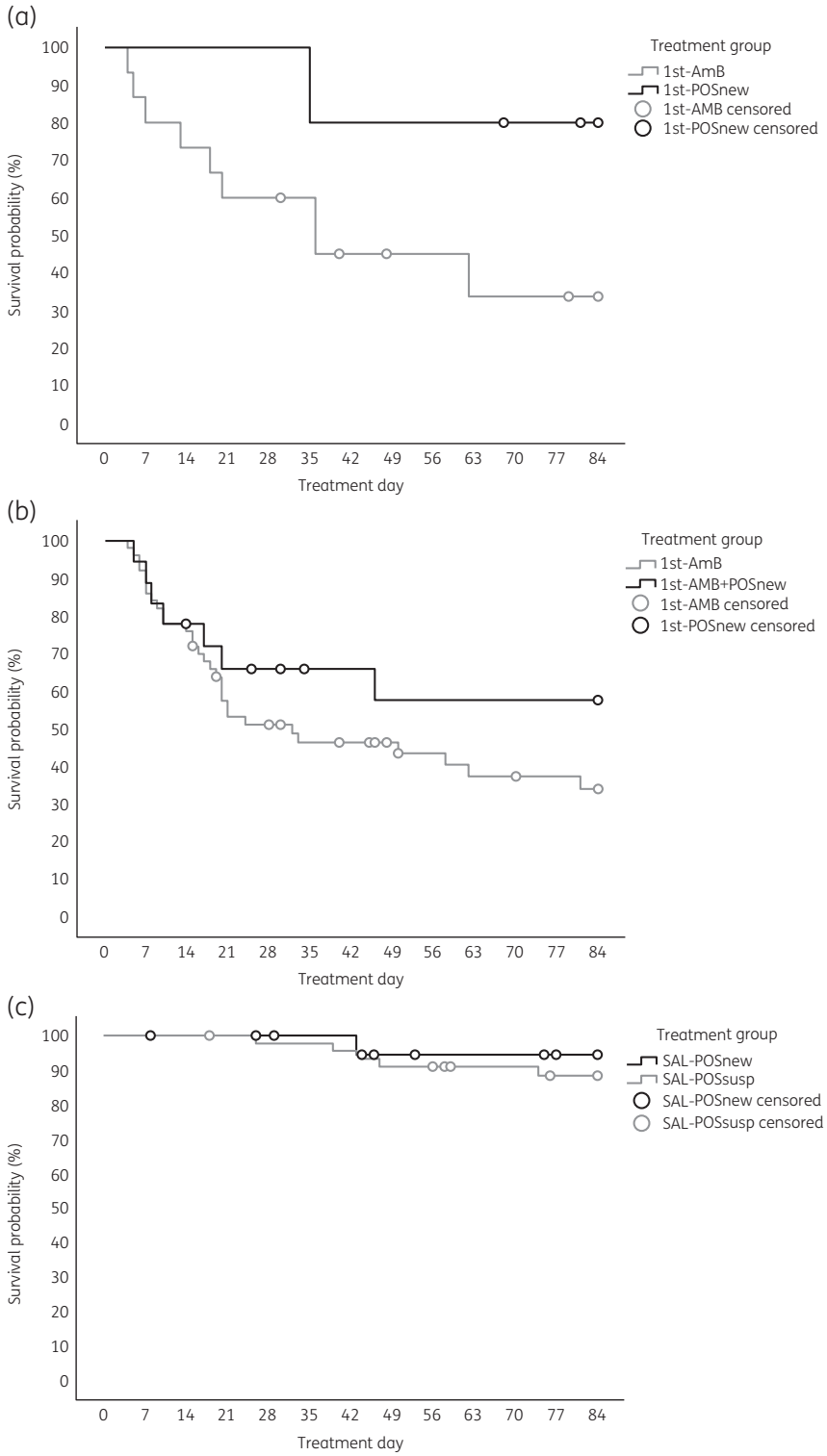

Figure 2. Kaplan–Meier analysis of patients receiving posaconazole new formulations versus standard treatments. Patients were censored on their last known survival status day, represented by open circles. (a) 1st-POS*new* compared with 1st-AMB matched controls at day 84 after treatment start. Day 84 after diagnosis (log rank *P*=0.117). (b) 1st-AMB+POS*new* compared with 1st-AMB matched controls at day 84 after treatment start. Day 84 after diagnosis (log rank *P*=0.202). (c) SAL-POS*new* compared with SAL-POS*susp* matched controls at day 84 after treatment start. Day 84 of treatment (log rank *P*=0.504).

available. Our study is, to our knowledge, the first matched-paired analysis that assesses the clinical effectiveness and safety of posaconazole new formulations in comparison with amphotericin B as first-line treatment and with posaconazole oral suspension as salvage treatment of IM.

Most of the patients recruited into the study were haematological/oncological patients and/or patients receiving immunosuppressive treatment, analogous to the previously described populations at risk (Table 1, Table S6).[1,2,11,31] In line with the available body of evidence, the lung is the organ most frequently affected by IM, followed by the paranasal sinuses and deep soft tissues.[6,11,31] Nevertheless, due to the small sample size available, as well as the low incidence, the site of infection appears to be heterogeneous among groups. However, the site of infection distribution according to severity, meaning CNS involvement and/or dissemination versus localized infection, was similar between all groups (Table 1, Table S7).

Concerning response, 1st-POS*new* and 1st-AMB+POS*new* treatment was associated with a higher proportion of favourable response to treatment and discharge alive at day 42 and 84 than their controls receiving 1st-AMB treatment (Table 3, Table S9). This suggests that posaconazole new formulations may be an alternative for the treatment of IM in the first-line and salvage setting.

IM is characterized by its high mortality rates, especially in patients with disseminated disease.[1,2,7] In this study, mortality rates, in both crude and weighted analyses, were lower for the 1st-POS*new* and 1st-AMB+POS*new* patients compared with their controls receiving 1st-AMB, resembling previously reported mortality rates.[11,31] Likewise, posaconazole new formulations were associated with a trend towards higher survival probability in salvage treatment patients compared with posaconazole oral suspension (Table 4, Figure 2). However, the three Kaplan–Meier analyses showed no significant difference between groups in which standard treatments (1st-AMB or SAL-POS*susp*) or posaconazole new formulations (1st-POS*new*, 1st-AMB+POS*new* or SAL-POS*new*) were used. These results should be interpreted with caution given the small sample size available for analysis.

Overall, drug-related adverse effects were rarely reported due to administration of posaconazole new formulations: liver dysfunction in two patients treated with 1st-AMB+POS*new*; giddiness in one patient in the SAL-POS*new* group; but no effects in the patients in the 1st-POS*new* group. Although drug-related renal dysfunction was reported in 7 (15.6%) of a total of 45 patients receiving posaconazole new formulations, as either first-line or salvage treatment, this adverse event was most probably attributable to the simultaneous administration of amphotericin B, as its nephrotoxicity is well known and documented.[8–12] The low rate of adverse drug events supports the utilization of posaconazole new formulations as an appropriate alternative for patients with IM,[32] especially in those with renal failure (Table 2, Table S8).

Besides the retrospective nature of its design, this survey is limited by several factors. Firstly, there is a selection bias, as we only considered patients with a proven or probable diagnosis through culture, microscopy, cytology and/or histology, following the recommendations of the EORTC/MSG criteria,[27] and excluded patients diagnosed through other methods, such as PCR. Further selection bias might have been caused by a tendency to select cases with a favourable outcome for documentation in the registry. Secondly, we were able to identify only a small number of patients in the posaconazole new formulations groups receiving first-line treatment. Despite our initial goal of 25 cases per group, we could not identify enough cases of patients receiving posaconazole new formulations, even after inclusion of patients with combined administration with amphotericin B in the analysis and extensive communications with national and international networks and colleagues worldwide. This is perhaps unsurprising given the limited usage of posaconazole new formulations alone for first-line treatment of IM, combined with the rarity of IM and the recent introduction of isavuconazole.[5] Unfortunately, this limitation in sample size is further complicated by the heterogeneous exposure to different drugs used to treat IM. Some patients in the posaconazole new formulations groups received both the intravenous and oral delayed-release formulation. Others received additional agents active against Mucorales, including isavuconazole, amphotericin B and/or posaconazole oral suspension, and experienced a switch in their original antifungal treatment. In the control group, there was also a certain degree of heterogeneity, as different amphotericin B formulations compared were grouped together. Finally, we were not able to include the influence of therapeutic drug monitoring in our analysis, as it was not performed in all cases. Overall, these limitations, and in particular the limited sample size, weaken the generalizability of our results and hamper further differentiation of specific effects of intravenous posaconazole and the oral delayed-release formulation.

In conclusion, even though amphotericin B remains the standard of care for treatment of IM, posaconazole new formulations may represent a suitable alternative for the treatment of IM, especially for patients with renal impairment. However, this recommendation must be interpreted with caution, mainly based on the limited sample size of our study.

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Author contributions

J. S.-G. enrolled patients and performed formal validation of the clinical details, extracted data from FungiScope® patients, performed the statistical analysis and interpreted the data, wrote the initial draft of the manuscript, created tables and figures and revised and approved the final manuscript. D. S. was the FungiScope® project manager, enrolled patients, performed formal and medical validation of the clinical details and revised and approved the final manuscript. P. K. and S. C. M. provided clinical details from local patients, performed medical validation of the clinical details and revised and approved the final manuscript. R. H., N. K., Z. R., I. F-R., P. I., M. A. B-P., J. Y. R., G. D., A. B., C. G-V., M. H., S. R. M., M. P. C., G. K., W. J. H., N. I., R. K., H. O., O. P., E. S., D. C. S., and B. W. provided clinical details from local patients and revised and approved the final manuscript. H. W. was in charge of FungiThek (the biobank of FungiScope®) and revised and approved the final manuscript. J. J. V. conceived the study idea and revised and approved the final manuscript. O. A. C. invented and led FungiScope®, conceived the study idea, provided clinical details from local patients and revised and approved the final manuscript. M. J. G. T. V. conceived the study idea, led the research consortium, provided clinical details from local patients and revised and approved the final manuscript.

Supplementary data

Tables S1 to S9 are available as Supplementary data at *JAC* Online.

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