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Systematic Review

Posaconazole as single or adjunctive antifungal in mucormycosis of the maxilla: systematic review and meta-analysis

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Abstract – Introduction: The aim of this systematic review was to analyse the benefits of utilizing posaconazole as a single drug therapy or in combination with other antifungals for the treatment of maxillary mucormycosis as opposed to sole use of amphotericin B. **Materials and methods:** Databases (MEDLINE via PubMed, Cochrane, EBSCO-host, Scopus, Science Direct, Clinical Trial Registry- India (CTRI) and Google scholar), review articles were searched from 1997 to 2022, using various MeSH terms.
Results: After application of the inclusion and exclusion criteria, four articles were finally selected. Three-month survival rate and duration of hospital stay were analysed as primary outcomes. There was no difference in survival among cases of maxillary mucormycosis treated with either drug alone. Death reported after treatment with combination treatment was less as compared to that with amphotericin B alone; however, there was non-significant difference in survival among cases treated with posaconazole in addition to amphotericin B or amphotericin B alone.
Conclusion: Posaconazole can be used a single drug therapy for the treatment of maxillary mucormycosis due to its benefits outweighing its risks. The limitations of this study are the paucity of studies and Randomized Controlled Trials available in the literature in this field of study.

Introduction

Zygomycosis (mucormycosis), previously regarded as an uncommon fungal infection, seems to be becoming more common [1]. It primarily affects immunocompromised individuals, including those with haematological malignancies, those who have undergone HSCT [2] or solid organ transplantation (SOT) [3], those with diabetes mellitus and ketoacidosis [4], premature infants [5], burns or trauma victims, as well as patients receiving deferoxamine medication who have increased serum iron levels. Recently this infection affected multitudes of SARS-CoV-2 infected individuals particularly during the 2nd wave of the COVID-19 pandemic in India facilitated by the state of systemic immunologic compromise of the patients due to immunosuppressive medications and rising incidence of diabetes mellitus. India recorded significant tolls of morbidity and mortality attributable to COVID-19 Associated Mucormycosis (CAM) [6]. Worst affected seemed to be those with uncontrolled diabetes, immune compromise, immunosuppression following organ transplantation, and those who received prolonged or high doses of systemic corticosteroids [7].

The invasive fungal infection caused by order Mucorales known as mucormycosis, also referred to as black fungus disease, is rare, time-sensitive, opportunistic, devastating with a high case fatality rate of 46% [8], which is partly explained by their inherent high level of resistance to several antifungal drugs. The Rhino-Orbito-Cerebral Mucormycosis (ROCM) is the most prevalent subtype of the disease [9].

The standard management of mucormycosis consists of aggressive debridement of the infected hard and soft tissue and parenteral antifungal therapy with amphotericin B. Despite this multimodal approach, reported mortality rates reach 91%. Currently the only antifungals with proven activity against Mucorales are amphotericin B (mainly the lipid formulations), posaconazole and the newly approved triazole isavuconazole [10]. Newer antifungal drugs like posaconazole, voriconazole and itraconazole have been used against mucor with variable results and evidence. Amphotericin B is the gold standard for medical therapy of mucor but it needs hospitalization and monitoring due to its side effects whereas posaconazole can be

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administered on an outpatient basis reducing the duration of hospital stay. Moreover, it can be administered by the oral route and is reported to have minimal side effects in comparison.

There are many studies on the efficacy of amphotericin B alone or with a combined administration of posaconazole in treatment of mucormycosis. Therefore, the current systematic review is planned to provide a comprehensive data pool regarding the use of posaconazole as a single drug therapy in the treatment of maxillary mucormycosis which is lacking in the literature.

Material and methods

Protocol and registration

The protocol of this systematic review was registered on PROSPERO (International prospective register of systematic reviews, National Institute for Health Research) (ID: CRD42021237783). This review follows the PRISMA statement 2009.

Eligibility criteria

The eligibility criteria of the included studies were determined a priority with the scope of evaluating the effectiveness of posaconazole as a single drug therapy in cases of maxillary mucormycosis. Only studies conducted in patients above 18 years with presence of chronic maxillary osteomyelitis due to mucormycosis and maxillary sinus mucormycosis only involving the bony walls of maxillary sinus were included. Studies on chronic maxillary osteomyelitis due to mucormycosis and maxillary sinus mucormycosis treated by antifungal agents amphotericin B alone, posaconazole alone, or combination of both were selected. Randomized and non-randomized controlled trials of posaconazole used alone as opposed to it being used in combination with amphotericin B or Amphotericin being used alone were collected.

Participant/population characteristics

Inclusion criteria: Clinical in-vivo studies conducted between 1997 and 2020 on patients above 18 years with chronic maxillary osteomyelitis due to mucormycosis and maxillary sinus mucormycosis only involving the bony walls of maxillary sinus were included.

Exclusion criteria were: 1. studies of maxillary osteomyelitis due to other aetiology, 2. reports of cases of maxillary sinus mucormycosis not involving bony margins of maxillary sinus, 3. mucormycosis of another anatomical region, and 4. Maxillary osteomyelitis due to other fungal/viral infections.

Intervention: Studies with cases treated by Posaconazole alone or amphotericin B + posaconazole were included; cases not treated by amphotericin B or pozaconazole were excluded.

Comparison/ control group: studies with cases treated with amphotericin B alone.

Outcomes reported were: (1) survival rate till three months of follow-up, and (2) hospital stay- in days.

Study design: Randomized clinical trials (RCTs), and non-randomized controlled trials were included; case reports, case series, review articles, conference abstracts, interviews, commentaries, replies to editor/author were excluded.

Information sources

Systematic search of major electronic databases was performed to include publications in English in the time period of 1997–2022. Electronic searches were performed in PUBMED, Cochrane Central Register of Clinical Trials (CENTRAL) and additionally in Google Scholar. The search keywords and strategy were developed and search was performed independently by two authors.

Search

For PUBMED, the search limits were set for time period of 1997–2022. The search on CENTRAL was carried out and search limits were set for only trials, published between 1997 and 2022 and search word variations were applied. The PUBMED and CENTRAL search strategy are depicted in Table I.

Additional search was also carried out on Google Scholar using search terms: posaconazole, amphotericin B + posaconazole, amphotericin B, maxillary mucormycosis.

Study selection

Study selection was performed by two independent authors and any discrepancy was resolved by the third author. Screening of title and abstracts was performed by two authors. Full text was located for abstracts adhering to the inclusion criteria and in cases where information from abstracts were inconclusive. A second stage consisted of reading the full texts and judging studies to be included based on the eligibility criteria through the PICOS strategy.

Disagreements on study inclusion were solved by consensus with a third author. Duplicated studies in the databases search were considered once.

Data collection process

Two authors collected the data independently from the included studies. Disagreements were solved by consensus with a third author.

Data items

Information related to the study including study design, authors, country, year, type of study, method of randomization, description of population in terms of age and gender, sample size, details of inclusion and exclusion criteria in study, control group, surgical treatment carried out, regimen of antifungal therapy followed, adverse drug reactions, follow-up duration, survival rate and statistical analysis were extracted. The data were sorted based on the outcome and intervention. The primary outcome was regarded as the 3-month survival

Table I. The PUBMED and CENTRAL search strategy.

Sr. no.	Category (based on)	Keywords
PUBMED search strategy		
1	Intervention	Amphotericin B; posaconazole
2	Intervention	Posaconazole
3	Intervention	Liposomal amphotericin B; posaconazole
4	Intervention	Amphotericin B deoxycholate; posaconazole
5		**#1 OR #2 OR #3 OR #4**
6	Control/comparison	Amphotericin B
7	Control/comparison	Liposomal amphotericin B
8	Control/comparison	Amphotericin B deoxycholate
9		**#6 OR #7 OR #8**
10	Outcome	3-month survival
11	Outcome	Duration of hospital stay
12		**#10 OR #11**
13		**#5 AND #9 AND #12**
14		**Limit #13 to English language**
Cochrane Central Register of Controlled Trials (CENTRAL) search strategy		
1	Intervention	Posaconazole/amphotericin B + posaconazole
2	Control/Comparison	Amphotericin B
3	Outcome	3-month survival/duration of hospital stay
4		**#1 AND #2 AND #3**

rate and the duration of hospital stay. The recovery criteria were considered to be the absence of symptoms, and the absence of signs of disease clinically and radiographically. The intervention in the studies thus included posaconazole used alone or amphotericin B with posaconazole combination therapy. In the comparator group were cases treated with amphotericin B alone. Details regarding the complete treatment given were recorded including the surgical intervention if any and the exact antifungal regimen followed with the route of drug administration. In case of missing data, the authors were contacted three times by electronic message.

The data were coded and inserted in an excel data sheet in software.

Quality assessment

The qualitative analysis of the studies was performed from the bias risk assessment using the Cochrane risk of bias tool: Bias Risk Assessment of Randomized Controlled Studies—Cochrane Handbook.

The following domains were considered: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other source of bias.

The blinding of operator was not considered since it is impossible to perform in these types of intervention.

To make general judgment of the risk of individual bias, each included study was judged as "high" risk of bias for negative domain (red), "low" risk of bias for positive domain response (green), and risk of "uncertain" bias (yellow) when response was not clear.

When the study was judged as "uncertain," the authors were contacted *via* e-mail at least three times for more information and allowed to be classified as "low" (green) or "high" (red) risk of bias.

Once this contact was not possible, the article remained with some "uncertain" bias risk.

Risk of bias in individual studies

Quality of included case-control studies was evaluated using JBI Critical Appraisal Tool for case-control studies. The JBI critical appraisal tool includes 10 questions addressing the internal validity and risk of bias of included studies, particularly confounding, selection, and information bias, in addition to the importance of clear reporting. The number of sub-items were converted to percentages. In each of the sub-items, the number of studies evaluated as "Yes," "No," "Unclear," and "Not applicable" were analysed. All the sub items were adequately reported in the study included.

Quality of included observational studies was evaluated using JBI Critical Appraisal Tool for Cross-sectional studies. The JBI critical appraisal tool includes eight questions addressing the internal validity and risk of bias of included studies,

particularly confounding, selection, and information bias, in addition to the importance of clear reporting. The number of sub-items were converted to percentages. In each of the sub-items, the number of studies evaluated as "Yes," "No," "Unclear," and "Not applicable" were analysed. All the sub items were adequately reported in both the studies included.

Quality of included case-series articles was evaluated using JBI Critical Appraisal Tool for Case-series. The JBI critical appraisal tool for case series studies includes 10 questions addressing the internal validity and risk of bias of case series designs, particularly confounding, selection, and information bias, in addition to the importance of clear reporting. The number of sub-items were converted to percentages. In each of the sub-items, the number of studies evaluated as "Yes," "No," "Unclear," and "Not applicable" were analysed. On evaluating the case series according to the checklist criteria for each of 10 sub-items, the following sub-items were not reported in both the case series: sub-item 1, "Were there clear criteria for inclusion in the case series?" and sub-item 6, "Was there clear reporting of the demographics of the participants in the study?". Following sub item was not clearly mentioned in one of the case series: "Did the case series have complete inclusion of participants?". Table II depicts the JBI Critical Appraisal Tool for case-control studies, Cross-sectional studies and Case-series.

Table III depicts the classification of each Case Series According to the Joanna Briggs Institute Critical Appraisal Checklist.

Analysis of the two case-series revealed the report rates classified as "Yes" to be a maximum of 80% and minimum of 40%. Those classified as "No" had a maximum report rate of 50% and minimum of 20%.

Table IV contains the data extraction of the studies included, with the details of the type of study, population, intervention and outcomes.

Results

Study selection

The initial search strategy yielded a total of 48 results including the studies obtained from Google Scholar. After duplication removal, 21 articles were evaluated for their abstracts and full texts. Finally, after strict and careful application of the inclusion and exclusion criteria, 4 articles were selected for the final systematic review. The PRISMA flowchart of the literature search and selection process is shown in Figure 1.

Statistical analysis

The meta-analyses, using random effects model, were applied with RevMan 5.4 (RevMan 5.4, The Nordic Cochrane Centre, Copenhagen). Heterogeneity was assessed by Q test and quantified with I^2 statistics. Data on event frequency and total sample size were obtained from selected studies. Survival among the cases of mucormycosis was considered as the main outcome. Two separate comparisons for survival were performed: comparison between posaconazole alone and amphotericin B alone, and comparison between posaconazole plus amphotericin B and amphotericin B alone, using no. of deaths among total sample size. For analyses, if the test showed substantial heterogeneity ($I^2 > 50\%$), a random effects model was applied, or else ($I^2 \leq 50\%$), a fixed effects model would be used.

Comparison of survival due to posaconazole alone or amphotericin B alone in mucormycosis cases: The meta-analysis was performed on four studies that have qualified with required data outcome that could be analysed quantitatively. The results of overall comparison have been depicted as forest plot in Figure 2. With the meta-analysis conducted for selected studies, heterogeneity was less than 50% ($I^2 = 17\%$); hence, fixed effect model was applied. There was no difference ($p = 0.92$) in survival among cases of mucormycosis treated with posaconazole alone or amphotericin B alone, with odds ratio of 0.95 (95% CI = 0.39–2.32; Z value = 0.11).

Comparison of survival due to posaconazole plus amphotericin B or amphotericin B alone in mucormycosis cases: The meta-analysis was performed on four studies that have qualified with required data outcome that could be analysed quantitatively. The results of overall comparison have been depicted as forest plot in Figure 3. With the meta-analysis conducted for selected studies, heterogeneity was less than 50% ($I^2 = 0\%$); hence, fixed effect model was applied. Death reported after treatment with combination of posaconazole plus amphotericin B were less as compared to deaths reported after treatment with amphotericin B alone; however, there was non-significant difference ($p = 0.22$) in survival among cases of mucormycosis treated with posaconazole plus amphotericin B or amphotericin B alone, with odds ratio of 0.70 (95% CI = 0.39–1.25; Z value = 1.22).

Discussion

Summary of evidence

Rhinocerebral mucormycosis, also called zygomycosis, is a rare disease caused by filamentous fungi involving the nose, paranasal sinuses, and brain. It is an opportunistic pathogen. Mucormycosis is generally subdivided into five clinical entities: (1) rhinocerebral, (2) pulmonary, (3) gastrointestinal, (4) cutaneous, and (5) disseminated disease [14]. With the rhinocerebral form which is the most common presentation the infection starts in the nasal cavity and extends to adjoining paranasal sinuses. Early implantation of fungi is common in maxillary sinus with a mass of fungal growth called a fungal ball. In undiagnosed or untreated cases, the infiltration of bone is common. It then progresses to the brain *via* either ethmoid sinuses, orbital apex, and through bone erosion or through angioinvasion [15]. All clinical subtypes progress rapidly because of angioinvasion, which leads to thrombosis and tissue necrosis, which prevents drug penetration to affected tissues and contributes to dissemination [16–18].

Table II. JBI Critical Appraisal Tool for case–control studies, cross-sectional studies and case-series.

JBI Critical Appraisal Tool for case–control studies:		
	Salmanton-Garcia, 2016 [11]	
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Y	
2. Were cases and controls matched appropriately?	Y	
3. Were the same criteria used for identification of cases and controls?	Y	
4. Was exposure measured in a standard, valid and reliable way?	Y	
5. Was exposure measured in the same way for cases and controls?	Y	
6. Were confounding factors identified?	Y	
7. Were strategies to deal with confounding factors stated?	Y	
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	Y	
9. Was the exposure period of interest long enough to be meaningful?	Y	
10. Was appropriate statistical analysis used?	Y	
Total Yes score	10/10 (100%)	
JBI Critical Appraisal Tool for cross-sectional studies:		
1. Were the criteria for inclusion in the sample clearly defined?	Y	
2. Were the study subjects and the setting described in detail?	Y	
3. Was the exposure measured in a valid and reliable way?	Y	
4. Were objective, standard criteria used for measurement of the condition?	Y	
5. Were confounding factors identified?	Y	
6. Were strategies to deal with confounding factors stated?	Y	
7. Were the outcomes measured in a valid and reliable way?	Y	
8. Was appropriate statistical analysis used?	Y	
Total Yes score	8/8 (100%)	
JBI Critical Appraisal Tool for case-series:		
	Esteak, 2022 [12]	Iqtdar, 2022 [13]
1. Were there clear criteria for inclusion in the case series?	N	N
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Y	Y
3. Were valid methods used for identification of the condition for all participants included in the case series?	Y	Y
4. Did the case series have consecutive inclusion of participants?	N	Y
5. Did the case series have complete inclusion of participants?	U	Y
6. Was there clear reporting of the demographics of the participants in the study?	N	N
7. Was there clear reporting of clinical information of the participants?	Y	Y
8. Were the outcomes or follow up results of cases clearly reported?	Y	Y
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	N	Y
10. Was statistical analysis appropriate?	N	Y

Early diagnosis is paramount for preventing tissue invasion and dissemination, but early diagnosis remains challenging (even in patients at high risk), because patients can exhibit nonspecific symptoms that are frequently attributed to other infections [19–22].

The treatment of mucormycosis is multimodal, involving antifungal therapy, surgery, immune restoration, and other adjunctive therapies [23].

The highest levels of therapeutic success have been achieved when aggressive surgical debridement and reversal of underlying host factors are combined with medical management [24,25].

European medical guidelines advocate amphotericin B (AmB) based drugs as first-line treatment. However, their utilization is restricted by significant nephrotoxicity, even when liposomal formulations are employed. Along with the

Table III. Classification of each case series according to the Joanna Briggs Institute Critical Appraisal Checklist.

Study	Yes [*n*/*N* (%)]	No [*n*/*N* (%)]	Unclear [*n*/*N* (%)]	NA [*n*/*N* (%)]
Esteak, 2022 [12]	4/10 (40)	5/10 (50)	1/10 (10)	–
Iqtadar, 2022 [13]	8/10 (80)	2/10 (10)	–	–

most recent triazole, isavuconazole, posaconazole is another antifungal with *in vitro* activity against Mucorales. To date, use of posaconazole for treating IM has been mainly restricted to salvage treatment, although there are case reports of patients treated with posaconazole new formulations (POSnew) as first-line treatment. 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. Previous studies demonstrated the benefits of posaconazole new formulations concerning pharmacokinetics, safety and tolerability [11].

Amphotericin B is a polyene macrolide antibiotic derived from the actinomycete *Streptomyces nodosus*. All polyenes have a common mechanism of action in that they preferentially bind to ergosterol, the primary sterol in the fungal cell membrane. The consequence of this binding includes disruption of the osmotic integrity of the membrane, with leakage of intracellular potassium and magnesium, and also the disruption of oxidative enzymes in target cells. Amphotericin B has a relatively broad spectrum of anti-fungal action. The main problems associated with the use of conventional amphotericin B have always been due to its poor aqueous solubility and toxicity rather than antifungal resistance [26]. AmB remains the cornerstone medical treatment for mucormycosis and early initiation of AmB is associated with improved survival rates [27–29]. The broad-spectrum polyene antifungal drug amphotericin B is available in a lipid-associated formulation called liposomal amphotericin B (AmBisome®). Clinical guidelines favour the lipid formulations of AmB, because they allow for higher doses to be given with less toxicity [30]. The optimal dosages for the lipid formulations of AmB ranges from 3 to 15 mg/kg per day [31]. It was created to enhance the tolerability profile of amphotericin B deoxycholate, which, although being linked to nephrotoxicity and infusion-related complications, was for a long time regarded as the gold standard of antifungal treatment. In studies with strict controls, liposomal amphotericin B was just as effective as amphotericin B deoxycholate and amphotericin B lipid complex in treating febrile neutropenia in adults and children [32]. Liposomal amphotericin B use is still somewhat constrained by these adverse events, despite having fewer infusion-related adverse events and less nephrotoxicity than amphotericin B deoxycholate and amphotericin B lipid complex. The cost of liposomal amphotericin B therapy may also restrict its use, but further pharmacoeconomic studies are required to fully define its cost effectiveness compared with other antifungal agents. Based on comparative data from well controlled trials, extensive clinical experience and its broad spectrum of activity, liposomal amphotericin B remains a first-line option for empirical therapy in patients with zygomycosis until the advent of newer triazoles which, although not having the formidable track record of the amphotericin B formulations, are finding a newfound place of importance not only as a second line or combination drug but, as newer research proves, can also be reasonably considered for single drug therapy. Due to not only their comparatively fewer side effects, safer routes of drug administration and also economic viability, they have gained great favour especially in the recent times and specifically in patients with COVID-19 associated mucormycosis.

An extended-spectrum triazole antifungal drug called posaconazole which is orally available is now being tested in patients to prevent and treat fungal infections in both immunocompetent and immunocompromised individuals. Similar to other azole derivatives, posaconazole inhibits the enzyme lanosterol 14-demethylase and consequently inhibits the biosynthesis of ergosterol, which is an essential component of fungal cell membrane. This results in an accumulation of methylated sterol precursors and depletion of ergosterol within the cell membrane, thereby weakening the structure and function of the fungal cell membrane, which is considered to be responsible for the antifungal activity of posaconazole.

Posaconazole has significant efficacy against a variety of types of infectious yeast and filamentous fungus, as shown by numerous *in vitro* investigations [33]. Posaconazole is available in oral and intravenous formulations, is highly lipophilic, and gets distributed extensively in tissues. It is better tolerated than amphotericin B and has lower toxicity. In a study by Courtney *et al.* [34], posaconazole was shown to be an effective treatment for patients with invasive fungal infections refractory to prolonged therapy with standard antifungal agents such as amphotericin B, fluconazole, and itraconazole. The need for efficacious, safe, and well-tolerated broad-spectrum antifungal agents that do not require dose modifications in patients with chronic renal disease was addressed in this study. Additionally, exposure to posaconazole after administration of a single 400-mg dose in all renal function groups was similar to that observed in previous studies of healthy volunteers. In addition, posaconazole had a large apparent volume of distribution and was slowly eliminated, suggesting extensive and prolonged exposure of the drug in the tissues. The study extrapolated that dosage adjustments for patients with varying degrees of chronic renal disease are not

Table IV. Data extraction describing type of study, population, intervention, control and outcomes.

Sr. no.	Study, year, country	Study design	Population	Inclusion and exclusion criteria	Intervention	Control/comparator group	Outcome
1	Somia Iqtadar, Masooma Hashmat, *et al.*, 2022, Pakistan [13]	Retrospective study	7 patients were included Mean age-53±10years Gender : Males- 4 Females −3	All the patients had confirmed COVID-19 infection and typical symptoms of ROCM at the time of admission and biopsy-proven mucormycosis	Group 1: 3 patients underwent surgical debridement with antifungal therapy with Amphotericin B + Posaconazole	Group 2: 4 patients underwent surgical debridement with antifungal therapy with only Amphotericin B	1 patient from Group 2 died. The remaining 6 patients in the study survived.
2	Kyvernitakis, Torres, *et al.*, USA, 2016 [10]	Retrospective study	106 patients were included Mean age −19 to 79 yrs Males − 69 Females- 40	Patients were eligible for inclusion if they met the European Organization for Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group definition for invasive mucormycosis infection. Patients were excluded if they were younger than 18 years old, had solid tumours, had possible mucormycosis, had a mixed fungal infection or died within 3 days of treatment initiation	Group 1: 7 patients received Posaconazole single drug therapy, 59 patients received combination of liposomal Amphotericin B + Posaconazole	Group 2: 40 patients received Liposomal Amphotericin B monotherapy	13% with monotherapy versus 15% with combination treatment died within 6 weeks
3	Jon Salmanton-Garcıa, Danila Seidel, *et al.* Germany, 2019 [11]	Prospective case-control study	79 patients were included Mean age- not mentioned Gender − not mentioned	Patients with biopsy proven maxillary mucormycosis were included.	Group 1: 5 patients received Posaconazole monotherapy, 18 patients received Amphotericin B + Posaconazole combination therapy	Group 2: 56 patients received Amphotericin B monotherapy	24 patients of Group 2 died and 6 patients of Group 1 died
4	Skiada, Pagano, *et al.*, Greece, 2011 [14]	Retrospective case-control study	230 cases were included in the study. The median age of the patients was 50 years. 60% of the patients were of male gender.	The Working Group on Zygomycosis of the European Confederation of Medical Mycology (ECMM) prospectively collected cases of proven zygomycosis in 13 European countries occurring between 2005 and 2007.	Group 1: 17 patients received Posaconazole monotherapy, 48 patients received Amphotericin B + Posaconazole combination therapy	Group 2: 90 patients received Amphotericin B monotherapy	19 patients in Group 1 died and 32 patients in Group 2 died.

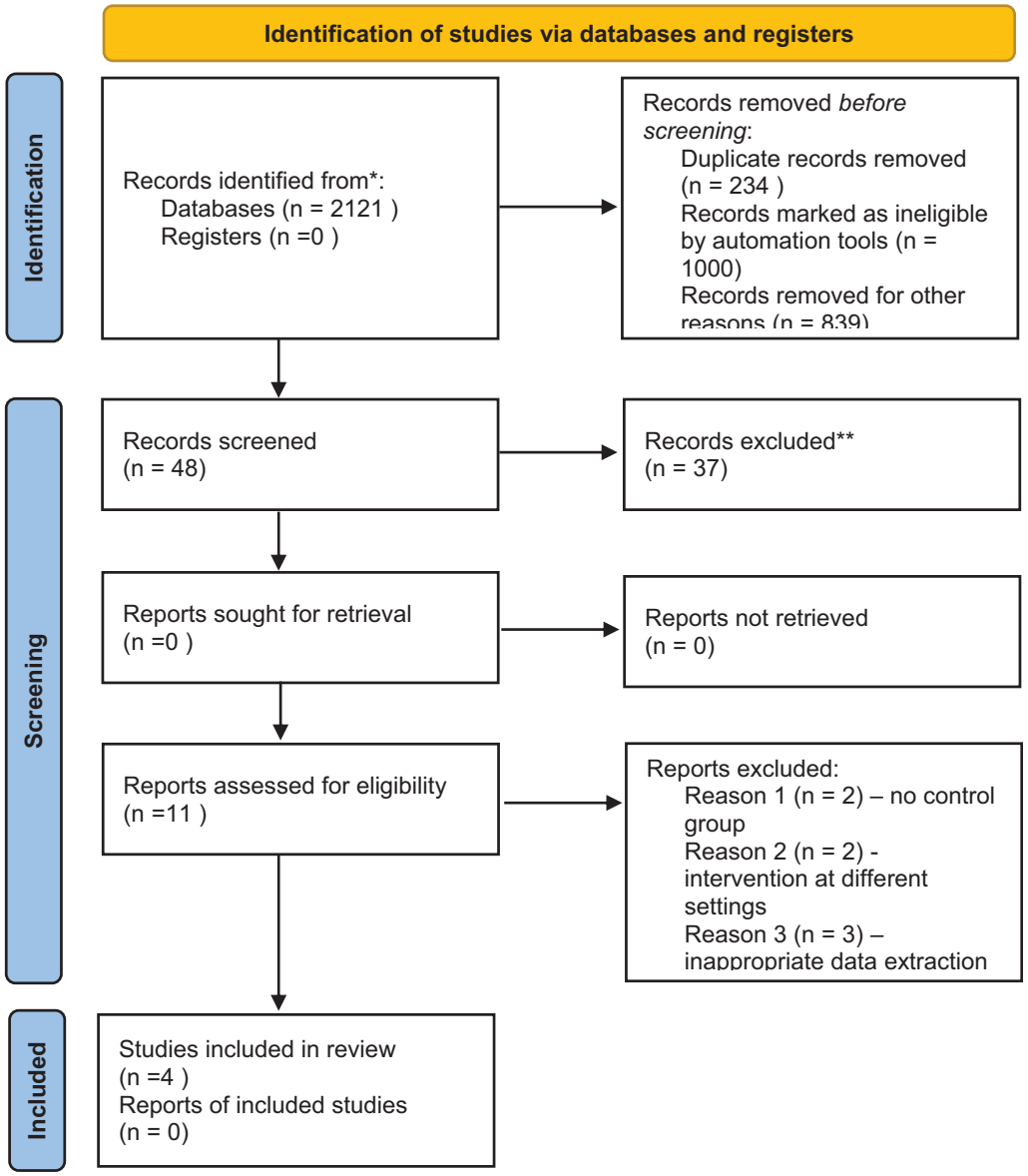

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

required [34]. The results of seven studies in the United States and Europe, comprising a total of 197 children and adolescents, suggest that oral posaconazole solution has good safety and tolerability and moderate efficacy against invasive fungal infection [23].

The use of oral posaconazole solution as salvage therapy has also been associated with increased survival rates in adult and pediatric populations [35,36]. In further detail on this drug, posaconazole (Noxafil®) is a systemic triazole antifungal drug derived from itraconazole and exerts the same antifungal mechanism of action as other azole derivatives. Three formulations are currently available, namely an oral suspension (40 mg/mL), a delayed-release tablet (100 mg), and an intravenous formulation (18 mg/mL).

The posaconazole suspension is indicated to be administered as 200 mg three times daily (TID) for prophylaxis or as 400 mg twice daily (BID), or 200 mg four times daily (QID) for treatment of refractory IFDs or for treatment of patients with IFD who are intolerant to first-line therapy. The delayed-release tablet and intravenous formulation are indicated to be given as a loading dose at 300 mg BID on the first day and a maintenance dose at 300 mg once daily (QD) thereafter.

In clinical practice, the posaconazole suspension has been used as salvage therapy of mucormycosis and showed satisfactory efficacy in many cases, which also indicates an encouraging prospect for the new formulations with higher drug exposures.

In our systematic review focused on the treatment of mucormycosis of the maxilla, posaconazole used as a single

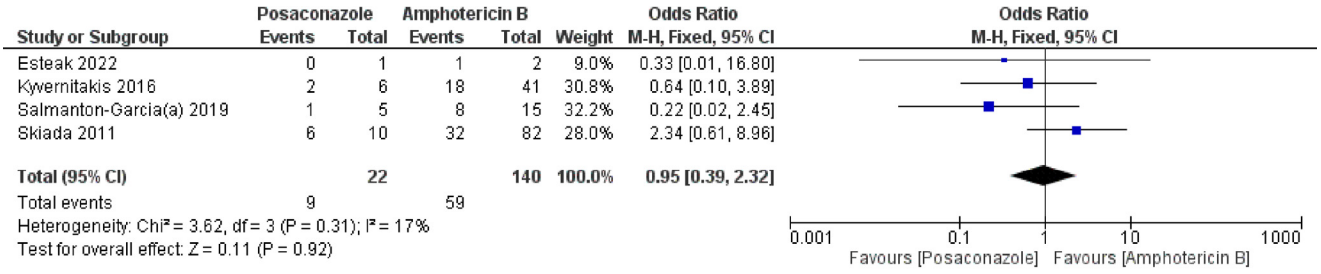

Fig. 2. Comparison of survival due to posaconazole alone or amphotericin B alone in mucormycosis cases.

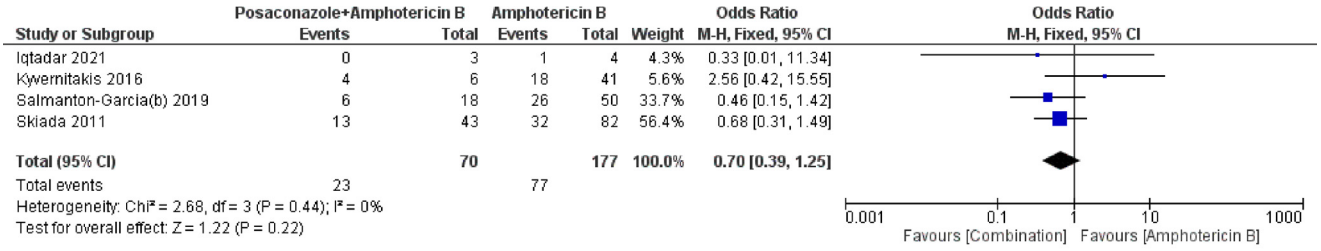

Fig. 3. Comparison of survival due to posaconazole plus amphotericin B or amphotericin B alone in mucormycosis cases.

drug therapy clearly had similar outcomes in terms of survival rate as of amphotericin B used alone. Death reported after treatment with combination of posaconazole plus amphotericin B were less as compared to deaths reported after treatment with amphotericin B alone. Based on scientific evidence of the findings posaconazole can be used a single drug therapy for the treatment of maxillary mucormycosis due to its many benefits outweighing its risks.

On the horizon, upon observations of the latest literature is the finding that posaconazole accumulates in human peripheral blood mononuclear cells and polymorphonuclear leukocytes triggered an investigation on the impact of posaconazole-loaded leukocytes on the antifungal activity and functional capacity of different leukocytes. This indicates the potential of posaconazole-loaded leukocytes as a novel antifungal strategy, in which leukocytes serve as a vehicle to target the infection site and further increase the antifungal effect [37].

Conclusion

Based on scientific evidence of the findings posaconazole can be used a single drug therapy for the treatment of maxillary mucormycosis due to its many benefits outweighing its risks. The limitations of this study are the paucity of studies available in the literature in this field of study. There is a need for more randomized controlled studies to be conducted to strengthen the knowledge base for further research.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

Ethical approval was not required.

Informed consent

Not applicable for this study.

Author contribution

A. Pardiwala: Writing original draft, Conceptualization, Methodology, Investigation. A. Datarkar: Conceptualization, Supervision, Visualization. V. Manekar: Visualization, Conceptualization, Methodology. S. Daware: Writing- Reviewing and Editing, Methodology.

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