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Original Article

Posaconazole as a Treatment for Rhinosinusitis Mucormycosis

Kamran Amir Khan,[1] Sameed Ullah Qureshi,[1] Zuhra Naheed Khan,[2] Maryam Saleem Raza[2] Imran Mohib Khan[1]

[1]North West General Hospital, Peshawar, Pakistan Kidney & Liver Institute, Lahore

Abstract

Objective: To determine the performance of Posaconazole as a salvage therapy in patients with rhino-orbital-cerebral mucormycosis.

Methods: After the ethical committee gave its approval, this cross-sectional study was performed at the Northwest General Hospital & Research Centre, Peshawar, Pakistan. It comprised of data of patients diagnosed with mucormycosis from February 2018 to June 2021. All the patients underwent surgical intervention and were given Posaconazole either as salvage therapy or along with Amphotericin B for the treatment of mucormycosis. Convenient sampling was used and a structured format was used for data collection. SPSS 21 was used for data analysis.

Results: Out of the 16 patients, 14 patients improved with Posaconazole with reduction in the lesions. All 16 patients underwent surgical procedure for debridement and given both Amphotericin and Posaconazole. One patient died due to sepsis, and another patient died due to complications of COVID-19 infection. The remaining 14 patients recovered from the surgery, one patient was lost to follow up, and one patient suffered a re-infection, but recovered with Posaconazole.

Conclusion: The study highlights the benefit of using Posaconazole either as combined therapy, single use or as a step down therapy for mucormycosis with minimal side effects.

Keywords: Posaconazole, mucormycosis, fungal, infection, rhinosinusitis

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Corresponding Author: Dr. Kamran Amir Khan **Email:** kkhan@nwgh.pk

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Introduction

Mucormycosis is an opportunistic fungal infection caused by the fungi belonging to the order Mucorales. It is transmitted mainly by inhalation of sporangiospores, occasionally by ingestion or traumatic inoculation of soil or foreign bodies. However, contaminated medical devices are responsible for a considerable percentage of cases.[1] Depending on the localization of the infection we can differentiate six types of mucormycosis: rhino-orbital-cerebral mucormycosis, pulmonary, cutaneous, gastrointestinal, disseminated, and mucormycosis of uncommon sites.[2] The most common form is the rhino-sinusitis with complications leading to orbito-cerebral involvement. The main risk factors for suffering this type of mucormycosis are Diabetes Mellitus, tumors of the hematopoietic and lymphoid tissues, hematopoietic stem cell and solid organ transplantations.[3,4] In immuno-compromised patients phagocytosis is inefficient, which allows germination of spores into hyphae which have the ability of invade the blood vessels (angioinvasion).

Rhinosinusitis fungal infection starts at the nasal turbinates, this leads to a sinusitis that can progresses into a pansinusitis in a few days. The infection may stay contained in the sinuses or progresses towards the plate and can dead to the development of a dark necrotic ulceration. From the ethmoid sinus the fungi may extend towards the orbit. The angioinvasion of the orbital veins, which drain into the cavernous sinuses, is a likely beginning of the brain infection. Affected tissues are damaged by ischemia and necrosis caused by the angioinvasion.[4]

The recommended treatment according to The European Conference on Infections in Leukemia (ECIL) and the European Confederation of Medical Mycology (ECMM) is liposomal Amphotericin B combined with surgical debridement of devitalized tissue when possible. Isavuconazole and Posaconazole have remained as second-line treatments. Combinations of treatments are not

yet recommended since there is not enough evidence of superiority compared to monotherapy.[5,6] However, Amphotericin B is nephrotoxic and can cause severe acute kidney injury. For that reason, patients must remain hospitalized for monitorization. Other lipid formulations of Amphotericin B have shown a decrease of the side effects.[7] Contrary, there is no toxicity associated to Posaconazole, which makes it an interesting alternative therapy for mucormycosis.[8] The ECMM recommends the use of Posaconazole delayed-release (DR) tablets or IV forms with moderate strength.[5] The aim of our study is to highlight the efficacy of Posaconazole, either alone or combined with Amphotericin B for ROCM.

Methods

This study includes thirteen patients from the Northwest General Hospital & Research Centre, Peshawar, Pakistan. The hospital is a tertiary care hospital situated in Peshawar to the residents of Khyber Pakhtunkhwa and Afghanistan. All of the patients taken in the study were diagnosed with rhinosinusitis mucormycosis between the timeframe of February 2018 and August 2021. The diagnosis was proven through biopsy and consequent fungal culture that revealed the presence of rhizopus species mucor. The cross-sectional study was conducted after the approval of the hospital ethical committee.

Their medical records were completed in with any other co-morbidities and a diabetic control with the analysis of HbA1c. Next, the surgery and the Amphotericin B and Posaconazole treatment protocol was programmed. Prior to the surgery, a computed tomography scan or magnetic resonance imaging were performed in order to define the diagnosis and extension of the infection. After the surgery was performed, Posaconazole was used either as salvage therapy or along with Amphotericin B for the treatment of mucormycosis. The Amphotericin B dosing was 1mg/kg body mass. Posaconazole was delivered in oral suspension with a dose of 200mg four times a day together with meals or with tablets form with 300 mg starting twice daily for one day followed by 300 mg daily. The length of the treatment for these drugs was variable depending on the patients' clinical situation. After the treatment regime was completed, the patient was re-evaluated with repeat scans and if deemed, another surgery was considered. The second surgery was performed where there was extension of the infection or developed complications.

After the surgical and chemical treatment 11/16 (73.33%) patients underwent a follow up computed tomography scan after 0.16-3 years. 13/16 (81.25%) of the patients were confirmed to have regressed or disease free after all the treatment and interventions were completed. There was one case which was lost on follow-up. The remaining two patients died, one due to sepsis caused by his leukemia and the other due to Covid-19 complications.

Convenient sampling was used, just including patients with a confirmed diagnosis for rhinosinusitis mucormycosis. A structured format was used for data collection and SPSS 21 was used for descriptive data analysis.

Results

Table 1 presents the demographic details of the study participants, including age, sex, co-morbidities, and HbA1c levels. It provides an overview of the patients' pre-existing health conditions, particularly their diabetic status, which is relevant to mucormycosis susceptibility.

Table 2 outlines the clinical presentation, surgical interventions, and treatment regimens for each patient. It includes details on the type of sinusitis, the specific surgical procedure performed, duration of Posaconazole and Amphotericin B treatment, and any complications encountered.

Table 3 summarizes the survival outcomes and follow-up scan results post-treatment. It provides insights into disease regression, static conditions, or continued disease presence in patients, indicating the efficacy of the treatment approach used.

Table 1: *Demographics of Study Subjects*

ID	Age(years)/ Sex	Co-Morbidities	HbA1c (%)
1	53/M	Hypertension, Ischemic heart disease	10,6
2	45/M	Hypertension	9,7
3	43/M	Acute myeloid leukemia	5.7 (Non-diabetic)
4	55/M	Nil	11.2
5	57/F	Nil	11.4
6	55/M	Hypertension	11.9
7	67/F	Nil	12.2
8	56/M	Hypertension	9.5
9	55/M	Hypertension	11.2
10	55/F	Nil	7.9
11	45/M	Nil	10.1
12	55/M	Nil	15.0
13	62/F	Nil	11.5
14	55/M	Nil	12.6
15	60/M	Nil	12.4
16	51/F	Nil	11.4

Summary table of patients' clinical records. ID, patient identification number; M, Male; F, Female; HbA1c, glycated hemoglobin.

Table 2: *Summary table of the status of the disease*

ID	Scan	Surgery	PSZ	AB	COM	Complications
1	Paranasal sinusitis	Debridement + Middle meatal antrostomy+BAWO+Posterior septum removed	4 weeks	14 days	No	Right Proptosis
2	Right sided sinusitis	Right Lateral Rhinotomy	4 weeks	21 days	No	Cavernous Sinus Thrombosis, Right Cerebral Ischemia
3	Paranasal sinusitis	Debridement	3 days	3 days	Yes	Sepsis
4	Right sided sinusitis	Right lateral rhinotomy	8 weeks	14 days	Yes	No
5	Left sided sinusitis	Left rhinotomy + debridement	8 weeks	21 days	No	Left Basal Ganglia Infarct, left orbital cellulitis
6	Left sided sinusitis	Left Total FESS (maxillary antrostomy, uncinectomy, turbinoplasty, and ethmoidectomy) with left orbital eventration	12 weeks	21 days	No	Cavernous Sinus Thrombosis
7	Extensive right sided sinusitis	Caldwell-Luc procedure and debridement	2 weeks	14 days	Yes	No
8	Sinusitis, intracranial (sellar, prepontine) extension and non communicating hydrocephalus	Debridement and VP shunt	4 weeks	14 days	No	Intracranial (sellar, prepontine) extension and non communicating hydrocephalus
9	Pansinusitis and fractures of maxilla, nasal bones	S/P ORIF right parasymphysis, Right zygomatric buttress and extensive debridement of the palate on the left side	4 weeks	14 days	Yes	Temporal abscess
10	Left sided sinusitis	Left endoscopic medial maxillectomy	12 weeks	14 days	Yes	No
11	Extensive infective disease involving the paranasal sinuses, soft tissues of the cheeks and bilateral orbits with deformed globes	Nasal, sinuses debridement and bilateral exenteration	4 weeks	14 days	Yes	Bilateral vision loss
12	Left sided sinusitis	Debridement and left maxillectomy	8 weeks	14 days	Yes	Cavernous sinus thrombosis
13	Right sided sinusitis	Debridement and right maxillectomy	8 weeks	14 days	Yes	Left vision loss
14	Pansinusitis with with skull base erosion	Debridement and Left Lateral Rhinotomy	4 weeks	14 days	Yes	Osteomyelitis of right maxilla
15	Left pan-sinusitis	Left medial maxillectomy	6 weeks	14 days	Yes	Cavernous sinus thrombosis
16	Left pan-sinusitis	Left medial maxillectomy	6 weeks	14 days	Yes	No

ID, Patient identification number; PSZ, Posaconazole; AB, Amphotericin B; COM, Combination treatment of Posaconazole and Amphotericin B; FESS, Functional Endoscopic Sinus Surgery; S/P, Status Post; BAWO, Bilateral Antral Washout; PNS, Paranasal sinus; ORIF, Open Reduction and Internal Fixation.

Table 3: *Outcomes of the disease and the result of the follow up scan*

Patient	Survival	Follow up Scan (time post-treatment, signs)
1	Yes	Yes (1 year, static)
2	Yes	Yes (3 years, static)
3	Expired due to sepsis	No
4	Yes	Yes (2 years, static)
5	Yes	Yes (3 years, regressed disease)
6	Expired due to post Covid-19 fibrosis	Yes (1.5 year, residual disease)
7	Yes	No
8	Yes	Yes (1 year static, brain atrophy with dilated ventricle)
9	Lost follow up	No
10	Yes	Yes (2 months, regressed disease)
11	Yes	Yes (1 year, disease free)
12	Yes	No
13	Yes	Yes (4 months, disease free)
14	Yes	Yes (2 months, static)
15	Yes	Yes (2 month, regressed disease)
16	Yes	Yes (1 month, regressed disease)

Discussion

This study has shown the efficacy of the use of Posaconazole together with surgical intervention for rhinosinusitis mucormycosis and complications. The overall estimated mortality for mucormycosis rate is very high (33-50%).[3,9–11] The mortality rate obtained in this descriptive study was 25%, which highlights the potential of Posaconazole for the treatment of mucormycosis, either combined or alone. A 2006 case series including 24 patients with active mucormycosis who were treated with Posaconazole as salvage therapy obtained a 79% complete or partial response to the drug.[12] A retrospective study including 91 patients who were treated with Posaconazole only documented a 60% complete or partial response.[13] Another case series analyzed 11 patients who underwent through a solid organ transplant and developed zygomycosis. They were treated with Posaconazole (6 combined with liposomal Amphotericin B) and the overall treatment success rate was 60%.[14]

Posaconazole is a systemic triazole antifungal drug. Currently there are three formulations available, oral suspension (40 mg/mL), delayed-release tablet (100 mg) and intravenous formulation (18 mg/mL). Posaconazole in vitro antifungal activity has been proved for several fungal species, for instance Candida, Aspergillus species, Mucorales and some Fusarium species.[8] The only evidence in vivo comes from case reports/series (observational studies), like the one we conducted. These are useful for hypothesis generation, but they have several limitations such as the lack of ability to generalize, there is no control arm, and over-interpretation is frequent because the clinician self-selects the cases. Unfortunately, no randomized clinical trials are available in literature that could provide stronger evidence. Further research is needed, and since rhinosinusitis mucormycosis is a deadly disease, a non-inferiority randomized clinical trial would be ideal.

The incidence of mucormycosis is increasing worldwide, especially among the diabetic population of India and China. Nevertheless, a recent review including 851 patients from 2000 to 2017 showed that Europe (34%) reports more mucormycosis cases than Asia (31%), followed by America (28%), Africa (3%), Australia and New Zealand (3%). This phenomenon may be caused by the underreporting of some Asian countries.[9] Pakistan has one of the highest prevalence of mucormycosis, reaching and estimate of 14 cases for 100.000 people. This high proportion of mucormycosis cases may be due to the high prevalence of diabetes mellitus, which are often uncontrolled.[11]

However, studies like this one contribute to the overall knowledge of mucormycosis and its treatment strategy. This study has shown that the use of Posaconazole is a valid salvage, combined or step down therapy for the treatment of rhinosinusitis mucormycosis with complications. Another highlight of the study was that posaconazole does not require in patient stay which makes it a lot easier to administer, economically viable in this part of the world and has lesser side effects. Considering the pandemic of COVID-19 and increasing incidence of mucormycosis, data suggests that Posaconazole can be used in such patients.

Ethical Approval: The IRB/EC approved this study via letter no.NwGH/EC/14 dated 06-02-2018.

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Authors' Contribution

KAK: Conception
SUQ, ZNK: Design of the work
MSR, IMK: Data acquisition, analysis, or interpretation
ZNK, MSR: Draft the work
KAK, SUQ, IMK: Review critically for important intellectual content
KAK, SUQ, ZNK, MSR, IMK: Approve the version to be published
KAK, SUQ, ZNK, MSR, IMK: Agree to be accountable for all aspects of the work

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