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Review Article

Mucormycosis and Treatment A Review

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Abstract

Mucormycosis (Black fungus infection) is a fungal type infection affecting the sinus nasal and lungs areas. There was a rise in the infection rates of mucormycosis in the patients undergoing treatment for COVID-19. These are opportunistic infection caused due to an underlying condition in the host. Rhizopusarhizus is most commonly found to cause mucormycosis. The article is written with the objective to summarize and spread the information regarding the types of mucormycosis as well as organisms (causing agent), statistics regarding the infection spread as well as treatment of mucormycosis within India and Europe. This article also contains the mechanism of iron absorption by fungal organisms along with the host-pathogen interaction. The characteristic of this infection is the extensive angioinvasion leading to vessel thrombosis and subsequently to tissue necrosis. While being an opportunistic infection it on its own is also very deadly with a mortality rate of around 50%. The immense administration of glucocorticoids in the treatment of CoVid-19 turned out to be the root of the secondary fungal infection in the respiratory tract. First-line treatment of this infection can be done by amphotericin B. In South India drugs like Isavuconazole, Posaconazole have also been tested for their safety and efficacy. Although some cases may also require surgery. The surgery along with the antifungal treatment has been found to be more effective for the treatment of infection.

Keywords: Mucormycosis; Glucocorticoids; Mucormycosis Mechanism; Mucormycosis Treatment; Amphotericin B; Covid-19

Introduction

Mucormycosis is a rare, yet dangerous infection, also known as a black fungus. recently mucormycosis widespread was found in covid-19 patients. The covid-19 disease which is found In December 2019, in Wuhan, Hubei Province, China, there was a series of acute typical respiratory diseases caused by a new coronavirus, known as SARS-CoV-2 [1]. The name of the disease caused by this virus was COVID-19. disease spread rapidly and causes new mucormycosis cases in recent times. Mucormycosis is a fungal infection that spread in The immunosuppressed patient.

In this pandemic situation, most people are immunocompromised. They may be rapidly necrotizing in patients with obvious immunocompromises(i.e. transplants, HIV, chronic steroid patients or disease modifiers of anti-rheumatic medications, leukaemia or others) [3] patients with these conditions are most likely risk factors. In most cases, the hosts are predisposed to the infection due to underlying conditions and Patients who are immunocompromised. Because the fungi in question are common environmental organisms, they are usually non-pathogenic in immunocompetent people [3]. The 2019 Coronavirus pandemic (COVID-19) remains a major global problem. No one except systemic glucocorticoids was shown to improve COVID-19 survival while several treatment options were evaluated [4]. The widespread use of glucocorticoids, unfortunately, could result in secondary bacterial or fungal infections. Invasive pulmonary aspergillosis that makes COVID-19 com-

plications is widely recognized. The rational use of steroids (glucocorticoids) increases secondary fungal infections.

Mucormycosis

Mucormycosis is a zygomycete-family opportunistic fungal infection that can cause a variety of infections**.** This is caused by several mucormycetes called moulds that often affect the sinuses, lungs, skin and brain [2]. The infection begins in the cavity of the nose and reaches adjacent paranasal sinuses. The nasal cavity and the sinus become implanted and growing. The wet nasal and paranasal environment promotes fungal development and invasion. The time, immunity and severity of the disease depend on the invasion of the mucosa and bone [5]. Mucormycosis is rapidly progressing because of its unique pathogenesis. The fungal hyphae invasion of the blood vessels damages the endothelium, which causes blood clotting, and which is causing ischemia and necrosis of the surrounding tissue [2]. Reduced amounts of monocyte and neutrophil function are significant risk factors of mucormycosis as they are known to inhibit germination in mucoral spores [7]. The most common invasion route is the inhalation of spores from fungi in soil or organic matter in immunocompromised patients.

The fungus grows rapidly and aggressively, causing a defined, life-threatening disease due to its involvement with already immunocompromised patients. Usually, after 10-14 days after hospitalization Mucormycosis developed. All but the index case was dead [4] patients have a skin injury, like the burn, cut, or wound, And in persons with COVID-19 cases it's also more likely reported with mucormycosis [2].

Mucormycosis is an angioinvasive disease that is characterized by tissue infarction And necrosis [6]. This includes those who have undergone a solid organ transplant with hematologic disease, AIDS or hepatic cirrhosis and those who have undergone a high-dose steroid. are major risk factors and Finally, natural disasters also present a risk due to damage to the water, soil or debris, such as following the 2004 tsunamour of the Indian Ocean following the Missouri tornado in 2011 [7].

Types

types of mucormycosis are classified on species and affecting an area mucormycosis species: Apophysomyces (*A. variabilis*), Cunninghamella (*C. bertholletiae*), Lichtheimia Absidia). (*L. corymbifera L. raosa*), Mucor (*M. circinelloides*), Rhizopus (*R. arrhizus* (oryzae) *R. microsporus*), Rhizomucor (*R. pusillus*), and Saksenaea were the most frequently isolated (*S. vasiformis*). These are common environmental organisms that pose no risk to immunocompetent humans.

Types mucormycosis based on affecting areas: 1) Rhino-orbital-cerebral mucormycosis (ROCM), (2) pulmonary, (3) cutaneous, (4) gastrointestinal (GI), (5) disseminated, and (6) mucormycosis of uncommon sites [8].

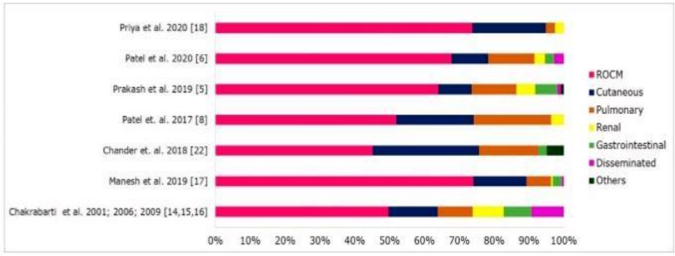

Figure 1: [6] Mucormycosis clinical forms in India. Short-summary: ROCM, cerebral-rhino mucormycosis. Other diseases include oral cavity mucormycosis, otitis media, bone infections and subglottis.

In figure 1 the stats in India by the types of mucormycosis are showing various studies. Rhinocerebral mucormycosis is higher in India. Rhinocerebral mucormycosis is a rare disease caused by nasal, paranasal and brain filamentous fungi, which is also known as zygomycosis [5] and The brain and orbit invasion is caused by the implication of sphenopalatine and internal maxillary arteries in rhinocerebral mucormycosis. Interior carotid artery and cavernous sinus thrombosis are common only in long term cases [5] and Phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by oxidative and non-oxidative systems in the case of hyperglycemia and low pH found in patients with diabetic ketoacidosis (DKA) [9] however, The most common invasion route is the inhalation of spores from fungi in soil or organic matter in immunocompromised patients [5].

The ROCM is the most common form of the disorder in India, followed by the pulmonary and the cutaneous types; however, in developed countries, the Pulmonary form is the most common

clinical form [6]. and *Rhizopus oryzae* is the commonest organism isolated from mucormycosis and accounts for approximately 70% of all Mucormycosis cases [9]. The locations for Mucormycosis are linked to the mucoral species; Rhizopusarhizus is 85% Rhino cerebral, compared to 17% of non-Rhino-cerebral species in the French study RetroZygo. This finding can be explained by the variation in virulence among Mucoral species.

Statistics

Here is the statistical data showing an outbreak of mucormycosis in this pandemic situation. The prevalence of mucormycosis in India is estimated to be around 70 times higher in global stats [6] and The overall mucormycosis frequency is approximately 4 out of 100 patients with malignancies [5] and because of the pandemic situation The specific annual rate of incidence inpatients increased by 24% per year [10].

Mucormycosis is a life-threatening disease. An overall death rate of 54per cent has been shown in a review of published cases of mucormycosis. The mortality rate varied depending on the condition, fungal type and affected body location of the patient (for example, the mortality rate was 46 percent among people with sinus infections, 76 percent for pulmonary infections, and 96 percent for disseminated mucormycosis) [11]. *Rhizopus oryzae* is the commonest organism isolated from mucormycosis and accounts for approximately 70% of all Mucormycosis cases [9] the locations for Mucormycosis are linked to the mucoral species; Rhizopusarhizus is 85% Rhino cerebral, compared to 17% of non-Rhino-cerebral species in the French study RetroZygo. This finding can be explained by the variation in virulence among Mucoral species [7].

Rhizopusmicrosporus and Rhizopushomothallicus infections have increased in India The clinical form of mucormycosis reported in different cases of India are presented according to an anatomical involvement. The ROCM is most commonly reported as MM (45-74%), followed by cutaneous (10-31%), pulmonary (3-22%), renal (0.5-9%), gastrointestinal (2-8%) and spread infections (0.5-9%). Other unusual sites of infection in Indian literature are the breast, ear and spine. Infections in the heart and bone. The underlying disease describes risk factors related to clinical forms of mucormycosis [6]. A South Indian Study Lichtheimia species contribute 0.5 percent to 13 percent of the Indian cases, reported that 29 percent of the Apophysomyces-based cases are nosocomial. Most of the cases in India are due to L. ramosa, Chander., *et al*. reported. Rhizomucorpusillus, Cunninghamella species, Mucor species, Syncephalastrum and Saksenaea are other Mucoral species linked with Mucormycosis in India [6].

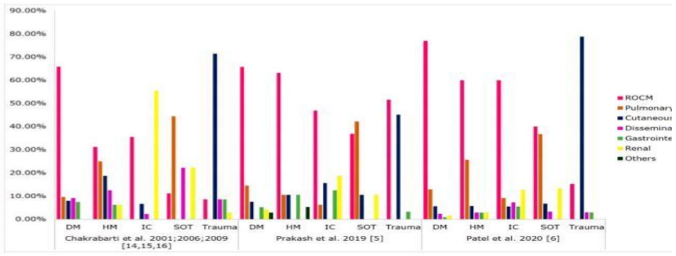

Figure 2: [6] Clinical forms of mucormycosis risk factors. Abbreviations: ROCM: Cerebral-rhino-mutation; DM: Diabetes Mellitus; HM: Haematological Malignancy; IC: Immunocompetent; SOT: Transplant to the Sound Organ Transplant.

Further surveillance among the 16,808 recipients of transplants carried out in 23 institutions between 2001-2006 showed that mucormycosis was the third most prevalent type of invasive fungal infection among stematic cell transplants, accounting for 8 percent of all invasive fungal infections (77 mucormycosis cases occurred among 983 stem cell transplant recipients who developed any fungal infection) [11] and Renal mucormycosis is a unique clinical entity in India in the immunocompromised host. In India, several cases 33-100 percent of cases of renal mucormycosis have been reported by an immunocompetent host [6] and Acute myeloid leukaemia (AML) is the most frequently involved of all haematological malignancies (62 percent) [5] and In those people without underlying diseases, only 6% to 10% occur [8].

Here are some treatment stats The survival rate of surgery with antifungal treatment is shown to be higher (70 percent) than that of surgery (57 percent) and chemotherapy alone (61 percent) [5].

In 230 European patients with 79%, surgical treatment decreased mortality, leading to surgery when possible, but mandatory for rheino-cerebral and post-traumatic mucormycosis When possible for any location [7]. In 45 percent of patients at Week 12, a positive response was observed. However, in 40 percent of patients, serum creatinine doubled but in 63 percent of cases, creatinine levels normalized once treatment had ended Three months

later [7]. As a first-line treatment, 21 patients were treated with isavuconazole; the 42-day response was only 14%, while weeks 12 were treated as 10% (compared to 45% in the AmBizygo study). The findings of this study found an equivalent mortality rate of day 42 to the one in the AmBizygo study. Isavuconazole was well-tolerated in the VITAL study, an uncommon cause of interruption were toxic effects. In the most recent guidance, the location of isavuconazole has not yet be indicated. Finally, the positive economic impact of isavuconazole as opposed to Amb in mucormycosis treatment was shown in a cost-effectiveness study [7]. Rhizopusmicrosporus and Rhizopushomothallicus infections have increased in India The clinical form of mucormycosis reported in different cases of India are presented according to an anatomical involvement. The ROCM is most commonly reported as MM (45-74%), followed by cutaneous (10-31%), pulmonary (3-22%), renal (0.5-9%), gastrointestinal (2-8%) and spread infections (0.5-9%). Other unusual sites of infection in Indian literature are The breast, ear and spine. Infections in the heart and bone. The underlying disease describes risk factors related to clinical forms of mucormycosis [6].

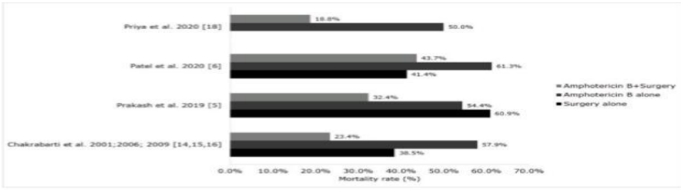

Figure 3: [6] Therapy modes and mortality rates for Indians. Data from the master paper provided by the authors were extracted from the figures of the Patel., *et al.* 2020 study.

In patients treated with the combination of AMB and surgical debridement of the infected tissue, there were existing data that showed low mortality (19-44%) compared to AMB monotherapy (50%–61%); the evidence is consistent with global information. As salvage therapy in the treatment of mucormycosis, posaconazol and isavuconazole are used. A South India study has evaluated the safety and effectiveness in ROCM patients of posaconazole [6].

Mechanism

Due to the angioinvasive nature, hem (H) may constitute an iron input for the invading fungus, which either intracellularly occupies hem or by the reductase-permease system strips ferric iron from hem. When the hem is intracellularly transported, the hemoxygenase in the cytoplasm produces ferric iron. B, The availability of iron that is transported intracellularly through a reductase-permease system in DKA proton(H+)-medial transferring of ferric iron (Fe^{3+}) from Transferrin (T) increases. C Deferoxamine (D) chelates transferrin iron directly, which results in ferrioxamine (iron-deferoxamine complex). The fungus then releases ferrous iron on the cell surface from ferrioxamine. The copper oxidase-ferrous permeases (FTR1) complex transmits iron across the cell membrane in all cases.

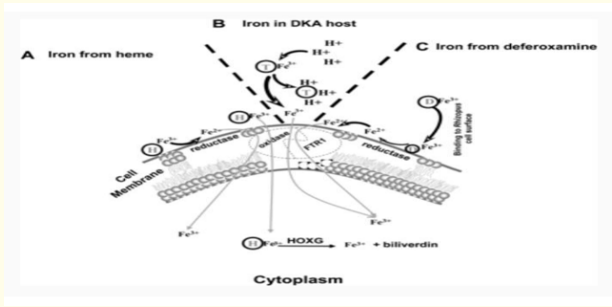

Figure 4: [9] Proposed iron intake mechanisms during mucormycosis by Mucorales.

Host-pathogen interactions [9]

Infections with Mucormycosis are characterised by extensive angioinvasion leading to vessel thrombosis and subsequent tissue necrosis. Infected tissue ischemic necrosis can prevent leucocyte and antifungal agents from being delivered to the FOCI. This angioinvasion probably contributes to the organism's ability to spread hematogenously to other target organs. Damage and penetration of blood vessels by endothelial cells or by extracellular matrix protein are likely to be a critical step in *R. oryzae's* pathogenetic strategy. Therefore, the understanding of these methods can lead to new ways of preventing and treating Mucormycosis. A previous study showed that *R. oryzae* can adhere to the laminin and IV collagen of the extracellular matrix We found that strains of *R. oryzae* adhere to human umbilical vein In vitro endothelial cells and induced endocytosis to invade these cells The prevention of endocytoses eliminates the capacity of the organisms to cause endoscopic cell damage and *R. oryzae* prevention Endocystosis Recently Glucose-regulated protein (GRP78) has been identified as an A receptor that

mediates Mucorales penetration and damage to endothelial cells. GRP78 has been found as a cellular protein induced by glucose starvation (also known as BiP/HSPA5). It belongs to the HSP70 protein family which is mainly found in the endoplasmic reticulum. It is a major chaperone involved in many cellular processes, including protein folding and assembly, which mark misfolded proteins for degradation of proteosome, Calcium homeostasis regulator and as an endoplasmic reticulum stress sensor. Regulation Despite its major function as a cellular protein for Chaperone, recent studies have found that a fraction of GRP78 has been translocated to the cell surface of various cells. High levels of glucose and iron are of interest, which is consistent with the levels noted during expression of DKA-enhanced Surface GRP78 and result in receptor-dependent insertion and damage of Mucorales' endothelial cells. The sensitivity of Mice with the increase of DKA.

In the sinuses, lungs, and brains, mucormycosis has increased GRP78 expression compared to regular mice. Please Note that Mucormycosis protected anti-GRP78 immune serum mice with DKA Whether the Anti-GRP78 immune system can protect the neutropenic host is currently unknown. These observations offer new insights into mucormycosis. The unique susceptibility to mucormycosis of DKA patients could be the basis for new therapeutic operations. In contrast to most fungi (e.g., fumigatus) that flow arenony in the melanogaster of Drosophila, Mucorales quickly infects and kills flies of the wild type. Expression of the whole genome Profiling of genes selectively downregulation by *R. oryzae*, acting in pathogen identity, immune defences, stress reactions, detoxification, metabolism, or repair of the tissue, in wild-type fliegers compared with *A. fumigatus*.

Treatments

First-line treatment for mucormycosis is considered Amphotericin B. Amphotericin B lipid formulation is administered as initial therapy in high doses once daily. The initial starting dose is 5 mg/kg IV every day, and 10 mg/kg IV is a maximum dose. The duration of treatment depends on the clinical image of the patient [3]. It spreads quickly and highly invasively, so aggressive treatment is needed. However, final therapy and a sequential management plan are not available. To confirm the clear therapy and develop optimal management strategies, a comprehensive clinical trial is required. If suspected, Amphotericin B should be administered immediately. In order to eradicate the disease 4 to 6 weeks of Amphotericin B therapy is necessary. The consistently effective antifungal is amphotericin B, but the exact ideal dose is not yet determined. The contemporary trial used a 50-mg daily dose that all patients tolerated. Some studies suggest an amphotericin-B dose of 1 mg/kg/day. In order to reach a 5 mg/ml concentration, amphotericin B can be combined with distilled water. It begins with 5mg/day doubling until it reaches 1 mg/day [5].

Surgical treatment may require in some cases.

The surgery is an invasive technique involving the removal, through drainage and irrigation of the sinuses, of involved corporal tissue and fungal growth. Operation sometimes changes body configuration when the palate, eye structures and nasal cavity are removed from the body [5].

Adverse effects

Treatment complications include nephrotoxicity, hypokalemia, protracted hospitalisation (specifically with the use of deoxycholate amphotericin B) [3].

Drugs and examples

Amphotericin B

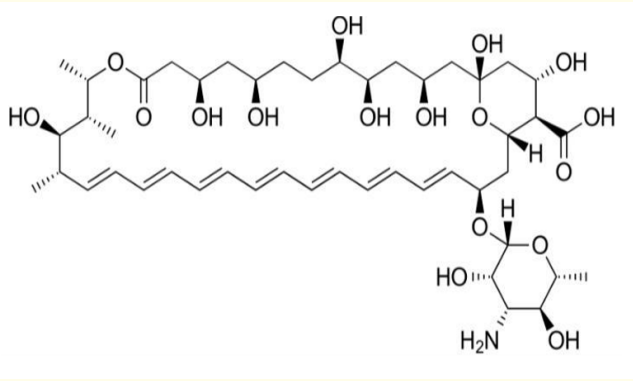

Figure a

Amphotericin B is a medication for antifungal use for severe fungal and leishmanniasis infections. The treatment for fungal infections includes aspergillosis, blastomycosis, candidiasis, coccidian mycosis and cryptococcosis. It is given with flucytosine for certain infections. It is usually given in a vein through injection [12].

Mechanism

Amphotericin B is either fungistatic or fungicidal according to body fluid concentration and fungal susceptibility. The medicine acts in the cell membrane of susceptible fungi through the binding of sterols (ergosterol). The resulting changes in the membrane permeability allow intracellular components to leak. This creates a trans-membrane canal. The target site for action of amphotericin B and the azoles is ergosterol, the main sterol in the fungal cytoplasmic membrane. Polyene Amphotericin B binds irreverently to ergosterol which disrupts the integrity of the membrane and ultimately causes death of cells. Amphotericin B is usually fungistatic in action at clinically obtained concentrations, but maybe highly fungicidal or very susceptible to very sensitive organisms. The antifungal activity of amphotericin B occurs primarily by binding it to sterols in the fungal membrane (e.g. ergosterol). This binding means that the cell membrane cannot function anymore as a selective barrier and intracellular content is not leaked. Partly due to changes in permeability, cell death occurs However, some fungal in vivo antifungal effects of amphotericin B can also contribute to other mechanisms. Amphotericin B is not in vitro active against sterol in the cell membranes of organisms (eg, bacteria). Some of the toxicities reported with conventional amphotericin B treatment may involve binding to sterols in mammalian cells (such as certain kidney cells and erythrocytes). The medication does not appear to hemolyze mature erythrocytes at usual therapeutic concentrations of amphotericin B and conventional IV amphotericin B can result in anaemia from a drug's action in active metabolization and breakdown of erythropoietic cells. There appear to be multiple mechanisms associated to nephrotoxicity with conventional IV amphotericin B, including a direct vasoconstrictive effect in renal arterios that reduces glomerular or renal tubular flow and lytic action on cholesterol-rich renal tubular membranes [13].

Uses

This medicine is usually taken once a day or daily by injection in a vein. It should be slowly injected for 2 to 6 hours. Your physician will first give you a smaller dose to test your medicine response. The dose depends on your health, weight, test dose-response and therapy response. This medicine should be resumed at the lowest dose and slowly increased if it is stopped for 7 days or longer [14].

Adverse effects

The infusion can start in 1 or 3 hours after fever, shaking, chills, flushing, a loss of appetite, dizziness, nausea, vomiting, headache, shortness of breath or fast breathing. In some cases, it may be necessary to prevent or alleviate these side effects for other medications (including acetaminophan, diphenhydramine, corticosteroids such as hydrocortisone) [14].

Isavuconazole

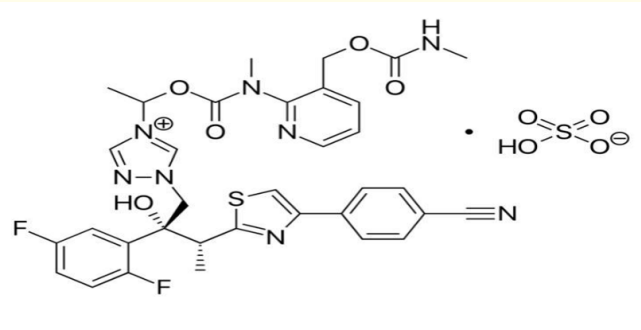

Figure b

Is a systemic triazole class antifungal drug used for treating invasive aspergilosis and Isavuconazole mucormycosis [15].

Mechanism

Isavuconazole displays fungicidal actions by disrupting the biosynthesis of ergosterol, which is a key component of fungal cell membrane. It inhibits cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase that mediates the conversion of lanosterol to ergosterol. The sidearm of the active isavuconazole molecule allows for greater affinity for the binding pocket in the fungal CYP51 protein by orienting the triazole ring of the molecule to engage with the heme moiety at the bottom of the binding pocket. This explains the wide antifungal spectrum of isavuconazole and possible cross-resistance to other triazoles. Inhibition of lanosterol 14- Alpha-Demethylase results in a change of the toxic function of the fungal membrane and accumulation within the fungal cytoplaxis due to precursors of toxic methylated sterols, including 14-α-methylated Lanosterol, 4,14-dimethylzymosterol, and 24-methylenedihydrolanosterol. Ergosterol depletion in fungal cell membranes leads to decreased structural integrity and cell membrane function inhibited growth and replication of fungal cell membrane [A32026], and eventually to cell death. Inhibition of the isavuconazole is less sensitive to mammalian cell demethylation. The resistance mechanism and reduced isavuconazole susceptibility arise from fungal mutations in the cyp51A and cyp51B genes coding 14-alpha-demethylase target protein lanosterol [L1482].

Other resistance mechanisms, including sterol profile changes and increased fungal efflux pumping activity, cannot be excluded [16].

Uses

This drug is used to treat some severe fungal infections. This medicine is called an antifungal azole. It functions by halting the fungal growth [17].

Adverse effects

Dizziness, nausea, vomiting, diarrhea, headache, constipation, cough, and trouble sleeping may occur [17].

Posaconazole

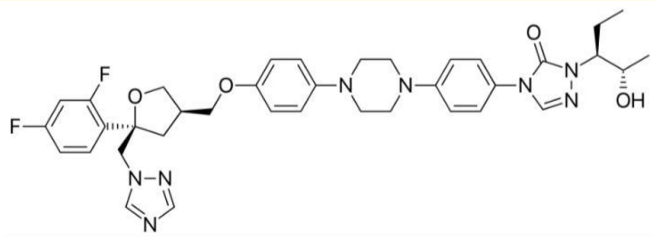

Figure c

Is an antifungal triazole. It was approved in September 2006 for medical use in the United States and is available as a generic drug [18].

Mechanism

The antifungal triazole, posaconazole, is an anti-fungal enzyme blocking 14α-demethylose in fungi Posaconazole, the cytochrome P-450, by the binding of the hem cofactor on the enzyme. This leads to inhibition and accumulation of precursors to methylated sterols of ergosterol as a key component of the fungal membrane. This inhibits the growth of fungal cells and ultimately the death of the cells. Posaconazole is a new lipophilic antifungal triazole, which hinders the biosynthetic pathway of ergosterol from cytochrome P450-dependent 14-alpha demethylase. Hemming this enzyme results in the accumulation of toxic 14-alpha methylsterols and ergosterol depletion which disrupts the function of the fungal cell membrane and blocks cell growth and division. Inhibition of parasite C-14 alpha demethylene sterol was the primary mechanism for action of the medicine Inhibition of the parasite C-14 alpha demethylase sterol was the primary mechanism for the drug to act [19].

Uses

Posaconazole is used in patients with severely weakened immune systems to prevent certain fungal infections (such as patients who have had chemotherapy). It is in a class of medicines known as antimicrobial azoles. It works by halting fungal growth [20].

Adverse effects

Nausea, vomiting, diarrhea, headache, abdominal pain, dizziness, trouble sleeping, or stomach upset may occur [20].

Future prospective

Mucormycosis is an opportunistic infection caused by a sudden increase in mucormycosis infection rates caused by the pandemic and medications used during the pandemic, which induce secondary infections. The most common risk factor for patients is rhino orbital-cerebral mucormycosis. Post-transplant, diabetic ketoacidosis, and post-skin trauma patients are the most vulnerable to infection. In a pandemic condition, rational use of steroids (glucocorticosteroids) and a lack of hygiene increase infection rates. The use of fugitive reactive T-cells in the identification of mucorale infections, as well as mould reactive T-cells in patients with invasive fungal infections, is being investigated. A mould helped to detect mucorale species quickly and accurately, but further clinical evidence was needed. The combined use of surgery and amphotericin-B reduced mortality from 50% to 18%. We can avoid infections like mucormycosis if adequate hygiene is maintained and drug rationing is avoided.

Conclusion

It can be concluded that the immunocompromised(immune suppression) patients were found to be more susceptible to the mucormycosis infection. There are also some other factors responsible for the cause of these infections like the increased serum iron levels making it easier for the growth of infection. Also in some cases, medication like glucocorticoids which are administered to treat another condition end up leading to the growth of secondary infections (mucormycosis). Although being an opportunistic infection it has a very high mortality rate of about 50% if left untreated. The severity of these infections may be determined by the underlying cause of the immunocompromised state. There are several types of this fungus, these fungal organisms are of little to no harm for healthy beings and are present in the environment freely. The main cause of the spread of these infections is the inhalation of spores.

These infections are more common in the patients after undergoing transplants (stem cell, organ, etc.), having diabetic ketoacidosis along with the increased level of serum iron.GP78 is the receptor responsible for the damage and invasion of the host by *Rhizopus oryzae*. The treatment of these fungal infections can be done by the administration of Amphotericin B as a first-line treatment. In India(South India)Posaconazole for patients with ROCM was evaluated and found to be effective and safe for use. The monotherapy of AMB had a much higher mortality rate (50%-61%) than the combination of the AMB with surgical debridement of around 19%-44%. But if the detections and treatment of the infection is done earlier there are greater chances of recovery of the patients.

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Conflict of Interest

The author declares that they have no conflict of interest.

Ethics Approval

Not applicable.

Consent to Participate

Not applicable.

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