CASPOFUNGIN: A NOVEL BROAD-SPECTRUM ANTIFUNGAL AGENT

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Summary

Caspofungin is the first agent in a new class of antifungal agents, the echinocandins, with a novel mechanism of action that damages the fungal cell wall by inhibiting glucan synthesis. United States Food and Drug Administration has approved caspofungin in January 2001 for the treatment of mucosal and invasive candidiasis, invasive aspergillosis and empirical use in patients with persistent fever and neutropenia. As additional clinical data becomes available, it seems likely that the therapeutic role of caspofungin will expand. Caspofungin has an excellent safety profile with very little potential for nephrotoxicity and hepatotoxicity. This review provides a comprehensive description of the drugs' mechanism of action, spectrum of activity, pharmacokinetics, drug interactions, safety, clinical uses, dose and administration.

Key words: Caspofungin, antifungal, echinocandins

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Introduction

Emerging fungal infections appear continuously globally.[1] The incidence of severe, invasive and opportunistic fungal infections in immunocompromised patients eg. patients on immunosuppressive drugs, intensive chemotherapy, organ transplant recipients, patients with AIDS (acquired immunodeficiency syndrome) and very low birth weight infants, is increasing drastically.[2,3,4] Hence treatment of these infections poses a great challenge to treating clinicians. Many a times the effective use of traditional agents is limited by inadequate spectrum of activity, drug resistance, toxicities and drug-drug interactions. It is a known fact that antifungal drugs for serious infections are either fungistatic and vulnerable to resistance or fungicidal but toxic to the host. Thus, new agents with improved activity and toxicity profiles are greatly needed. Caspofungin is an echinocandin group of antifungal drug, the first in a new class of antifungals, which is fungicidal and is less toxic to the host by virtue of their novel mechanism of action. Other agents in this class include micafungin and anidulafungin.

Caspofungin has exciting advantages of a broad-spectrum antifungal agent. It exhibits both in vitro and in vivo efficacy against a wide range of fungi and yeasts such as Aspergillosis and Candida spp., including the azole resistant strains.[4,5] The US Food and Drug Administration (FDA) has approved caspofungin in January 2001 for treatment of invasive aspergillosis in patients who are refractory to or intolerant to other therapies as well as for the treatment of oropharyngeal candidiasis and invasive candidiasis in adults and empiric antifungal therapy in patients with febrile neutropenia.[6]

Mechanism of Action

Caspofungin acts by non-competitive inhibition of the synthesis of 1,3-β-glucan synthase in the fungal cell wall, thus resulting in defective cell wall polymerization and renders the fungal organism susceptible to lysis and cell death. [7,8] Glucan is the major component of the fungal cell wall, which imparts strength and shape to the cell wall and plays an important role in cell division and cell growth. Loss of glucan in the cell wall results in osmotic instability.[9] This process does not exist in mammalian eukryotic cells and therefore less toxicity to humans.[10]

Inhibition of synthesis of β (1,3)-D glucan produces a double effect, both fungistatic and fungicidal. The fungistatic effect results from blockade of the cell wall synthesis, reducing fungal growth. The fungicidal effect results from a change in the integrity of the cell wall, which loses its mechanical strength and becomes unable to resist the intracellular osmotic pressure; leading ultimately to destruction of the fungal cell. This mechanism of action differs from that of other antifungal families, which act on the cell membrane (polyenes eg.amphotericin B, azoles eg. fluconazole), or inhibit DNA and protein synthesis (5-flucytosine). [4]

Spectrum of Activity

Caspofungin has a broad spectrum of antifungal activity both in vitro and in vivo. It is fungicidal in vitro and in vivo against most isolates of Candida spp like *C.albicans, C.glabrata, C.guilliermondii, C.kefyr, C.krusei, C.lusitaniae, C.parapsilosis, C.pseudotropicalis, C.tropicalis*, [11] and fungistatic against Aspergillus spp such as *A.fumigatus, A.flavus, A.nidulans, A.niger and A.terreus*. [12] In addition caspofungin is highly active against azole-resistant strains. Its activity results from affecting *Aspergillus* spp at branch points and growing hyphae tips.[13, 14] Caspofungin is also active against *Pneumocystis carnii* because the cell wall of the cyst form of the fungus contains the β (1,3)-D glucan synthase enzyme.[15] However, it lacks activity against *Cr.neoformans*, since this pathogen has little or no β (1,3)-D glucan in its cell wall.[16,17,18,19] Caspofungin lacks sufficient activity against *Fusarium, Paecilomyces, Rhyzopus, Histoplasma* and *Blastomyces* spp.[17, 18, 20]

Pharmacokinetics

Caspofungin has very limited oral bioavailability and is only available for intravenous (IV) administration. It exhibits dose-proportional plasma pharmacokinetics with a β-half life of between 10 to 15 hours, which allows once daily dosing.[21] Caspofungin is extensively bound to plasma protein (97%) and is distributed into all major organ sites including the brain, however if the meninges is not inflamed the CSF concentration of the drug is low.[22] Caspofungin has a volume of distribution of 9.7 L. Metabolism of caspofungin is thought to be independent of the cytochrome system, and it does not inhibit the cytochrome P450 isoenzymes. It is metabolized slowly in the liver by hydrolysis and N-acetylation, with less than 2% excreted unchanged in urine.[12] Hence, dosage adjustment is not necessary in the presence of renal insufficiency and the drug is not removed during hemodialysis.[23] No change in dosing is needed in the presence of mild hepatic disease, however in the presence of moderate hepatic insufficiency dose alteration is recommended- i.e. after the initial 70 milligram (mg) loading dose, the subsequent daily dose should be 35 mg. [24] Insufficient data are available in patients with severe hepatic failure.

Drug Interactions

Fewer drug interactions are described for echinocandins than for the azoles. Preclinical studies showed that caspofungin is neither a significant substrate nor a potent inhibitor of P-glycoprotein or of hepatic cytochrome enzymes. However, analysis of pharmacokinetic data from therapeutic trials has found potentially significant reductions (≈20%) in the caspofungin concentrations with coadministration of efavirenz, nevirapine, rifampin, dexamethasone, phenytoin or carbamazepine. Hence the daily dose of caspofungin has to be maintained at 70 mg in patients concomitantly receiving one of these agents. [11]
Caspofungin does not have significant pharmacokinetic interactions with amphotericin B, itraconazole and mycophenolate.[11,12,21]

Caspofungin can reduce the concentration of tacrolimus by approximately 20% but has no effect on cyclosporin levels. Cyclosporin however increases the concentration of caspofungin by approximately 35%. So the concomitant use of both drugs currently is not recommended. [12] No drug interactions have been described with micafungin and other highly protein bound compounds including warfarin, diazepam, salicylic acid, and methotrexate.[11]

Safety

In general caspofungin is well tolerated.[9] The most frequently seen adverse effects are fever, flushing, nausea, anemia, headache, vomiting, diarrhea, tachycardia and infusion related phlebitis. Caspofungin may cause histamine release from mast cells when administered intravenously and produce possible histamine-mediated symptoms as rash, facial swelling, pruritis, sensation of warmth, or bronchospasm. Allergic reactions have been infrequent, and anaphylaxis is rare.[9] Transient elevations in liver transaminase levels (14%) were observed but there was no significant drug-related nephrotoxicity.[25] Caspofungin is not genotoxic or mutagenic, but is embryo toxic in rats and rabbits. Hence, pregnant women should only use it if the potential benefit outweighs the fetal risk.[26]

Precaution

Caspofungin is contraindicated for use in patients with hypersensitivity to caspofungin acetate. It has to be used with caution in liver impairment, myelosuppression and concomitantly with cyclosporin.[26]

Clinical Uses

US FDA approved indications for the use of caspofungin includes, invasive aspergillosis in patients who are refractory to or intolerant to other therapies, the treatment of oropharyngeal and invasive candidiasis in adults and empiric antifungal therapy for patients with febrile neutropenia.[6]

Clinical Trials:- Monotherapy:

Invasive Aspergillosis

IV caspofungin demonstrated efficacy in immunocompromised patients (e.g., hematologic malignancy, marrow or stem-cell transplant) with invasive aspergillosis who were either refractory to or intolerant of prior therapy, including amphotericin B, amphotericin B lipid formulations, or itraconazole. A complete or partial response was observed in 50% of those treated for longer than 7 days. Response rates were higher in those patients with pulmonary disease (47%) than in those with extra pulmonary disease (28%). There was some evidence of efficacy in the few patients with extra pulmonary disease and CNS involvement. [27]

Invasive candidiasis

In the randomized study conducted by Mora-Duarte et al in patients with invasive candidiasis, patients were randomized to receive either caspofungin (70 mg on day 1, then 50 mg q.d.) or conventional amphotericin B (0.6-1.0 mg/kg q.d.) for 14 days. Success was defined as both symptom resolution and microbiological clearance and was observed in 73% of caspofungin recipients and in 62% of amphotericin B recipients. All adverse events occurred significantly more frequently among amphotericin B recipients than among caspofungin recipients. Nephrotoxicity, was observed less in patients on caspofungin (8%) compared to those on amphotericin (25%).[28]

Candida esophagitis

Favorable clinical and endoscopic responses in patients with esophageal infection were observed in 67-90% of caspofungin recipients compared to 61% of amphotericin B recipients and the drug related adverse events were less frequent among the caspofungin recipients.[29] In another study conducted by Villanueva A et al. in a group of patients with endoscopically demonstrated candida esophagitis, a higher rate of endoscopically documented clinical success was observed with caspofungin (74% vs. 63%) when compared to amphotericin B. [30]

Caspofungin demonstrated a similar efficacy to flucanozole (81% vs. 85%) in symptomatic patients with documented esophageal candidiasis (most infected with HIV) who were given either IV caspofungin 50 mg/day or IV fluconazole 200 mg/day administered once daily for 7 to 21 days. Drug related adverse events were comparable in patients taking caspofungin or fluconazole.[31]

Febrile neutropenia.

Caspofungin is better tolerated and as effective as amphotericin B liposome when given as an empirical antifungal therapy in patients with persistent fever and neutropenia. In a prospective, double-blind study patients were randomized to receive either IV caspofungin (70 mg on day 1 and 50 mg once daily thereafter) or amphotericin B liposome (3 mg/kg daily). The overall success rates were similar for both agents (caspofungin 33.9% vs. amphotericin B liposome 33.7%). Among patients with baseline fungal infections, 51.9% and 25.9% of those treated with caspofungin and amphotericin B liposome had a successful outcome, respectively. Compared with amphotericin B liposome, there were fewer premature study discontinuations, nephrotoxic effects, or infusion-related events among patients given caspofungin. The rates of breakthrough fungal infections and resolution of fever during neutropenia were similar between both the groups.[32]

Case documentation studies

Candoni A et al. reported safe and effective use of caspofungin as a first-line therapy for proven or probable pulmonary invasive fungal infections in 32 immunocompromised patients with hematologic malignancies. All the 31 neutropenic patients received concomitant granulocyte colony-stimulating factor. The overall response rate was 56%. No clinical adverse events were reported.[33]

The efficacy and safety of caspofungin in the treatment of fungal infections in severely ill, immunocompromised patients in Germany was reported recently by Glasmacher A et al. A similar response rate was reported in proven (63%) and probable (59%) infections, and in neutropenic patients (75%). Caspofungin was well tolerated and even in 14 patients, who were concomitantly treated with ciclosporin A, no drug-related elevations of bilirubin, alanine aminotransferase or creatinine were found. This open case study of severely ill patients with invasive fungal infections demonstrated both excellent efficacy and very low toxicity of caspofungin. [34]

Combination Therapy

Compared to monotherapy there is limited clinical data on the use of caspofungin in combination with other antifungal agents. Pre-clinical and clinical studies show that combinations of echinocandin with azoles and amphotericin B do not produce antagonistic effects, rather may produce synergistic effects against pathogenic fungi.[11,35,36,37] Caspofungin has been administered in combination with other antifungal agents. Six patients with leukemia whose illness failed to respond to amphotericin B therapy were provided caspofungin together with voriconazole; infection improved in all 6, and there were no drug related events.[38] Further, when patients with hematologic malignancies and invasive aspergillosis were treated with caspofungin and liposomal amphotericin B in combination a good response rate was observed (21% in those documented and 77% in those with possible invasive aspergillosis). There was no significant toxicity ascribed to the combination.[39]

Rubin et al has reported the successful use of caspofungin in combination with itraconazole in 2 immunocompromised patients to eradicate invasive aspergillosis. Patients received caspofungin IV 50 mg a day and itraconazole orally 200 mg three times daily for 8 weeks or caspofungin IV 70 mg a day and itraconazole orally 400 mg a day for 12 weeks. Based on the limited experience this combination is suggested to be an useful alternative when standard therapy, such as treatment with amphotericin B, is either ineffective or intolerable. [40]

Aliff TB et al has reported the treatment of 30 patients (26 patients had acute leukemia) with amphotericin-refractory invasive fungal infections with combination of caspofungin and amphotericin (or liposomal amphotericin). Among the group, 20 patients with acute leukemia received combination therapy for fungal (aspergillus) pneumonias arising during intensive chemotherapy treatments. Eighteen of the 30 patients (60%) experienced a favorable antifungal response. Authors concluded that this antifungal combination can

be administered safely to high-risk patients with hematologic malignancies. Although an absolute assessment of efficacy was not possible, outcomes were encouraging. [41]

Dose, Administration and Availability

Caspofungin is available as 70mg and 50mg IV preparation. Caspofungin is administered once daily by IV route and has to be infused over one hour. It is recommended that diluents that contain dextrose not to be used with the drug.

Invasive Aspergillosis

- In patients with invasive aspergillosis who have progressed on or failed to prior antifungal therapy, including itraconazole, an initial loading dose of 70 mg on the first day, then 50 mg daily thereafter has been effective. [6] Duration of therapy is based on clinical response; the average duration in clinical studies was about 30 days, with some patients receiving daily therapy for up to 160 days.

Candidiasis of the esophagus

- IV doses of 50 or 70 mg daily for 2 weeks have been effective in treating candidial esophagitis, including patients with HIV infection and low CD4 counts.[42]

Disseminated candidiasis

- A single 70 mg loading dose on day 1 should be followed by 50 mg/day thereafter for at least 14 days after the last positive culture. Patients who remain persistently neutropenic may require a longer course of therapy pending resolution of the neutropenia.[6]

Febrile neutropenia, Empiric antifungal therapy

- The recommended dose is 70 mg IV on day 1, followed by 50 mg IV daily for empirical therapy of presumed fungal infection in febrile neutropenic patients. Duration is based on clinical response. Continue for 7 days after resolution of neutropenia and clinical symptoms. A minimum of 14 days of treatment in patients found to have fungal infections is recommended.[43] Dose may be increased to 70 mg IV daily, if there is a lack of clinical response and 50 mg was well tolerated.

Conclusion

In response to the increasing incidence of fungal infections and resistance, the development of new antifungal agents with new mode of action is necessary. The introduction of echinocandins including caspofungin, represents an opportunity to address these issues. Caspofungin, among the echinocandins has been studied vastly and offers exciting advantages of being a broad spectrum antifungal agent with activity against various fungi including strains of fungi resistant to other antifungal agents and a better tolerability profile, with almost no nephrotoxicity and hepatotoxicity. It has the additional advantage of having a lesser potential for drug-drug interactions compared to other antifungal agents. Its activity against all candida species makes it a useful choice for the initial empirical treatment of patients with suspected or proven candida infections. It is a good choice of empirical antifungal therapy in patients with persistent fever and neutropenia. Further, it is a promising agent for the treatment of invasive aspergillosis, including in combination with other antifungal agents due to it lesser potential of interaction with them. Most of the comparative studies of this agent was with amphotericin B, and it has revealed to be of comparable efficacy and better tolerability than this established antifungal agent. Primarily, caspofungin is an effective and safe choice for those infections in patients who have not responded or did not tolerate the existing antifungal agents.

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