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## UPDATE ON STATINS IN ACS


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The importance of early, aggressive treatment of lipid disorders following an acute coronary syndrome (ACS) is now well documented.[1] Patients that experience ACS are at high risk of suffering from recurrent events. Patients who have experienced ACS are 5 to 7 times more likely to have another ischemic event than a person without such history.[2] Consequently, secondary prevention of coronary heart disease (CHD) must be considered early after ACS. The Adult Treatment Panel III (ATP III) Guidelines were recently updated by the National Cholesterol Education Program (NCEP). The document advocates a more aggressive approach to lowering of low density lipoprotein cholesterol (LDL-C) than ever before. The update supports early, aggressive lowering of LDL-C with hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in patients with ACS, as well as other patient populations, such as patients with multiple uncontrolled risk factors.[4] This article will explore the rationale for early, aggressive LDL-C lowering in ACS patients in the context of the ATP III update.

**Pathophysiological Basis of Achieving Lower Goals**

Ironically, the value of achieving lower LDL-C targets by way of higher statin doses may be as much related to pleiotropic effects of statins as to actual LDL-C reduction. This is especially true given the diminishing returns of doubling a statin dose, an event that only confers an additional 7% reduction in LDL-C. Thus, the maximum attainable reduction in LDL-C that can be achieved by increasing the dose of a statin is 21% if the dose is increased from 10 mg to 80 mg.[5] This observation highlights the concept that statins may be reducing events at higher doses independent of their effects on LDL-C

Atherosclerotic disorders start with the retention of (LDL-C) in the sub-endothelial space of arteries. Once in the sub-endothelial space, LDL-C becomes oxidized, recruiting macrophages to the site, which are then able to oxidize LDL-C at an accelerated rate.[2] When LDL-C is oxidized it has four potentially detrimental functions. First, it increases tissue plasminogen activator inhibitor (PAI-1), leading to increased coagulation. Second, oxidized LDL-C induces the expression of endothelial vasoconstrictive substances.[2] Third, it inhibits the expression of nitric oxide, a potent vasodilator and platelet inhibitor. Lastly, it may promote macrophage cell death. Large cholesterol-rich reservoirs called "foam cells" eventually develop.[2] Stored beneath the endothelial layer, oxidized cholesterol derivatives provoke an inflammatory response, causing the release of cytokines that further worsen the inflammatory response.

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Eventually, the endothelial layer may rupture, exposing highly oxidized cholesterol and other substances that are strong initiators of platelet aggregation. The downstream consequence is myocardial ischemia and if unabated, infarction may occur. Independent of their effects on cholesterol, statins exhibit anti-inflammatory activity, they favorably modify thrombotic balance, and stabilize the vascular endothelium. It is these pleiotropic actions that serve as the basis for aggressive dosing of statins for ACS.

**Pleiotropic Effects of Statins**

The treatment of choice for hyperlipidemia in most patients with or without a history of ACS are statins. Statins significantly decrease total mortality. Statins provide the greatest degree of LDL-C lowering, with minimal increases in high density lipoprotein cholesterol (HDL-C), and decrease triglycerides.[1] (Table 2)

Recently the pleiotropic effects of statins have been documented. Atherosclerotic disorders stem from inflammatory processes reacting to oxidized LDL-C particles.[3] In the PRINCE study, researchers found that pravastatin therapy caused a decrease in high-sensitivity C-reactive protein (hs-CRP) (a clinical marker of inflammation). Furthermore, it was demonstrated that decreases in hs-CRP were associated with a lower incidence of ACS.[3] The REVERSAL trial supported these conclusions by showing that a decrease in hs-CRP by at least 2 mg/L was associated with a significant decrease in atherosclerotic progression. Thus, the anti-inflammatory effect of statins may be as important as the ability to lower LDL-C levels, especially around the time of an acute event.[3]

Statins also improve vascular endothelial function. Atherosclerosis involves vascular dysfunction, which manifests as an imbalance between nitric oxide (NO), a local vasodilator, and endothelin-1 (ET-1), a vasoconstrictor, leading to a state of enhanced vasoconstriction. Notably, this imbalance is most often seen in patients that have diabetes mellitus, hypertension, elevated LDL-C, elevated homocysteine levels, or smoke cigarettes. [3] Statins function to restore balance by increasing nitric oxide, decreasing ET-1, or both. [3]

An additional action of the statins is plaque stabilization. ACS usually begin with plaque rupture and exposure of subendothelial substances to platelets and other thrombotic mediators. Plaques rupture when inflammatory cells (mainly macrophages) release proteolytic enzymes from within the plaque leading to a breach of the intima tunica.[3]Almuti et al. described the statins' role in interfering with several functions of these inflammatory cells. These actions include inhibiting the inflammatory cells from adhering to the vascular endothelium, trans-migrating into tissue, or secreting pro-inflammatory cytokines and free radicals.[3]

In addition to these pleiotropic benefits of statins, there have been additional findings to support their use. Overproduction of smooth muscle cells in the intimal layer of blood vessels contributes to artherosclerosis. Statins interfere with these processes by blocking the effects of growth factors while at the same time promoting NO production. In addition, patients with atherosclerosis are at increased risk of platelet aggregation due to accelerated production of thromboxane A2.[3] Finally, statins have been shown to decrease the oxidation of LDL-C, which prevents the attraction of macrophages.[3]

**Update to the ATP III Guidelines**

In September 2004 the ATP III guidelines were updated to address the publication of landmark studies in the field of hyperlipidemia. One of the major implications of the updated guidelines is the support of more aggressive lipid-lowering in high risk patients.

The updated ATP III guidelines suggest that an LDL-C goal of <70mg/dL is a therapeutic option in very high risk patients.[4] (Table 1) The decision of when and where to implement the goal is left to practitioners who must exercise clinical judgment given a specific patient scenario.

**Appropriate Dosage Selection**

Statins are clearly established as first-line therapy for elevated LDL-C due to their lipid lowering potential as well as their pleiotropic benefits. However, it is important to realize that while all statins are thought to share these pleiotropic effects, they do not all exhibit the same potency as lipid lowering agents. The ATP III guidelines suggest lowering LDL-C levels by at least 30 to 40% since this level of LDL-C reduction is consistent with clinical trial data. Thus, in order to achieve this decrease in LDL-C a "standard minimum dose" has been identified for each agent, to help clinicians select an evidence based dose of a statin needed to achieve the desired decrease in LDL-C. Table 2 shows the relative potencies of the statins at the "standard" dose identified

**Table 1. Patients at very high risk of CHD events.[4]**

| |
|---|
| Multiple major risk factors (especially diabetes mellitus) |
| Cigarette smoking |
| Metabolic Syndrome (especially with concurrent triglycerides of 200mg/dL or greater, non-HDL-C of 130 or greater, and HDL-C less or equal to 40mg/dL.) |
| Patients with acute coronary syndromes |

in the guidelines. In most cases, this should be considered the lowest effective dose of a statin, with effective being defined as the lowest dose supported by the literature.

## Clinical Trial Data

*PROVE-IT Trial*[6]

The Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE IT) was a randomized treatment-controlled trial comparing pravastatin 40 mg with atorvastatin 80 mg. The primary endpoint was a composite of all-cause mortality, unstable angina, revascularization, MI, and stroke in patients recently hospitalized with ACS. The trial followed 4,162 patients for 2 years. Of these patients, 75% had never been treated with a statin prior to enrollment. In the 75% of patients that had never been treated with a statin, LDL-C levels decreased by 22% in the pravastatin arm and 51% in the atorvastatin arm after 30 days ($p<0.001$). The remaining 25% had been on statin therapy previously, and experienced a virtually unchanged LDL-C level in the pravastatin arm, but experienced an additional 32% decrease in LDL-C in the atorvastatin arm ($p<0.001$). The average LDL-C level achieved after therapy was 95 mg/dl in the pravastatin arm and 62 mg/dl in the atorvastatin arm. After the two year follow-up, the primary endpoint was reduced by an additional 16% in the atorvastatin group compared to the pravastatin group ($p<0.005$). In summary, aggressive statin therapy conferred a greater overall benefit in this patient population compared with conventional statin dosing. There was no cases of rhabdomyolysis and no increase in the rate of discontinuation of therapy due to side effects.[6] The rate of liver function test elevations to greater than 3 times the upper limit of normal was significantly increased in the atovastatin arm (3.3% vs. 1.1%, $p<0.001$).

*AtoZ Trial*[7]

The A to Z Trial was a randomized, double-blind study using two different doses of simvastatin in post-MI patients. The primary endpoints were cardiovascular death, MI, hospital readmission for ACS, and stroke. Patients received either 40 mg/day of simvastatin for one month followed by 80 mg/day (40/80) thereafter, or placebo for four months followed by 20 mg/day (0/20) of simvastatin thereafter. This study was comprised of 4,497 patients. In the simvastatin 0/20 group there was a 31% decrease in LDL-C. In the simvastatin 40/80 group, the median LDL-C level decreased by 39%, with an additional 6% decrease after boosting the dose to 80 mg/day. The primary end points occurred in 16.7% of the placebo plus simvastatin patients compared with 14.4% in the simvastatin only group (p= NS). In this trial there were 10 cases of myopathy (9 in the simvastatin 40/80 arm), including 3 cases of rhabdomyolysis (all in the simvastatin 40/80 arm), which suggests that caution may be warranted with 80 mg dose simvastatin.[7]

*MIRACL Trial*[8]

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial was a prospective, randomized, multi-center, placebo-controlled clinical trial, which tested the ability of high dose atorvastatin to prevent recurrent ischemic events in patients with unstable angina or non-Q wave myocardial infarction (NSTEMI). More

**Table 2: Comparison of the currently available statins.[5,7]**

| Drug | fluvastatin (Lescol) | lovastatin* (Mevacor) | pravastatin* (Pravachol) | simvastatin (Zocor) | atorvastatin (Lipitor) | rosuvastatin (Crestor) |
|---|---|---|---|---|---|---|
| **Standard Dose **** | 40-80mg | 40mg | 40mg | 20-40mg | 5-10mg | 5mg |
| **Increase in HDL at standard dose** | | | ~7% | | | ~7% |
| **Decrease in LDL-C at Standard dose** | 25-35% | 31% | 34% | 35-41% | 39-45% | 34% |
| **Dosages available** | 20-80mg | 10-60mg | 10-80mg | 5-80 mg | 10-80mg | 5-40mg |

*Potencies increase moving from left to right with the exception of lovastatin and pravastatin , which are equipotent
**Standard dose is the dose required to achieve a approximate decrease in LDL-C of 30 to 40%

than 3,000 patients hospitalized over 43 months for unstable angina or non-Q wave MI with concurrent cholesterol levels <270 mg/dL were enrolled. Patients were randomized within 96 hours of hospital admission to atorvastatin 80 mg or placebo and all patients were encouraged to follow NCEP Step One Diet. While baseline cholesterol levels were equal in the treatment and placebo group, by the end of the study LDL-C declined 40% in the atorvastatin arm. The primary endpoint of the MIRACL trial was the time to first event, including all-cause death, resuscitated cardiac arrest, nonfatal MI, or worsening angina pectoris with new objective evidence of myocardial ischemia requiring urgent re-hospitalization. The secondary endpoints were stroke, cardiac revascularization, worsening congestive heart failure, or worsening angina without objective evidence of ischemia. A primary endpoint event occurred in 17.4% of patients in the placebo group and 14.8% of patients in the atorvastatin group (p=0.48). This translates to a 2.6% absolute risk reduction and 16% relative risk reduction. Of the secondary endpoints, notably, stroke was reduced by 50% in the atorvastatin group (p=0.045), but other secondary endpoints did not differ significantly between the groups.[8]

**Conclusion**

Clinical trial evidence supports the early, aggressive dosing of statins in an effort to decrease morbidity related to atherosclerotic disease. Statins are currently the drug of choice for treating hyperlipidemia due to their ability to decrease LDL-C and their pleiotropic effects. Future studies should help to identify optimal LDL-C thresholds for patients at different levels of risk for cardiovascular disease.

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# MICAFUNGIN (MYCAMINE™): A NEW ANTIFUNGAL AGENT


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Immunocompromised patients are extremely susceptible to invasive fungal infections. Over the last few decades, fungal infections have increased both in frequency and severity.[1] Many factors contributed to this increase, including advances in immunosuppressive therapy, decreased mortality, and the widespread use of antibiotics.[3] Invasive fungal infections increase mortality in hospitals and are estimated to cost the US health care system $25,000 per episode with the total cost exceeding $300 million.[4] *Candida* spp. are responsible for up to 8% of central venous catheter-related blood stream infections.[4] It is estimated that 15% of allogeneic hemopoietic stem cell transplant recipients develop an infection and about 20% of AIDS patients develop esophageal candidiasis.[3] Clearly, the projected increase in fungal infections is of clinical importance.

Traditionally, several antifungals have been used when treating invasive fungal infections. Amphotericin B disrupts the fungal cell membrane by binding to ergosterol. The azoles (fluconazole and itraconazole) inhibit the synthesis of ergosterol. However, resistance to these agents is increasing. It has been reported that in the US, 10% of C. *albicans* causing bloodstream infections were resistant to fluconazole.[4] Of even greater concern, is that 48% of candidal bloodstream infections were associated with

**Table 1. Spectrum of micafungin activity.** [1,3,4]

| | |
|---|---|
| **Indicated for infections caused by:** | Invasive aspergillosis (fungistatic)<br>*Candida albicans* (including azole-resistant strains) (fungicidal)<br>Non-albicans Candida |
| **Also active against:** | The mycelial form of *H. capsulatum*<br>*B. dermatitidis*<br>*C. immitis* |
| **Not active against:** | Zygomycetes<br>*Cryptococcus neoformans*<br>Fusarium<br>Cunninghamella |

non-albicans species like *C.glabrata* and *C. krusei.*[4] These species are more likely to be resistant to azoles than *C. albicans.*[4] With resistance to azoles on the rise and the adverse effects of ampotericin B, the need for new drugs is apparent. Micafungin (Mycamine ™) is a novel antifungal agent that works by inhibiting the production of B- (1,3)-D-glucan, which is important to fungal cell wall synthesis. It was developed because of the need for safe, broad-spectrum antifungals with few drug interactions. Mycamine ™ was identified in 1990. The FDA approved it on March 16, 2005. It is co-marketed by Fujisawa Healthcare, Inc., its manufacturer, and Roche Pharmaceuticals. Micafungin is indicated for the treatment of esophageal candidiasis and for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. The objectives of this article are to review the efficacy, safety, and place of micafungin in antifungal pharmacotherapy.

## Pharmacology and Pharmacokinetics

Micafungin, a large water-soluble lipopeptide, is a cell wall synthesis inhibitor belonging to the echinocandin class.[1] It is derived from chemical modification of the mould, *Coleophoma empedri.* Micafungin has a complex aromatic side chain (3,5-diphenyl-substituted isoxazole) that distinguishes it from the other echinocandins.[3] It inhibits the synthesis of *B*- (1,3)-D-glucan which is an essential component of the fungal cell wall.[1-2] This inhibition causes changes to the cell wall resulting in osmotic stress, lysis and eventual cell death.[1] Because *B*- (1,3)-D-glucan is not present in mammalian cells, micafungin poses a low risk for mechanistic toxicity in humans.[1-2] Micafungin is fungicidal against *Candida* spp., including isolates resistant to fluconazole and itraconazole, and has potency against clinical isolates of *Aspergillus* spp.[1] (Table 1).

Due to its poor oral bioavailability, micafungin is only available in an intravenous formulation.[1-2] It has a small volume of distribution and is highly protein bound (99%). However, only a small amount is bound to albumin.[3] Micafungin is not dialyzable. The mean half-life of micafungin is 13 hours.[7] Steady state concentrations are reached after approximately four days of treatment.[3] Fecal excretion is the major route of elimination.[8] Micafungin is metabolized in the liver by hydrolysis and N-acetylation.[3] It has fewer drug interactions than the azoles because it is a poor substrate for CYP450 enzymes and P-glycoprotein. However, micafungin has been shown to increase systemic exposure to sirolimus by 21% and nifedipine by 18%.[2] It has been noted by some researchers that this drug has increased uptake by red blood cells.[3] Micafungin has two metabolites that have antifungal activity; they are mainly excreted in the bile over several days.[3] There is no antagonism between echinocandin-azole or echinocandin-amphotericin B combinations. In fact, there may be an additive or synergistic effect. Studies have indicated that micafungin has no clinically relevant interactions with cyclosporin or tacrolimus.

## Clinical Trials

Several studies have investigated the efficacy of micafungin in esophageal candidiasis and for prophylaxis of fungal infections in adult patients undergoing bone marrow or peripheral stem cell transplants. One study explored the pharmacokinetics and maximum tolerated dose of micafungin in combination with fluconazole versus fluconazole alone. Another study compared the efficacy and safety of micafungin vs. fluconazole for the treatment of esophageal candidiasis. Also, the minimum effective dose and safety of micafungin for the treatment of HIV-related esophageal candidiasis was evaluated.

**Table 2. Clinical studies of micafungin.** [5,6,7]

| Study | Demographics | N | Design | Dose (mg/day) | Result |
|---|---|---|---|---|---|
| **Pettengell et al.**[5] | HIV-related esophageal candidiasis | 120 | OL study of the effects of M | 12.5<br>25<br>50<br>75<br>100 | *Defined minimum effective dose to be 12.5 mg<br>*Well tolerated and safe |
| **Hiemenz et al.**[7] | Prophylactic antifungal therapy after bone marrow or stem cell transplantation | 74 | RDB, dose escalation, tolerance study of M + F vs. F alone | M: 12.5<br>25<br>50<br>75<br>100<br>150<br>200<br>F: 400 | *M+F deemed safe<br>*Indicates that the maximum dose of M is above 200mg/day<br>*Doses up to 200mg/day were well-tolerated |
| **De Wet et al.**[6] | Esophageal candidiasis | 523 | RDB, study of M vs. F | M: 150<br>F: 200 | *M is an efficacious and safe alternative to F |

M= micafungin, F= fluconazole, OL= open label, RDB= randomized double blind

The results from these studies are summarized in Tables 2 and 3 and the ensuing section.

*HIV-related esophageal candidiasis*

Pettengell et al. [5] determined the clinical safety and efficacy of micafungin in patients with a documented *Candida* infection. The minimum effective dose of micafungin in patients with HIV-related esophageal candidiasis was evaluated. One- hundred and twenty patients were recruited for this open-label study. The patients consisted of men and women over the age of eighteen with a diagnosis of HIV. Esophageal candidiasis was confirmed by endoscopy. The patients were administered daily one-hour infusions of micafungin and were randomly assigned to doses of 12.5, 25, 50, 75, and 100 mg. The minimum effective dose was defined as the lowest dose achieving clinical cure or improvement in at least 65% of patients after 10 days of therapy. Patients were evaluated at baseline and on days 3, 7, and 14 after the start of micafungin, and at 2 weeks post treatment. The primary outcome measured was defined as cure or improvement of signs and symptoms. The secondary outcome measures were improvement in esophageal mucosal lesions, mycological response, the rate of relapse in the 2 weeks post-treatment, quantitative clinical assessments, and the overall therapeutic success.

Each dosing group had a positive clinical response except one patient in the 12.5 mg group. A decrease in symptoms was demonstrated within 3 to 5 days of treatment. There was a noticeable dose-response relationship, which was statistically significant ($p = 0.001$). With respect to mucosal lesions, the 75 mg and 100 mg doses were superior based on a 2 to 3 fold greater decline from baseline. The 12.5 mg dose was deemed the minimum effective dose. Adverse events attributed to micafungin occurred in 29.2% of patients. The most frequent adverse effects were vomiting (6.7%), liver function test abnormalities (5.8%), nausea (5.0%), and rash (3.3%). There were no cases of nephrotoxicity or infusion-related reactions. Histamine-like reactions and hepatotoxcicity were not observed. Micafungin was well tolerated and effective in this study and the results were comparable to other drugs used to treat esophageal candidiasis.

*Comparative trial of micafungin vs. fluconazole*

A randomized, double blind, multicenter, multinational trial of micafungin versus. fluconazole was conducted by De Wet et al.[6] The study involved 523 patients, age 16 or older, with documented esophageal candididasis. Each patient either received intravenous micafungin (150 mg per day) or intravenous fluconazole (200 mg per day). The drug was administered as a 1-hour infusion once a day for a minimum of 14 days or for 7 days after successful elimination of the signs and symptoms of the infection. At the end of therapy, a mucosal grade of zero was defined as treatment success and was the primary outcome. The frequency of relapse at 2 and 4 weeks post treatment, the change in mucosal grade, and overall therapeutic response (improvement) were secondary endpoints. Micafungin patients had an 87.7% endoscopic cure rate, whereas fluconazole

**Table 3. Adverse reactions.** [5,6,7]

| Study | Adverse Reactions |
|---|---|
| **Pettengell et al.[5] (N= 120)** | Vomiting (6.7%)<br>Liver function test abnormalities (5.8%)<br>Nausea (5.0%)<br>Rash (3.3%) |
| **Hiemenz et al.[7] (N= 74)** | Headache (6.8%)<br>Arthralgia (6.8%)<br>Maculopapular rash (4.1%)<br>Rash (4.1%)<br>Hypophosphatemia (4.1%)<br>Insomnia (4.1%) |
| **De Wet et al.[6] (N= 523)** | Rash (3 patients)<br>Rash + delirium (1 patient)<br>Delirium (1 patient) |

had an 88% endoscopic cure rate (95% CI, –5.9 to 5.3). Patients treated with either medication improved within 3 to 5 days of starting therapy. Fluconazole reported an 87.2% overall therapeutic success rate and micafungin reported an overall therapeutic success rate of 87.3% (95% CI, -5.6 to 5.8). The frequency of drug related adverse events were 27.7% for micafungin and 21.3% for fluconazole ($p = 0.102$). Rash (three patients), rash and delirium (one patient), delirium (one patient), and AIDS progression (one patient) led to the discontinuation of micafungin. In the case of fluonazole, there were two patients who discontinued the medication: one due to rash and one due to asthenia and delirium. Treatment success and relapse rates were comparable with the two medications. Micafungin had a relapse rate of 15.2% versus 11.3% with fluconazole through week 4 ($p > 0.25$). One disadvantage of micafungin is that it can only be dosed intravenously; however, oral medications are often hard for HIV/AIDS patients to take especially those who have mucosal lesions.

*Micafungin in combination with fluconazole vs. fluconazole alone*

A pharmacokinetic and maximum tolerated dose study was performed by Hiemenz et al.[7] This study compared micafungin in combination with fluconazole versus. fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Seventy-four patients were chosen to participate in this randomized, double blind, dose escalation, and tolerance study. The patients received either fluconazole (400 mg/day) with micafungin (8 patients at each dose level) or fluconazole (400 mg/day) with normal saline (control group). The doses used for micafungin were: 12.5, 25, 50, 75, 100, 150, 200 mg/day. The patients consisted of men and women between the ages of 18 and 55 years old who had underwent a bone marrow or peripheral stem cell transplant. Treatment was started between 48 hours prior to transplant and 24 hours post transplant. Fluconazole was given either by mouth, the preferred route, or by intravenous infusion. Micafungin was given by intravenous infusion of 100 ml over 1 hour. There were four patients in the micafungin treatment group who developed a grade three or greater toxicity. Three of these events occurred at the 150 mg and 200mg doses. However, the criterion for the maximum tolerated dose was not met, indicating that the maximum dose in this study is within the range of doses that merit further study. The frequency of adverse events between the control group and the micafungin-fluconazole groups were not clinically significant. There were several events possibly related to micafungin: headache (6.8%), arthralgia (6.8%), hypophosphatemia (4.1%), insomnia (4.1%), maculopapular rash (4.1%), and rash (4.1%).[7] No reports were made of infusion-related reactions. There were no dose-limiting toxicities noted. The pharmacokinectic profiles of micafungin on days one and seven were comparable. From zero to twenty-four hours, the mean maximum concentrations of the drug in serum and area under the concentration time curve were relatively proportional. Several patients had a possible fungal infection by the end of treatment: 41.7% of patients in the control group compared with 22.6% of patients in the micafungin-fluconazole group (regardless of micafungin dose).[7]

Overall, micafungin in combination with fluconazole was safe in this patient population. Doses up to 200 mg/day were safe. Gender and race appear to have no effect on outcomes. Drug interactions between micafungin and fluconazole were absent. Further research is warranted to elucidate whether the combination is safe and effective for the prevention of fungal infections in patients undergoing bone marrow or peripheral stem cell transplants.

**Dosing and Administration**

An advantage of micafungin is that it can be dosed once daily by intravenous infusion. However,

**Table 4. Cost analysis.** [8]

| Drug | Mg/Day | AWP/Day |
|---|---|---|
| **Micafungin** | 150 mg | $280.50 |
| **Caspofungin** | 50 mg | $372.68 |
| **Amphotericin B** | 18.75-75 mg | $11.64-$23.28 |
| **Fluconazole Oral** | 100-200 mg | $9.39-$15.36 |
| **Fluconazole IV** | 100-200 mg | $110.97 |

AWP=average wholesale price.

there is no oral formulation. There are several starting doses recommended with dose escalation permitted: for invasive aspergillosis - 75 mg/day (1.5 mg/kg/day if weight <40 kg), for *Candida albicans*- 50 mg/day (1 mg/kg/day if weight <40 kg), and for Non-albicans *Candida* spp.- 100 mg /day (2 mg/kg/day if wt under <40 kg).[4] For candidiasis prophylaxis in hematopoietic stem cell transplant patients, a dose of 50 mg/day as an IV infusion over one hour should be administered. The duration of treatment in clinical trials was between 6 and 51 days with a mean of 19 days.[2] For the treatment of esophageal candidiasis, 150 mg/day administered as an IV infusion over one hour is recommended. The treatment duration was between 10-30 days.[2] The safety and efficacy has not been established in infants, children, or adolescents. There are no dosage adjustments needed in patients who have renal impairment or who have mild to moderate hepatic impairment.[2] There is no data on patients with severe hepatic impairment. Micafungin is not dialyzable so supplemental dosing is not necessary.[2]

## Cost

Table 4 depicts pricing for micafungin and other frequently used antifungal agents.

## Summary

Fungal infections are increasing at an alarming pace. Micafungin is a new antifungal indicated in the treatment of esophageal candidiasis and for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. With resistance to the azoles on the rise and the nephrotoxic effects of Amphotericin B, micafungin could be a useful alternative. It is well- tolerated with no apparent dose related adverse effects. Micafungin does not cause a histamine-like reaction like other drugs in its class (eg., caspofungin). It has few drug interactions and may be synergistic with azoles or amphotericin B. Bilirubinemia, nausea, vomiting, diarrhea, and increased liver function tests have been the most common adverse effects. Additional studies are required to establish the role of micafungin in practice. Ideally, studies comparing micafungin with caspofungin will be conducted.

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