Drugs 2004; 64 (19): 2249-2258
0012-6667/04/0019-2249/$34.00/0

Anidulafungin

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Abstract

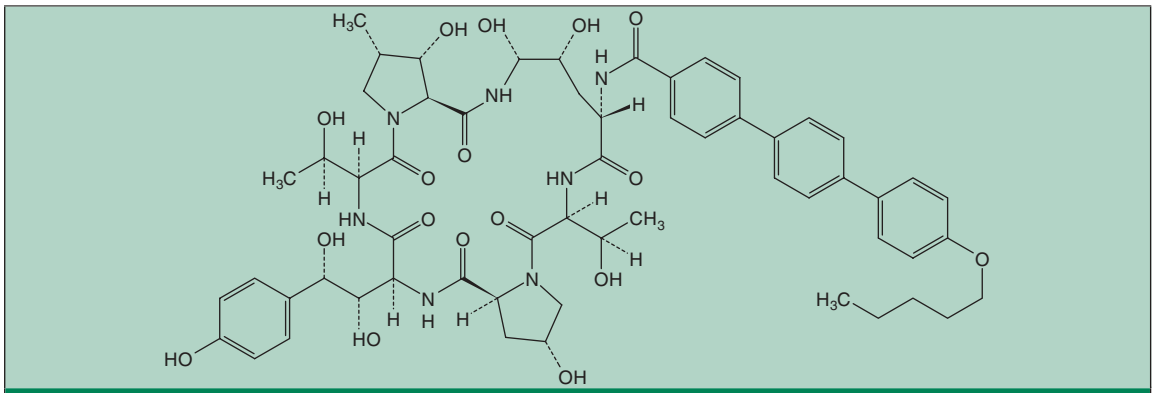
▲ Anidulafungin is a novel antifungal agent which, like other echinocandins, inhibits β-(1,3)-D-glucan synthase and disrupts fungal cell-wall synthesis. It has marked antifungal activity against a broad spectrum of *Candida* spp. and *Aspergillus* spp., including amphotericin B- and triazole-resistant strains.

▲ In clinical trials, anidulafungin has primarily been evaluated in patients with oesophageal and invasive candidiasis. Preliminary data are emerging for other indications such as invasive aspergillosis.

▲ In a large, multicentre, double-blind, double-dummy, randomised trial in patients with oesophageal candidiasis, intravenous anidulafungin 50 mg/day was as effective as oral fluconazole 100 mg/day regarding end-of-treatment rates of endoscopic cure and clinical and microbiological success. Duration of treatment was approximately 2–3 weeks, and patients in both groups received a loading dose of study drug (twice the daily maintenance dose) on day 1.

▲ Anidulafungin is generally well tolerated. Across the dosage range 50–100 mg/day, adverse events appear not to be dose- or infusion-related. In the largest clinical trial to date, the most common treatment-related adverse events were phlebitis/thrombophlebitis, headache, nausea, vomiting and pyrexia.

Features and properties of anidulafungin (LY303366, VER002)	
Indication	
Oesophageal candidiasis (focus of this profile) and invasive candidiasis	
Mechanism of action	
Interferes with fungal cell-wall synthesis by inhibiting β-(1,3)-D-glucan synthase	
Dosage and administration (based on clinical trial dosages)	
Oesophageal candidiasis: 50 mg/day, after a loading dose of 100mg	
Invasive candidiasis: 100 mg/day, after a loading dose of 200mg	
Route of administration	Intravenous infusion
Frequency of administration	Once daily
Mean pharmacokinetic parameters (steady-state values after administration of 50 mg/day to patients with oesophageal candidiasis)	
Peak plasma concentration	3.5 mg/L
Area under the plasma concentration-time curve	53 mg • h/L
Volume of distribution	33.4L
Elimination half-life	25.6h
Clearance	0.93 L/h
Adverse events (based on the largest clinical trial)	
Most common treatment-emergent	Phlebitis/thrombophlebitis, headache, nausea, vomiting and pyrexia



A major increase in the incidence of systemic fungal infections, especially those due to *Candida* (including non-albicans) spp. and *Aspergillus* spp., has occurred during the past 20 years.[1-3] Reasons for this increase include the growing number of patients receiving broad-spectrum antibiotics, chemotherapy, or undergoing organ or haematopoietic stem cell transplantation and subsequent immunosuppression.[2-4] In addition, the rising number of AIDS patients is at particular risk from fungal infections, including oesophageal candidiasis.[2,5]

Oesophageal candidiasis occurs in approximately 10–20% of patients with AIDS or immunodeficiency from other causes (e.g. underlying disease, chemotherapy, radiation therapy), and relapse occurs in about 60% of patients within 3–6 months of the initial infection if the underlying immunodeficiency is not corrected.[5,6] Triazole antifungals (e.g. fluconazole, itraconazole) have gradually replaced the use of amphotericin B for oesophageal candidiasis. These first-line agents generally achieve a rapid clinical response with minimal adverse events following oral administration,[5,6] whereas amphotericin B requires intravenous administration and is associated with substantial rates of infusion-related adverse events and nephrotoxicity, even with newer lipid formulations of the compound.[7] However, increasing resistance to triazole antifungals, especially resistance of *Candida* spp. to fluconazole, is becoming a major concern,[3,6,8] as is cross-resistance between triazole antifungals that is emerging in many regions.[4] In addition, considerable potential exists for drug interactions between triazole antifungal agents, which are metabolised extensively by the hepatic cytochrome P450 (CYP) system, and other compounds.[3,8]

Systemic antifungal agents such as amphotericin B and triazoles have traditionally targeted ergosterol in fungal cell membranes.[9] Echinocandins such as anidulafungin, caspofungin and micafungin are a new class of antifungal compounds with a unique mechanism of action and a broad spectrum of activity, including activity against fluconazole-resistant *Candida* spp.[6,10] They inhibit the synthesis of β-(1,3)-D-glucan in fungal cell walls, thus causing changes to fungal cell-wall structure;[3,9] host cells are unaffected since they do not contain β-(1,3)-D-glucan.[3,10] However, echinocandin antifungals have poor oral bioavailability and their use is limited to the intravenous route.[10] In oesophageal candidiasis, their use is generally reserved for patients refractory to or intolerant of other antifungal agents such as the triazoles.[3,6]

Anidulafungin is a semisynthetic, lipopeptide antifungal agent derived from echinocandin B_0, a fermentation product of the fungus *Aspergillus nidulans*.[7,11] Through specific, noncompetitive inhibition of the enzyme complex β-(1,3)-D-glucan synthase, and subsequent interference with fungal cell-wall synthesis, anidulafungin causes osmotic instability and the death of fungal cells.[3,6] Anidulafungin has been most extensively evaluated in

patients with oesophageal candidiasis (the focus of this profile) and invasive candidiasis. Promising data are also emerging on the use of anidulafungin in invasive aspergillosis,[12] although this potential indication is beyond the scope of this article.

1. Pharmacodynamic Profile

In Vitro Activity

The *in vitro* antifungal properties of anidulafungin have been widely studied, despite the absence of a clinically relevant susceptibility testing method;[4,10] that is, susceptibility breakpoints for echinocandins, including anidulafungin, have not yet been established.[9,13] Nevertheless, the *in vitro* antifungal activity of anidulafungin has generally been assessed using National Committee for Clinical Laboratory Standards (NCCLS) broth-dilution methods,[13,14] although other methods (e.g. disc diffusion testing, E-test) warrant further investigation.[7,15]

- Anidulafungin has potent and rapid fungicidal activity, as indicated by flow cytometry,[16] against most *Candida* spp., including strains resistant to triazoles.[17-19] Against numerous clinical isolates of *Candida* spp., anidulafungin demonstrated marked activity against *C. albicans* (minimum inhibitory concentration range for 90% of strains [MIC_{90}] 0.03–0.5 mg/L), *C. glabrata* (0.13–0.5 mg/L), *C. krusei* (0.13–0.5 mg/L) and *C. tropicalis* (0.13–2 mg/L),[17,19-22] but tended to have less activity *in vitro* against *C. parapsilosis* (MIC_{90} >2–4 mg/L)[17,19-22] and *C. guilliermondii* (MIC 0.06–>32 mg/L).[20,21,23,24]
- The overall *in vitro* activity of anidulafungin was greater than that of other antifungal agents (amphotericin B, caspofungin, fluconazole, itraconazole and voriconazole) against a large panel of yeast isolates obtained from patients with superficial and deep infections in five centres in Europe.[25] *Candida* spp. included *C. albicans* (505 isolates), *C. glabrata* (89), *C. krusei* (53), *C. parapsilosis* (41), *C. tropicalis* (65) and others (23). MIC_{90} results tested by an NCCLS method and read after 24 and 48 hours were as follows: anidulafungin 0.06 and 0.12 mg/L, amphotericin B 0.5 and 0.5 mg/L, caspofungin 1.0 and 2.0 mg/L, fluconazole 16 and 32 mg/L, itraconazole 0.5 and 1.0 mg/L and voriconazole 0.25 and 0.5 mg/L.
- Minimum fungicidal concentrations of anidulafungin against *Candida* spp. were similar to, or did not differ more than 2-fold from, corresponding MIC_{90} values.[22] Furthermore, in time-kill assays at concentrations greater than MIC values, a concentration-dependent postantifungal effect of >12 hours was documented for anidulafungin against *C. albicans*.[26]
- The addition of 50–80% human serum to RPMI 1640 culture medium led to a 4- to 8-fold increase in MIC values for anidulafungin against *Candida* spp. in two *in vitro* studies.[27,28]
- The *in vitro* growth of *Candida* spp. resistant to fluconazole and itraconazole was inhibited by anidulafungin concentrations of ≤0.5 mg/L in two trials.[17,19] Moreover, in a Spanish study including 148 isolates of *Candida* spp. with reduced susceptibility to fluconazole, anidulafungin had markedly greater *in vitro* antifungal activity than both amphotericin B and itraconazole; MIC_{90} values are shown in figure 1. Overall, 49 isolates had an MIC ≥1 mg/L for itraconazole.[23]
- Anidulafungin inhibited the *in vitro* growth of *Aspergillus* spp., including *A. flavus*, *A. fumigatus*, *A. terreus* and *A. niger*, with an MIC_{90} range of ≤0.03–0.06 mg/L.[29,30] Neutrophils and anidulafungin had additive antifungal activity against *A. fumigatus* in one *in vitro* model.[31] Anidulafungin is generally less active against filamentous fungi other than *Aspergillus* spp. (MIC 1 to >16 mg/L), and is inactive against *Fusarium* spp. (≥16 mg/L).[32]
- Anidulafungin appears to have variable activity against dimorphic fungi such as *Blastomyces dermatitidis* and *Histoplasma capsulatum*; however, it is largely inactive against *Cryptococcus neoformans*.[32,33]
- *In vitro* studies have indicated synergistic antifungal activity for anidulafungin and nikkomycin Z against *A. fumigatus* and *Coccidioides immitis* (mycelial phase),[34] and for anidulafungin plus

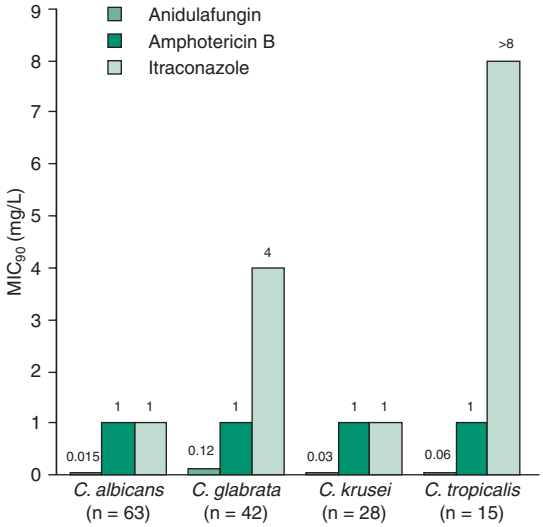


Fig. 1. *In vitro* activity of anidulafungin against clinical isolates of *Candida* spp. with reduced susceptibility to fluconazole (MIC ≥16 mg/L).[23] *In vitro* activity was determined using a broth microdilution assay (based on the National Committee for Clinical Laboratory Standards) for 156 isolates of *Candida* spp. obtained from 51 Spanish hospitals during a 5-year period; MIC values for *C. parapsilosis* (five isolates) and *C. guilliermondii* (three isolates) are not shown. **MIC**$_{90}$ = minimum inhibitory concentration for 90% of strains.

itraconazole or voriconazole against *Aspergillus* spp.[35] Synergistic to indifferent effects were documented for a combination of anidulafungin with amphotericin B against *Aspergillus* and *Fusarium* spp.[36] In another *in vitro* study, antifungal effects were generally additive or indifferent against *Candida* spp. when anidulafungin was combined with amphotericin B, flucytosine, fluconazole or itraconazole.[37]

In Animal Studies

• Anidulafungin has been evaluated in several animal models of fungal infection. Indeed, anidulafungin showed marked antifungal activity in models of superficial and disseminated candidiasis in mice,[4,38] and in a model of disseminated candidiasis in persistently neutropenic rabbits.[39] In the latter trial, intravenous anidulafungin 0.5 and 1 mg/kg/day significantly and dose-dependently cleared *C. albicans* from the brain, kidneys, liver, lungs, spleen and vena cava.[39]

• In a model of oropharyngeal and oesophageal candidiasis in immunocompromised rabbits, intravenous anidulafungin 1–5 mg/kg/day significantly and dose-dependently cleared fluconazole-resistant strains of *C. albicans* from the tongue, oropharynx, oesophagus, stomach and duodenum.[40]

• Anidulafungin was also markedly effective in rabbit models of disseminated and invasive pulmonary aspergillosis[41,42] and murine models of disseminated/invasive aspergillosis,[4,38,43,44] and in normal and immunocompromised animals with *Pneumocystis carinii* (*P. jiroveci*) pneumonia.[4,38]

2. Pharmacokinetic Profile

The pharmacokinetic profile of anidulafungin has been evaluated in healthy volunteers,[45,46] patients with candidiasis or aspergillosis,[47,48] and patients with hepatic or renal impairment.[49-52] Various drug interaction studies have also assessed the pharmacokinetics of anidulafungin in healthy volunteers[53,54] and patients with serious fungal infections.[55,56]

Absorption and Distribution

• Pharmacokinetic data were modelled from phase II/III clinical trials of intravenous anidulafungin in a total of 225 patients, 96% of whom had candidiasis.[57] Calculations revealed the following estimates for mean steady-state pharmacokinetic parameters for a 50 mg/day anidulafungin regimen in a typical male patient weighing 60kg: peak plasma concentration (C_{max}) 3.5 mg/L, area under the plasma concentration-time cure (AUC) 53 mg • h/L and volume of distribution (Vd) 33.4L.[47,57]

• A similar modelling study suggested that intravenous anidulafungin 50 mg/day produced a steady-state AUC of approximately 50 mg • h/L, which exceeded the anidulafungin exposure required for a >95% probability of successful clinical outcome (i.e. resolution of clinical signs or symptoms, or an endoscopic response) in patients with oesophageal candidiasis.[48] Furthermore, plasma anidulafungin concentrations were >1 mg/L for the entire dosage interval, and interpatient variability in anidulafungin pharmacokinetics was low.[48]

Metabolism and Elimination

- Anidulafungin is not metabolised, but undergoes slow chemical degradation to inactive moieties (ring-opened products or smaller linear peptides) that lack the cyclic structure necessary for activity.[46]
- A study in healthy volunteers indicated that almost all of a single radiolabelled dose of anidulafungin ≈90mg was recovered in the faeces: <10% as intact anidulafungin, and >90% as small, tertiary degradation products; renal excretion of anidulafungin or its degradants was negligible.[46]
- In the latter trial[46] and another single-dose study,[45] values for anidulafungin clearance and elimination half-life ($t_{1/2}$) were documented as 0.87 L/h and 27.7–45.6 hours, respectively. Corresponding estimated mean steady-state values after administration of intravenous anidulafungin 50 mg/day to patients with oesophageal candidiasis were 0.93 L/h and 25.6 hours.[47,57] Intersubject variability for anidulafungin clearance and $t_{1/2}$ was estimated to be approximately 28% and 29% in a population pharmacokinetic model.[57]

Special Patient Populations

- Administration of a single intravenous dose of anidulafungin 50mg to 18 patients with mild, moderate or severe renal impairment, and to eight patients with end-stage renal failure undergoing haemodialysis, revealed no significant differences in anidulafungin pharmacokinetics relative to healthy control subjects.[50] Anidulafungin was not detected in dialysate.[50]
- Anidulafungin pharmacokinetics after administration of single intravenous 50mg doses were not markedly different in six patients with Child-Pugh mild hepatic impairment, relative to six with moderate impairment,[49] or relative to individuals without hepatic impairment.[45,47,57] Interestingly, in five patients with severe (Child-Pugh class C) hepatic impairment, anidulafungin C_{max} and AUC values were approximately 45% and 39% lower, whereas values for clearance and steady-state Vd were approximately 2-fold greater, than corresponding values in six healthy volunteers.[52] The clinical significance of these changes is unclear, and the mechanisms for the changes in pharmacokinetic parameters observed in this single-dose study are being further explored.[52]

Drug Interactions

- In 12 healthy volunteers, a regimen comprising a loading dose of intravenous anidulafungin 200mg, followed by 100 mg/day for 7 days, was administered with or without concomitant ciclosporin (cyclosporine), which increased anidulafungin C_{max} and AUC values by 4% and 21%, respectively.[53] The clinical relevance of these changes appears to be minimal, although two individuals had mild, reversible elevations of serum transaminase levels, the relationship of which to the anidulafungin-ciclosporin interaction was unclear.[53]
- Although the effect of anidulafungin on ciclosporin pharmacokinetics was not assessed in the above study in healthy volunteers,[53] *in vitro* data from another study indicate that anidulafungin, in concentrations up to 30 mg/L, had no effect on the metabolism of radiolabelled ciclosporin by pooled human hepatic microsomal fractions.[58]
- Steady-state anidulafungin pharmacokinetics were not significantly affected by concomitant administration of the triazole antifungal agent voriconazole in 17 healthy volunteers.[54] Anidulafungin C_{max} (7.87 mg/L) and AUC (120 mg • h/L) values after intravenous administration of anidulafungin 200mg on day 1, then 100 mg/day on days 2–4 were essentially unchanged (7.89 mg/L and 117 mg • h/L) by concurrent oral administration of voriconazole 400mg every 12 hours on day 1, then 200mg every 12 hours on days 2–4. In addition, anidulafungin did not affect the pharmacokinetics of voriconazole.[54]
- The pharmacokinetic parameters of anidulafungin in patients with invasive aspergillosis do not appear to be significantly affected by concurrent administration of liposomal amphotericin B.[55] The study used a population pharmacokinetic model developed from plasma anidulafungin samples collected from 225 patients in four clinical trials, which

included seven patients with invasive aspergillosis treated with intravenous anidulafungin 100 mg/day and liposomal amphotericin B 3–5 mg/kg/day.

- Population pharmacokinetic analyses using the model described above showed little effect of disease (e.g. oesophageal and invasive candidiasis, invasive aspergillosis),[55] or concomitant use of substrates, inducers and inhibitors of CYP,[56] on the pharmacokinetics of anidulafungin.
- There was no evidence of toxicity with concomitant administration of anidulafungin (25 mg/day intravenously for 10 days) plus cortisone acetate (single 125 mg/kg subcutaneous dose) in a well designed, controlled study involving two strains of inbred mice (DBA/2 [n = 30] and BALB/c [n = 30]).[59] Mice were randomised into three groups treated with either anidulafungin, cortisone or both drugs combined. No mortality, morbidity or toxicity was observed in any of the groups of mice. A previous study in mice (infected with *A. fumigatus* in most instances) suggested a possible increase in mortality when cortisone (or certain other glucocorticoids) was administered prior to anidulafungin.[60] However, cortisone and anidulafungin doses were very high and an appropriate control group (i.e. high-dose corticosteroid in the absence of either infection or anidulafungin therapy) was not included. In addition, concomitant administration of corticosteroids and anidulafungin was not associated with increased toxicity in a rabbit model of aspergillosis.[41,42]

3. Therapeutic Efficacy

The clinical efficacy of anidulafungin in oesophageal candidiasis has been evaluated in a large, phase III, randomised, double-blind, double-dummy study comparing intravenous anidulafungin with oral fluconazole,[61] and an open-label, phase II, dose-ranging trial.[62] Data are also available from a phase II, randomised, dose-finding study evaluating anidulafungin in patients with invasive candidiasis.[63]

A total of 601 immunocompromised patients with endoscopically and microbiologically confirmed oesophageal candidiasis, and most of whom had AIDS, were enrolled in a randomised, double-blind, multicentre study of intravenous anidulafungin 50 mg/day (after a loading dose of 100mg on day 1) compared with oral fluconazole 100 mg/day (after a loading dose of 200mg on day 1), each administered for 2–3 weeks.[61]

- End-of-treatment assessments in 504 evaluable patients revealed endoscopic cure in 242 of 249 anidulafungin-treated patients (97.2%) versus 252 of 255 fluconazole recipients (98.8%; figure 2). The between-group difference was −1.6% (95% CI −4.1, 0.8), within the a priori criteria to establish equivalence.[61] Similarly, no major differences were noted between the two groups regarding clinical and microbiological success rates.[61,64]
- The above study[61] demonstrated that anidulafungin and fluconazole were equally effective in terms of endoscopic cure at the end of treatment, but anidulafungin was less effective than fluconazole at a follow-up visit 2 weeks after treatment completion (cure rate 64.4% vs 89.5%; 95% CI −32.5 to −17.8%, $p < 0.001$).[61] However, the latter finding was thought to be of little clinical relevance, since relapse rates were considerable in both groups, and

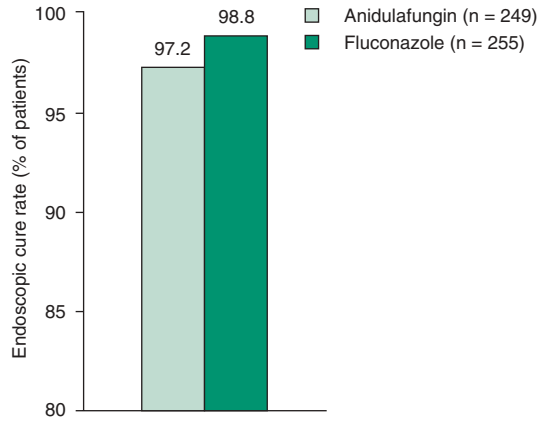


Fig. 2. Efficacy of intravenous anidulafungin compared with that of oral fluconazole in immunocompromised patients with oesophageal candidiasis in a large-scale, randomised, double-blind, multicentre study.[61] Intravenous anidulafungin therapy comprised 50 mg/day (after a loading dose of 100mg), whereas the oral fluconazole regimen was 100 mg/day (after a loading dose of 200mg), each administered for 2–3 weeks. At the end of treatment, 504 patients were clinically evaluable for endoscopic cure; the evaluation revealed that anidulafungin and fluconazole were equally effective.

standard clinical practice dictates that patients with treatment-responsive oesophageal candidiasis should receive follow-up therapy to prevent relapse.[65]

- The efficacy of two intravenous dosage regimens of anidulafungin was compared in a randomised, open-label, dose-ranging study in 29 patients with oesophageal candidiasis (reported as an abstract).[62] Endoscopic improvement (grade 0 or a 1-grade improvement) was achieved in 11 of 13 patients (85%) who received the higher dosage regimen of 70mg on day 1, then 35 mg/day, compared with 13 of 16 patients (81%) who received the lower dosage regimen of 50mg on day 1, then 25 mg/day. Clinical scores (based on resolution of dysphagia and retrosternal pain) were 81.8% and 68.8% for the higher- and lower-dose groups, respectively. Patients in both groups received therapy for 2–3 weeks. Statistical analysis was not reported, although both regimens were deemed to be efficacious in treating oesophageal candidiasis.[62]

- Encouraging results were reported with anidulafungin in patients with invasive candidiasis (most with candidaemia) in a phase II, randomised, dose-finding study.[63] The primary endpoint was global response (i.e. clinical and microbiological responses) in evaluable (per protocol) patients at the follow-up visit 2 weeks after the end of therapy. Among 68 evaluable patients who were treated with intravenous anidulafungin 50, 75 or 100 mg/day (after a loading dose of twice the daily maintenance dose on day 1), global response rates were 72%, 85% and 83% at the 2-week follow-up visit. Corresponding global response rates among 83 evaluable patients at the end of therapy were 84%, 90% and 89%. Tolerability data, which are reported in section 4, were analysed for the intent-to-treat population of 120 patients. There were 33 fatalities in the study, although none related to drug therapy. The study authors suggested that phase III studies of the 100 mg/day dosage of anidulafungin are warranted for this indication.[63]

4. Tolerability

- In the largest controlled efficacy study conducted to date in patients with oesophageal candidiasis, 601 patients, most of whom had AIDS, were treated with intravenous anidulafungin or oral fluconazole in a randomised, double-blind, double-dummy fashion.[61] The most frequently reported drug-related adverse events in the anidulafungin and fluconazole treatment groups were phlebitis/thrombophlebitis (1.3% vs 1.3%), headache (1.3% vs 1%), nausea (1% vs 1%), vomiting (0.7% vs 1%), pyrexia (0.7% vs 1%) and dyspepsia (0.3% vs 1%). Neutropenia and leucopenia were reported in 1% and 0.7% of anidulafungin recipients compared with 0% and 1.3% of patients treated with fluconazole.
- Overall, treatment-related adverse events were documented in 9.3% of anidulafungin recipients and 12.0% of fluconazole-treated patients.[61] No patient experienced hypotension, wheezing or anaphylaxis, and the only infusion-related event was a subjective sensation of flushing, reported by one individual who received anidulafungin. Treatment-related serious adverse events were rare and occurred in only two patients from each group. Neither treatment had a clinically relevant effect on the QT interval. Minor laboratory abnormalities were reported in both groups at a similar frequency.
- In a separate analysis of hepatobiliary parameters in the large, phase III study in patients with oesophageal candidiasis, no apparent differences between treatment groups were noted for clinically significant increases in alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase and bilirubin levels.[66] Clinically significant changes in ALT levels were reported in 0.8% of anidulafungin recipients and 3.3% of fluconazole recipients after 14 days of therapy; broadly similar results were observed for the other parameters.[66]
- No, or only a few, treatment-related serious adverse events were noted in phase II, dose-ranging studies of anidulafungin in patients with oesophageal candidiasis[62] or invasive candidiasis.[63] In the latter study, only three serious adverse events were reported (one instance of non-neutropenic fever, and two of seizure), and no systemic infusion-

related adverse events were noted.[63] There were also no anaphylactic reactions or haemolytic episodes.

- In the dose-ranging study in 120 patients with invasive candidiasis, approximately 30% of patients experienced drug-related adverse events, although there was no evidence of a dose-response relationship for such events.[63] The most common adverse events, whether considered to be related to therapy or not, were hypotension, vomiting, constipation, nausea and pyrexia, each reported in 11–13% of patients. The most common laboratory abnormalities were hypokalaemia, elevated γ-glutamyl transferase levels and hypomagnesaemia.[63]

5. Dosage and Administration

In the large, phase III clinical trial of anidulafungin in patients with oesophageal candidiasis, anidulafungin was administered intravenously as a 100mg loading dose on day 1, followed by a 50 mg/day maintenance dose for 2–3 weeks.[61] Daily maintenance doses were administered over 45 minutes and the loading dose was administered over 90 minutes.

In a dose-ranging study of anidulafungin in patients with invasive candidiasis, the optimal regimen was deemed to be an intravenous loading dose of 200mg on day 1, followed by a maintenance dose of 100 mg/day.[63] The protocol used an infusion rate of 1 mg/min for anidulafungin, and the drug was administered for 2 weeks beyond resolution or improvement of signs and symptoms.

6. Anidulafungin: Current Status

The efficacy of intravenous anidulafungin, as assessed by endoscopic cure rates and clinical and microbiological success rates, was similar to that of oral fluconazole in a large phase III trial in patients with oesophageal candidiasis. Both drugs were generally well tolerated, and treatment-related adverse events were similar in both groups.

A new drug application for anidulafungin in the treatment of oesophageal candidiasis is currently under review by the US FDA,[67,68] as is a marketing authorisation application for the drug in the same indication by the European Medicines Evaluation Agency.[69] In addition, anidulafungin is currently undergoing clinical investigation for the treatment of invasive candidiasis[63] and invasive aspergillosis.[12]

References

1. Denning DW, Kibbler CC, Barnes RA. British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections. Lancet Infect Dis 2003 Apr; 3 (4): 230-40
2. Sobel JD. Practice guidelines for the treatment of fungal infections: Mycoses Study Group. Clin Infect Dis 2000; 30: 652
3. Keating GM, Figgitt DP. Caspofungin: a review of its use in oesophageal candidiasis, invasive candidiasis and invasive aspergillosis. Drugs 2003; 63 (20): 2235-63
4. Arathoon EG. Clinical efficacy of echinocandin antifungals. Curr Opin Infect Dis 2001 Dec; 14 (6): 685-91
5. Ruhnke M. Advances in the treatment of oral and esophageal candidiasis [abstract no. S15]. Clin Microbiol Infect 1999 Mar; 5 Suppl. 3: 6
6. Vazquez JA. Invasive oesophageal candidiasis: current and developing treatment options. Drugs 2003; 63 (10): 971-89
7. Feldmesser M. New and emerging antifungal agents: impact on respiratory infections. Am J Resp Med 2003; 2 (5): 371-83
8. Dismukes WE. Introduction to antifungal drugs. Clin Infect Dis 2000 Apr; 30 (4): 653-7
9. Jarvis B, Figgitt DP, Scott LJ. Micafungin. Drugs 2004; 64 (9): 969-82
10. Denning DW. Echinocandin antifungal drugs. Lancet 2003; 362 (9390): 1142-51
11. Hodges RL, Kelkar HS, Xuei X, et al. Characterization of an echinocandin B-producing strain blocked for sterigmatocystin biosynthesis reveals a translocation in the *stcW* gene of the aflatoxin biosynthetic pathway. J Ind Microbiol Biotechnol 2000 Dec; 25 (6): 333-41
12. Vicuron Pharmaceuticals Inc. Vicuron Pharmaceuticals announces phase III results of anidulafungin combination regimen for treatment of invasive aspergillosis [online]. Available from URL: http://www.vicuron.com [Accessed 2004 May 5]
13. Espinel-Ingroff A. Antifungal susceptibility methods and their potential clinical relevance. Lab Med 2002 Aug; 33 (8): 626-31
14. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts; approved standard (document M27-A). Wayne (PA): NCCLS, 1997; 17 (9)
15. Wiederhold NP, Lewis RE. The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy. Expert Opin Investig Drugs 2003 Aug; 12 (8): 1313-33
16. Green LJ, Marder P, Mann LL, et al. LY303366 exhibits rapid and potent fungicidal activity in flow cytometric assays of yeast viability. Antimicrob Agents Chemother 1999 Apr; 43 (4): 830-5
17. Marco F, Pfaller MA, Messer SA, et al. Activity of MK-0991 (L-743,872), a new echinocandin, compared with those of LY303366 and four other antifungal agents tested against

blood stream isolates of *Candida* spp. Diagn Microbiol Infect Dis 1998; 31: 33-7

18. Karlowsky JA, Harding GA, Zelenitsky SA, et al. *In vitro* kill curves of a new semisynthetic echinocandin, LY-303366, against fluconazole-sensitive and -resistant *Candida* species. Antimicrob Agents Chemother 1997 Nov; 41 (11): 2576-8
19. Pfaller MA, Messer SA, Coffman S. *In vitro* susceptibilities of clinical yeast isolates to a new echinocandin derivative, LY303366, and other antifungal agents. Antimicrob Agents Chemother 1997 Apr; 41 (4): 763-6
20. Ostrosky-Zeichner L, Rex JH, Pappas PG, et al. Antifungal susceptibility survey of 2,000 bloodstream *Candida* isolates in the United States. Antimicrob Agents Chemother 2003 Oct; 47 (10): 3149-54
21. Marco F, Danés C, Almela M, et al. Trends in frequency and *in vitro* susceptibilities to antifungal agents, including voriconazole and anidulafungin, of *Candida* bloodstream isolates. Results from a six-year study (1996-2001). Diagn Microbiol Infect Dis 2003 Aug; 46 (4): 259-64
22. Arévalo MP, Carrillo-Muñoz AJ, Salgado J, et al. Antifungal activity of the echinocandin anidulafungin (VER002, LY-303366) against yeast pathogens: a comparative study with M27-A microdilution method. J Antimicrob Chemother 2003 Jan; 51 (1): 163-6
23. Cuenca-Estrella M, Mellado E, Díaz-Guerra TM, et al. Susceptibility of fluconazole-resistant clinical isolates of *Candida* spp. to echinocandin LY303366, itraconazole and amphotericin B. J Antimicrob Chemother 2000 Sep; 46 (3): 475-7
24. Moore CB, Oakley KL, Denning DW. *In vitro* activity of a new echinocandin, LY303366, and comparison with fluconazole, flucytosine and amphotericin B against *Candida* species. Clin Microbiol Infect 2001; 7: 11-6
25. Johnson EM, Goldstein BP, Davey KG, et al. Comparison of the *in vitro* activity of anidulafungin with amphotericin B, caspofungin, fluconazole, itraconazole and voriconazole against a panel of 780 yeast isolates obtained from five European centres [abstract no. 513]. 14th European Congress of Clinical Microbiology and Infectious Diseases; 2004 May 1-4; Prague
26. Ernst EJ, Klepser ME, Pfaller MA. Postantifungal effects of echinocandin, azole, and polyene antifungal agents against *Candida albicans* and *Cryptococcus neoformans*. Antimicrob Agents Chemother 2000 Apr; 44 (4): 1108-11
27. Zhanel GG, Saunders DG, Hoban DJ, et al. Influence of human serum on antifungal pharmacodynamics with *Candida albicans*. Antimicrob Agents Chemother 2001 Jul; 45 (7): 2018-22
28. Hoban D, Balko T, Saunders D, et al. Influence of human serum on *Candida* species susceptibility to LY303366 [abstract no. J-9]. 38th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27; San Diego
29. Serrano MdC, Valverde-Conde A, Chávez M, et al. *In vitro* activity of voriconazole, itraconazole, caspofungin, anidulafungin (VER002, LY303366) and amphotericin B against *Aspergillus* spp. Diagn Microbiol Infect Dis 2003 Feb; 45 (2): 131-5
30. Pfaller MA, Marco F, Messer SA, et al. *In vitro* activity of two echinocandin derivatives, LY303366 and MK-0991 (L-743,792), against clinical isolates of *Aspergillus*, *Fusarium*, *Rhizopus*, and other filamentous fungi. Diagn Microbiol Infect Dis 1998 Apr; 30 (4): 251-5
31. Brummer E, Chauhan SD, Stevens DA. Collaboration of human phagocytes with LY 303366 for antifungal activity against *Aspergillus fumigatus*. J Antimicrob Chemother 1999 Apr; 43 (4): 491-6
32. Espinel-Ingroff A. Comparison of *in vitro* activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol 1998 Oct; 36 (10): 2950-6
33. Zhanel GG, Karlowsky JA, Harding GA, et al. *In vitro* activity of a new semisynthetic echinocandin, LY-303366, against systemic isolates of *Candida* species, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Aspergillus* species. Antimicrob Agents Chemother 1997 Apr; 41 (4): 863-5
34. Stevens DA. Drug interaction studies of a glucan synthase inhibitor (LY 303366) and a chitin synthase inhibitor (Nikkomycin Z) for inhibition and killing of fungal pathogens. Antimicrob Agents Chemother 2000 Sep; 44 (9): 2547-8
35. Philip A, Odabasi Z, Rodriguez JR, et al. *In vitro* synergy testing of anidulafungin (ANID) with itraconazole (ITR) and voriconazole (VOR) against *Aspergillus* spp. and *Fusarium* spp [abstract no. M-988]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003 Sep 14-17; Chicago
36. Ostrosky-Zeichner L, Matar M, Paetznick VL, et al. *In-vitro* synergy testing of anidulafungin (AFG) and micafungin (MFG) in combination with amphotericin B (AMB) against *Aspergillus* spp. and *Fusarium* spp [abstract no. M-1816]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 Sep 27-30; San Diego, 415
37. Karlowsky JA, Zelenitsky SA, Hoban DJ, et al. *In vitro* synergy determinations using an investigational echinocandin, LY303366, in combination with other systemic antifungal agents against *Candida* species [abstract no. F-70]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep 28-Oct 1; Toronto, 157
38. Walsh TJ, Viviani MA, Arathoon E, et al. New targets and delivery systems for antifungal therapy. Med Mycol 2000; 38 Suppl. 1: 335-47
39. Petraitiene R, Petraitis V, Groll AH, et al. Antifungal activity of LY303366, a novel echinocandin B, in experimental disseminated candidiasis in rabbits. Antimicrob Agents Chemother 1999 Sep; 43 (9): 2148-55
40. Petraitis V, Petraitiene R, Groll AH, et al. Dosage-dependent antifungal efficacy of V-echinocandin (LY303366) against experimental fluconazole-resistant oropharyngeal and esophageal candidiasis. Antimicrob Agents Chemother 2001 Feb; 45 (2): 471-9
41. Petraitis V, Petraitiene R, Groll AH, et al. Antifungal efficacy, safety, and single-dose pharmacokinetics of LY303366, a novel echinocandin B, in experimental pulmonary aspergillosis in persistently neutropenic rabbits. Antimicrob Agents Chemother 1998 Nov; 42 (11): 2898-905
42. Roberts J, Schock K, Marino S, et al. Efficacies of two new antifungal agents, the triazole ravuconazole and the echinocandin LY-303366, in an experimental model of invasive aspergillosis. Antimicrob Agents Chemother 2000 Dec; 44 (12): 3381-8
43. Verweij PE, Oakley KL, Morrissey J, et al. Efficacy of LY303366 against amphotericin B-susceptible and -resistant *Aspergillus fumigatus* in a murine model of invasive aspergillosis. Antimicrob Agents Chemother 1998 Apr; 42 (4): 873-8
44. Najvar LK, Bocanegra R, Sanche SE, et al. Efficacy of LY303366 (LY) in mice with itraconazole (ITRA)-resistant aspergillosis [abstract no. 2002]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco

45. Rajman I, Desante K, Hatcher B, et al. LY303366 single intravenous dose pharmacokinetics and safety in healthy volunteers [abstract no. F-74]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sep 28-Oct 1; Toronto, 158

46. Dowell J, Pu F, Lee J, et al. A clinical mass balance study of anidulafungin showing complete fecal elimination [abstract no. A-1576 and poster]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003 Sep 14-17; Chicago

47. Dowell J, Knebel W, Ludden T, et al. A population pharmacokinetic analysis of anidulafungin [abstract no. A-1575 and poster]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003 Sep 14-17; Chicago

48. Dowell J, Stogniew M, Krause D, et al. Anidulafungin (ANID) pharmacokinetic (PK)/pharmacodynamic (PD) correlation: treatment of esophageal candidiasis [abstract no. A-1578 and poster]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003 Sep 14-17; Chicago

49. Thye D, Kilfoil T, White RJ, et al. Anidulafungin: pharmacokinetics in subjects with mild and moderate hepatic impairment [abstract no. A-34 plus poster]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Sep 22-25; Chicago

50. Thye D, Marbury T, Kilfoil T, et al. Anidulafungin: pharmacokinetics in subjects receiving hemodialysis [abstract no. A-1390]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 Sep 27-30; San Diego, 19

51. Thye D, Marbury T, Kilfoil T, et al. Anidulafungin: pharmacokinetics in subjects with renal impairment [abstract no. A-1391]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 Sep 27-30; San Diego, 19

52. Thye D, Kilfoil T, Kilfoil G, et al. Anidulafungin: pharmacokinetics (PK) in subjects with severe hepatic impairment (HI) [abstract no. A-1392]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 Sep 27-30, 19

53. Thye D, Kilfoil T, Kilfoil G, et al. Anidulafungin: safety and pharmacokinetics in subjects receiving concomitant cyclosporine [abstract no. A-1836]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 Sep 27-30; San Diego, 29

54. Dowell J, Schranz J, Wilson J, et al. Anidulafungin (ANID) pharmacokinetics are not affected by concomitant voriconazole (VORI) [abstract no. 1034]. 14th European Congress of Clinical Microbiology and Infectious Diseases; 2004 May 1-4; Prague

55. Dowell J, Schranz J, Stogniew M, et al. Assessment of the pharmacokinetics of anidulafungin in patients with invasive aspergillosis receiving concomitant liposomal amphotericin [abstract no. 1036]. 14th European Congress of Clinical Microbiology and Infectious Diseases; 2004 May 1-4; Prague

56. Stogniew M, Dowell J, Krause D, et al. Population pharmacokinetics confirms absence of anidulafungin drug-drug interactions [abstract no. 1035]. 14th European Congress of Clinical Microbiology and Infectious Diseases; 2004 May 1-4; Prague

57. Dowell JA, Knebel W, Ludden T, et al. Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. J Clin Pharmacol 2004; 44: 590-8

58. White RJ, Thye D. Anidulafungin does not affect the metabolism of cyclosporin by human hepatic microsomes [abstract no. A-35]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Sep 22-25; Chicago, 6

59. Stogniew M, Seng JE, Hoberman A, et al. Anidulafungin, a novel antifungal agent, produces no detectable toxicity when administered to DBA/2 and BALB/c mice, with or without cortisone acetate. King of Prussia (PA): Versicor, Inc., 2004. (Data on file)

60. Clemons KV, Sobel RA, Stevens DA. Toxicity of LY303366, an echinocandin antifungal, in mice pretreated with glucocorticoids. Antimicrob Agents Chemother 2000 Feb; 44 (2): 378-81

61. Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. Clin Infect Dis 2004; 39: 770-5

62. Brown GL, White RJ, Turik M. Phase II, randomized, open label study of two intravenous dosing regimens of V-echinocandin in the treatment of esophageal candidiasis [abstract no. 1106]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto

63. Krause DS, Reinhardt J, Vazquez JA, et al. Phase 2, randomized, dose-ranging study evaluating the safety and efficacy of anidulafungin in invasive candidiasis and candidemia. Antimicrobial Agent and Chemotherapy 2004 Jun; 48 (6): 2021-4

64. Versicor Inc. Versicor announces positive phase III clinical trial results with anidulafungin for esophageal candidiasis [media release]. 2003 Mar 17

65. Laine L. The natural history of esophageal candidiasis after successful treatment in patients with AIDS. Gastroenterology 1994 Sep; 107 (3): 744-6

66. Krause D, Schranz J, Birmingham W. Lack of hepatic effect of anidulafungin [abstract no. 1789]. 14th European Congress of Clinical Microbiology and Infectious Diseases; 2004 May 1-4; Prague

67. Vicuron Pharmaceuticals Inc. Vicuron submits New Drug Application for anidulafungin to FDA [media release]. 2003 Apr 28

68. Vicuron Pharmaceuticals Inc. Vicuron Pharmaceuticals announces 90-day extension of FDA review of anidulafungin New Drug Application [media release]. 2004 Jan 22

69. Vicuron Pharmaceuticals Inc. Vicuron Pharmaceuticals files EMEA marketing application for anidulafungin [media release]. 2003

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