

Defining the place of novel antifungal agents in current clinical practice: a review of trial data and a discussion of the evidence for efficacy and effectiveness of new triazoles and candins

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Introduction

After a considerable lull and several false starts, the antifungal armamentarium will be expanded by new triazoles and candins for treating invasive fungal infectious diseases (IFID). Before considering them individually, it is worth reviewing the requirements for new drugs to gain a licence.

Prerequisites for licensure

The past decade has witnessed a change in the expectations clinicians have of an antifungal agent. From being more or less resigned to having to use amphotericin B desoxycholate to treat IFIDs, clinicians have grown used to the ease and safety afforded by fluconazole, and now expect much more of new antifungal drugs. The optimum drug should possess a broad spectrum of activity against yeasts and moulds, be fungicidal and effective in a wide range of clinical settings, should be capable of being given orally and parenterally and be well tolerated. In addition, there should be sufficient evidence that the drug is effective clinically and safe.

At the time of writing none of the drugs available meet all these requirements. Amphotericin B is poorly tolerated and can only be given parenterally and although the lipid formulations of the drug are less toxic they can still only be given intravenously (Table 9.1). Moreover there are no proper randomised controlled trials to show these drugs are more effective than the original desoxycholate formulation. There are also four distinct settings in which antifungal drugs are considered: namely, prophylaxis, empirical treatment, pre-emptive therapy and specific treatment. Apart from liposomal amphotericin B (AmBisome) which has been shown to be equally effective but safer than desoxycholate amphotericin B (Walsh *et al.* 1999) there is no conclusive evidence from large clinical trials for any other indication or formulation of amphotericin B. Fluconazole meets all the requirements of an antifungal drug except that its spectrum of activity does not include moulds. On the

practice given the nature of the patients likely to be treated. More knowledge is necessary about dosing and duration of treatment (Table 9.3) and there is still much to learn about how and when to use the drugs. The principal weakness of the candins is the lack of an oral form. To overcome this they will most likely be used the same way as amphotericin B and its lipid formulations, namely, for empirical, pre-emptive and specific therapy. Then, once a favourable response is obtained, treatment will be continued orally with the triazoles. Assuming posaconazole and ravuconazole gain approval, they will probably be used for primary prophylaxis and follow-up or maintenance therapy (also referred to as secondary prophylaxis). An alternative approach would be to make a triazole like voriconazole the core or first-line treatment simply because of equal efficacy, better toleration and the provision of flexible administration allowing the drug to be delivered by whatever route for as long as the patient is at risk. The candins, most likely caspofungin, will then be reserved for cases where the triazoles are not considered suitable. As the needs of patients continue to evolve and the population at risk of developing IFID continues to expand, the place of each of the antifungal agents may need to be redefined. Only time will tell. However, one thing is certain. None of the novel antifungal agents is likely to be cheap and so the current concerns about the economics of lipid formulations of amphotericin B will

Table 9.3 Strengths and weaknesses of the newer antifungal drugs

<i>Drug</i>	<i>Uses</i>	<i>Potential strengths</i>	<i>Potential weaknesses</i>
Voriconazole	Empirical Specific	Broad-spectrum Effective Safe Oral and parenteral forms	Drug interactions common. Optimum dose and duration unknown in special populations
Posaconazole	Prophylaxis Specific	Broad-spectrum Effective Safe	Drug interactions common. No parenteral form. Optimum dose and duration unknown in special populations
Ravuconazole	Prophylaxis Specific	Broad-spectrum Effective Safe Oral and parenteral form likely possibly fewer drug interactions than other triazoles	Optimum dose and duration unknown in special populations
Caspofungin	Treatment	Broad-spectrum Effective Safe	No oral form Optimum dose and duration unknown in special populations

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