Review

New Directions in Antifungal Therapy

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Abstract

Development of antifungal therapy continues to be lively, as we strive to approach the ideal therapy. The newest agents include lipid delivery systems for amphotericin B, which promise relief from some of that drug's side effects. The triazoles, itraconazole and fluconazole, have proven their value as non-toxic and orally effective therapy. Newer members of this class, e.g., SCH 56592 and voriconazole, appear to be promising extensions. To date the triazoles' properties enable new strategies of prophylaxis and of early intervention. Areas needing improvement include treatment for newer fungal pathogens not covered by available therapy, and the need for rapid diagnostic capabilities, comparative clinical trials, and better definitions and scoring in trials. Drugs with new and fungal-specific targets may provide a quantum leap in our weaponry. Examples included drugs targeted at chitin synthase (e.g., nikkomycin Z) or beta glucan synthase (e.g., LY303366). Another approach is immunomodulation, and several cytokines can stimulate the host synergistically with conventional antifungal therapy.

Key words: Antifungal drugs, lipid complexed amphotericin, triazoles, cell wall active drugs, immunomodulators

Antifungal therapy development for deep mycoses to date begins with iodides almost a century ago, and resumes with the polyenes, imidazoles and now the triazoles. The goal is an ideal drug which would have a broad spectrum, be fungicidal in vivo, have good tissue penetration (especially into the central nervous system), deliver high urine levels, have low toxicity, minimal drug interactions, not cause development of resistance, be available for oral and intravenous use, and be inexpensive. As you will see, we have not achieved this, but important strides have been made.

A current area of interest is lipid delivery systems for amphotericin B. The latter drug in its deoxycholate form is responsible for acute side effects such as fever, chills, nausea, vomiting, headache, myalgia and arthralgia in 48-94% of patients at conventional doses, and dose limiting nephrotoxicity (renal tubular acidosis, hypokalemia, azotemia, hyposthenuria) in 24-60%. The lipid formulations promise to reduce at least the renal complications. The current delivery systems include true liposomes and lipid complexes (ribbons, disks). Their activity in vitro versus deoxycholate amphotericin is variable. Their toxicology and pharmacology reflect the type of lipid, size of the vehicle and surface charge. In general, compared to deoxycholate amphotericin, more drug is delivered with the lipid preparations to the liver and spleen, less circulates in serum or is delivered to the kidneys (probably explaining their lessened nephrotoxicity), and delivery to the lung is variable. The lipid preparations are generally therapeutically less potent on a mg amphotericin/kg basis, but much higher doses can be given, to produce a superior outcome. It is not clear that higher drug concentrations developed in some tissues are available there for fungal inhibition, nor that in comparative studies maximally tolerated doses of deoxycholate amphotericin have been used. The lipid preparations may be effective because they deliver more drug to macrophages, and less toxic because the lipid blocks or alters affinity of amphotericin for the mammalian cell target sites which result in toxicity. Our own experience includes superior results in murine coccidioidomycosis, where complete cure was possible with deoxycholate amphotericin B only at toxic doses, whereas safe
doses of the lipid preparation were curative\(^1\). Of the current triazoles, itraconazole is of particular interest because of its anti-aspergillus activity\(^2\). There are a number of important drug interactions of which the clinical needs to be aware\(^3\). Recent work indicates an important part of this drug’s activity is related to its metabolite, hydroxyitraconazole\(^4\). Delivery of itraconazole in new routes, development of prophylactic regimens will become increasingly important. Empiric therapy based on a high index of suspicion in a high-risk patient group also becomes a viable strategy for the same reasons. Such early treatment can control occult infection and prevent dissemination, and deliver drug to tissues before infarction, necrosis, granuloma formation and fibrosis might impair drug penetration.

Other new agents heading toward clinical trials include voriconazole, another triazole, which appears to have activity vs. *Aspergillus* and fluconazole-resistant yeasts in vivo, and *Fusarium* and the agents of the endemic mycoses in vitro. It has promising activity against central nervous system infections in animals. It is metabolized and produces low urine levels (unlike fluconazole), and there is considerable intersubject variation in pharmacokinetics (like itraconazole). Transient visual abnormalities have been noted in early studies. The cell wall active agents include nikkomycin Z, a natural product that specifically inhibits chitin synthase, an enzyme not found in man, by competitive inhibition of UDP-N-acetylglucosamine. It shows particular promise vs. *Coccidioides*, *Blastomyces* and *Sporothrix*. Another approach is beta glucan synthase inhibition (another enzyme unique to fungi), of which LY303366 is a representative new drug. These drugs act as noncompetitive inhibitors, and appear to act at two protein targets. LY303366 is highly active vs. *Candida* species, particularly *C. albicans*, *Coccidioides* and *Sporothrix*. It is rapidly cidal, penetrates the central nervous system, is active orally, and has active metabolites.

Finally, another thrust for the future is to modulate the host component in the host-fungal interplay. This approach has its roots in the clinical association of cellular immunity with the natural history of fungal diseases, experimental systems where cellular immunity was impaired or reconstituted, and early experience with complex or synthetic immunomodulators, such as transfer factor and muramyl dipeptide. Most provocative is cytokine effects on antifungal activities of effector cells. Gamma interferon is the prototype of such molecules, and our laboratory has reported effects on killing of various fungal targets and on phase transformation (e.g., *P. brasiliensis* conidia to yeast) by in vivo treated murine tissue macrophages, fungal intracellular growth inhibition by treated human monocyte-derived macrophages, killing or growth inhibition of fungal targets by murine pulmonary macrophages after in vitro or in vivo treatment, and killing by murine neutrophils after in vitro or in vivo treatment\(^10\). We have shown in vivo activity alone in therapy of cryptococcosis and histoplasmosis, and potentiation of conventional antifungal therapy in these diseases and paracoccidioidomycosis\(^11\). Blockade of molecules which stimulate the T helper cell type 2 pathway, such as with antibody

**References**

1. Study Group, will be an essential part of understanding the place of new agents. There are important gaps in our antifungal armamentarium; these include *Candida* species other than *C. albicans*, and *Fusarium*, *Alternaria* and *Malassezia*. New weapons will need to be devised for that group of agents. With the development of less toxic drugs that can be administered conveniently by different routes, development of prophylactic regimens will become increasingly important. Empiric therapy based on a high index of suspicion in a high-risk patient group also becomes a viable strategy for the same reasons. Such early treatment can control occult infection and prevent dissemination, and
to interleukin 4, also reduced infection. Interleukin 12, which stimulates NK cells as well as inducing gamma interferon, was another agent with anti-fungal activity in vivo by itself, and which potentiated conventional antifungal therapy. Macrophage colony-stimulating factor (M-CSF) is another molecule which can energize effector cells for antifungal activity. Our laboratory has reported, with respect to C. neoformans, in vitro enhancement of murine tissue macrophage fungistasis and increased fungistasis and killing by murine pulmonary macrophages, and enhanced fungistasis by both kinds of cells after in vivo treatment, as well as induction of fungistasis by human macrophages derived from monocytes after 3 days, and increasing the fungistasis which naturally develops in such cells after 7 days. With H. capsulatum as the target, murine tissue macrophage fungistasis was enhanced, in vivo treatment enhanced murine pulmonary macrophage fungistasis, and fungistasis was enhanced and killing induced after in vitro treatment of human monocyte-derived macrophages.

There are several examples of synergy between antifungal therapy and cytokines besides those already cited. This includes examples of gamma interferon-induced effector cell synergy with antifungals in vitro, the same with M-CSF, the use of colony-stimulating factors in vivo to restore depleted effector cell populations, and synergy between colony-stimulating factors and antifungals in vivo where effector cell numbers are not depleted but effector cell function is either impaired by immunosuppression or is normal. The use of colony-stimulating factors to reduce fungal infection in leukemia patients has already achieved clinical reality.

References


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