Report

New developments in antifungals

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Drug names
phosphatidyl-choline, cholesterol + distearoylphosphatidylglycerol: AmBisome
amphotericin B colloidal dispersion: Amphocil
amphotericin B lipid complex: Abelcet
liposomal nystatin: Nyotran

There have been many changes in the range and efficacy of medications designed to treat fungal infections over the past 20 years. In order to understand the potential for new treatments it is important to view antifungals as a whole, whether the target infections are superficial or systemic. In the superficial mycoses, we have seen the replacement of griseofulvin as the sole oral agent with a choice of antifungals such as terbinafine, itraconazole, and fluconazole. There has also been a great change in the use of these drugs. Treatment regimens for superficial mycoses have altered with an increasing emphasis on shorter daily treatments (terbinafine), intermittent therapies given for a week (itraconazole), or weekly single doses of drugs (fluconazole). In the management of superficial mycoses by topical therapy, the main change has been the demonstration that the reduction of treatment lengths from one month to a single day, the case of terbinafine in tinea pedis,[1] is a possibility. In deep mycoses, the changes have been equally dramatic with a new focus on the selection of appropriate antifungals for different infections and clinical situations, rather than complete reliance on drugs with a broad spectrum activity. These developments have brought about a better choice of agents for a wide range of mycoses. For instance, while amphotericin B has many advantages, such as its broad spectrum of activity and the availability of an intravenous formulation critical in the care of the acutely ill patient, it still carries the stigma of a highly toxic drug with a significant risk of renal, hematologic, or immediate adverse reactions.[2] However, fluconazole now has an established position in the management of a number of different systemic mycoses, from candidemia[3] to the long-term suppressive therapy in HIV positive patients with infections such as cryptococcosis. Itraconazole has a place in the management of certain endemic mycoses such a histoplasmosis and aspergillosis as well as in the prophylaxis and suppressive treatment of systemic infections.[4] A second approach to the quest for better methods of treatment has been the development of novel drug formulations which improve either delivery, efficacy, or toxicity. An important example of this is in the pursuit of more potent topical treatments for onychomycosis such as amorolfine and bifonazole/urea combinations, and in the systemic infections, the lipid-associated amphotericin B derivatives. A third approach to improve therapy has been through the use of adjunctive treatments. Although mainly confined to therapy for deep infections, the main focus here has been on immunotherapy ranging from passive antibody therapy to the use of cytokines. A final approach to improve on existing treatments has been the use of combinations of drugs. If carefully selected, certain combinations may prove to be synergistic, where the combined effect of two drugs is greater than either individually; this approach may also have important disadvantages if the two drugs antagonize each other's mode of action.

The chief goals for the development of new approaches to antifungal therapy are improved efficacy, low toxicity or a high benefit to risk ratio, low cost, and simplicity of administration such as that achieved by short courses. The relative influence of these criteria on the assessment of the potential for any new treatment modality depends on the target infection and the behavior of alternative drugs. In systemic mycoses a moderate level of drug-related toxicity is probably

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acceptable, if the drug in question has improved efficacy, compared to existing treatments, in a potentially life threatening infection. By contrast, in superficial mycoses the use of treatment regimens, that have to be given over long periods or which are complicated, is likely to be accompanied by a low level of compliance; even low levels of drug toxicity are unlikely to be acceptable. Cost is also a factor which limits the availability of medications to the widest possible constituency. Increasing pressure by regulatory agencies or health authorities such as Health Maintenance Organizations (HMOs) in the USA and Primary Care Groups (PMGs) in the UK to limit costs of drugs will play an increasing role in the deployment and subsequent development of new medicines. This emphasis on cost–benefit is unlikely to alter in the near future, although there may be important trade-offs, for instance if the accuracy of diagnosis can be improved. For instance, the accuracy of laboratory diagnosis for onychomycosis is less than 50%[5] depending, to some extent, on local laboratory expertise and if this could be improved the pressure on limiting drug costs may lessen as unnecessary use through misdiagnosis will be reduced or eliminated. A similar low rate of success with diagnostic tests is seen in systemic mycoses such as aspergillosis[6] leading to an increasing reliance on the use of empiric therapy, treatment administered on the basis of perceived risk rather than confirmed diagnosis, in patients susceptible to life-threatening fungal infections.

Need for new treatments

In order to understand the strategies evolving for the development of new approaches to treatment it is important to realize that, unless there is a new approach to the financing of drug development, 'market demands' are key determinants of strategy. For this reason it is important to review clinical needs in both the superficial and systemic markets as the impetus for the future will depend, in part, in an understanding of both areas. Current status of drug treatments for mycoses can be summarized as follows: treatment of most superficial mycoses is now excellent using topical therapies; improvements here are likely to focus on regimens which aid compliance, for instance through reduced treatment duration. The single day treatment with terbinafine for tinea pedis is an example, although therapy of this length is still not widely accepted by physicians. However, similar short-duration topical treatments could be applied to other infections such as pityriasis versicolor or tinea corporis. With oral treatments, the current new drugs are highly effective but there is scope for improvement. For example, the treatment of tinea corporis and dry type tinea pedis with terbinafine or itraconazole produces clinical and mycologic cure rates in the range of 80–90%. Although modern treatments for onychomycosis are excellent and a major improvement on griseofulvin, the published cure rates, which range from 50 to 70%[7] could be improved, particularly as treatment is expensive. These 'cure' results are based on figures generated under clinical trial conditions and it is not clear yet whether similar responses will be seen in day-to-day clinical practice. It is likely, however, that under less stringent conditions success rates will fall by a further 10% at least. Tinea capitis is still endemic in many areas and has become a problem in urban areas of the USA and some European countries over the past few years. Treatment with griseofulvin is still the main therapy available and the duration of treatment is approximately 6 weeks. There are data to show that fluconazole, itraconazole and terbinafine are all effective in this infection[8] yet paediatric use of these agents, in this indication, is only approved in a few countries.

The subcutaneous mycoses are uncommon infections, mainly seen in the developing world, which are less likely to be selected as potential targets for drug development. The twin goals of cheap and effective treatment may seem unrealistic. Unfortunately, infections such as mycetoma, chromoblastomycosis and sporotrichosis are likely to remain treatment problems unless they respond to a new therapy designed for use in another infection.

Systemic mycoses vary enormously in frequency and behavior depending on the status of medical and surgical therapy and of underlying disease states such as HIV infection. For example, life-threatening candidosis and aspergillosis are seen in the neutropenic patient, but are a particular problem in the recipients of allogeneic bone marrow transplants where the prognosis even with existing therapy, usually amphotericin B or fluconazole, is poor. The position of mycoses in AIDS patients has changed in those countries where multiple antiretroviral therapies are available. In these areas the incidence of cases of oropharyngeal candidosis and cryptococcosis have fallen by a factor of 60–70%. The future needs in this area will depend on the long-term effect of multiple antiretroviral drug regimens and the development of other strategies for combating HIV. In countries where such drug regimens are not available, HIV-related mycoses are still an important problem and, although it is possible to control them with long-term administration of drugs such as fluconazole or itraconazole, remissions are rare. In addition, there is the added problem that yeast infections, mainly those due to *Candida* species, may be resistant to azole antifungals.[9] For these reasons in the USA and Europe the patient populations whose need is perceived to be greatest are those in the ITU or those with severe neutropenia. The mortality of treated aspergillosis in the bone marrow transplant recipient, for instance, is still greater that 70%, and probably higher in allograft recipients.[10]

New drugs

From the above it will be understood why the majority of the new drugs, currently in development have been designed

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to meet a need in the systemic mycosis market. There are exceptions, though. For instance butenafine, a benzylamine available in the USA and Japan but not Europe, is a highly effective topical treatment for a range of superficial mycoses. Studies with the drug show that short-term treatments of one week for dermatophytosis are very effective.[11] This suggests that its profile is similar to topical terbinafine but there are no data on even shorter treatment durations. Amongst systemically active agents there are few new drugs in development and the further development of some potentially promising antifungals, such as saperconazole and SCH39304, has been halted.[12,13] The most advanced, in product development terms, of the new drugs belonging to existing families is voriconazole,[14] a triazole whose pharmacokinetic properties are somewhat similar to fluconazole yet whose *in vitro* spectrum of antifungal activity is similar to that of itraconazole. It can be given by either the oral or intravenous route. *In vitro* and in experimental infections, voriconazole is effective against a range of infections including aspergillosis. It is also active against most superficial pathogens *in vitro* including dermatophytes; although this spectrum of antifungal activity covers a wide range of pathogens, it is less active against *Sporothrix schenckii*.[14] However, clinical trials have not been designed to examine its activity in superficial infections, with the exception of oropharyngeal candidosis in HIV positive patients. Other triazoles such as SCH 56592 are still in development.[15] This compound has been shown to be active against a wide range of experimental infections such as disseminated aspergillosis, cryptococcosis and blastomycosis. Another new triazole, D 0870, also has a wide range of biological activity and affects fluconazole-resistant *Candida* species amongst others; *in vitro* it is somewhat less active against *Aspergillus* species.[16] In short, although many of these new compounds show promise as antifungals, their development thus far has not been specifically designed to meet a need in the superficial mycosis market.

The latter antifungals have all been azole derivatives but there are other classes of drugs in development such as the cell wall inhibitors. Generally these fall into one of two groups, the echinocandins and papulocandins or the nikkomycins. The echino- or papulocandins act against the cell wall by inhibiting β 1–3 –glucan synthetase. At present there have been a number of candidate molecules but the only ones in current development belong to the echinocandin or pneumocandin series. The echinocandin, LY 303366, is potentially active both orally and intravenously.[17] It is highly active *in vitro* against *Candida* species and *Aspergillus fumigatus*. It is also not cross-reactive with azole-resistant yeasts. The pneumocandin, L 743872, is the most promising of these derivatives and is active against *Candida* and *Aspergillus* species, although it is not very active against *Cryptococcus neoformans*.[18] However, it is well tolerated and appears to have a low level of toxicity. The other main group of cell wall inhibitors includes the polyoxins and nikkomycins which act against chitin synthetase. One potential problem with these compounds is that they have to be taken up by cells through an active transport process (permeases) which can be antagonized. Nikkomycin Z has been evaluated both *in vitro* and in experimental infection with endemic mycoses such as histoplasmosis where it appears to be active.[19] However, at present there are no clinical studies with compounds belonging to these groups and once again no data on superficial mycoses.

One other class of antifungal agents, which act by complexing with cell surface mannoproteins, has also been investigated. The pradimicins and benanomycins are derived from actinomycetes. They have broad spectrum antifungal activity including dermatophytes. BMS 181184, for example, is fungicidal against dermatophytes as well as yeasts and *A. fumigatus*.[20] Various other potential targets for antifungal drugs, ranging from sphingolipid synthesis blockers to antifungal peptides, have been examined but as yet there are no new agents in development.

Adjunctive treatments

Other new strategies have involved looking at gene therapy or immunotherapy using vaccines or cytokines including colony stimulating factors. With the exception of the latter, there have been no great advances. The main compounds examined have been granulocyte macrophage colony stimulating factor (GMCSF),[21] granulocyte colony stimulating factor (G-CSF), interferon γ and interleukin (IL)12. Again, these are designed as adjunctive treatments for deep mycoses.

New formulations

At present the new formulations of drugs used for superficial mycoses are still in development. There are new approaches to the formulation of several of the newer agents which would improve bioavailability and their ability to treat children. Attempts to enhance the ability of topical formulations to penetrate the nail plate, which led to the production of 5% amorolfine lacquer and 28% ticonazole solution, have not improved on the treatment results seen with systemic treatments for nail disease. So once again it is in the systemic sphere that most activity has been seen. The new intravenous form of itraconazole is an example of a new development. The largest group of the reformulated antifungals comprises the lipid associated polyene compounds.

At present, four amphotericin B lipid preparations are either in use or under development in the USA or Europe. The first is a preparation of unilamellar liposomes,[22] containing phosphatidyl-choline, cholesterol and distearoylphosphatidylglycerol. Most studies with the drug have been open and,

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based on these, the drug appears to be effective in a range of systemic mycoses including aspergillosis and cryptococcosis in patients who have either failed on conventional amphotericin B (AMB) or been unable to continue through toxicity. In addition, more recent studies have used comparisons with AMB as both specific (aspergillosis) and empiric therapies. Importantly, there is also a reduction in renal toxicity as well as in immediate toxicity with patients tolerating doses of this formulation considerably in excess of those used with AMB.

The second amphotericin B lipid preparation to be developed is amphotericin B colloidal dispersion (ABCD),[23] in which the drug is bound to microdiscs. Open studies suggest similar results to Ambisome when it is used as rescue therapy; there is, however, a higher frequency of immediate type side-effects, such as chills and fever, but renal toxicity appears to be substantially reduced.

A third preparation is amphotericin B lipid complex, (ABLC), which contains amphotericin B complexed to microscopic ribbons.[24] Experience with the compound is largely based on compassionate use data using 5 mg/kg daily, where treatment responses have been seen, particularly in solid organ transplant recipients. The renal toxicity is significantly lower than with AMB, but as with ABCD there is still a significant proportion of immediate reactions of fever and chills. A further potential treatment option is the combination of conventional amphotericin B (AMB) mixed with 20% Intralipid. At present there is also little published experience with this mixture, the early data being largely derived from the use of the mixture as empiric therapy in cancer patients with fever of unknown origin (FUO)[25] or cryptococcosis. The formulation is produced by mixing the two components and as yet only little acute or chronic toxicological data are available. Liposomal nystatin has similar *in vitro* activity to nystatin against a range of fungal pathogens although its *in vitro* activity is less than amphotericin B.[26] Its value in human infection is under assessment.

Combination therapy

The use of combinations of antifungals has a well established clinical precedent, mainly with the combination of amphotericin B and flucytosine. Combinations of azoles with polyenes have been less popular largely through the fear that at certain relative concentrations the combination may prove to be antagonistic. However, with some of the newer agents there may be possibilities for combination treatment in superficial mycoses including onychomycosis. In nail disease, one potential combination is the use of oral terbinafine with topical amorolfine, which had greater activity in one study than the terbinafine on its own (R. Baran, personal communication). Combinations of azoles with either amorolfine, cyclopyroxolamine or allylamines are other possibilities which should be explored. For example, terbinafine and azoles or polyenes show increased synergistic activity against aspergilli *in vitro*.[27] The same may well be true for dermatophytes or moulds, such as *Scytalidium*, which cause nail disease. There are therefore two potentially useful strategies for the treatment of onychomycosis, oral/topical or oral/oral, which could be explored further. It remains to be seen whether other combinations such as different formulations of urea combined with a topical antifungal might be successful as well.

Conclusions

The development t of new agents for the treatment of fungal infections in recent times has focused chiefly on the systemic infections because there are serious unresolved problems in the current management of these conditions. Yet there are still needs for better approaches to the treatment of the superficial mycoses including onychomycosis. However, it is equally important that some attention is given to explaining the reasons why treatments for onychomycosis fail in some patients. The explanations are likely to be various and include poor compliance and aberrant drug absorption. In addition, local variations in drug diffusion such as at the lateral nail margins[28] may also account for some treatment failures. The accumulation of masses of fungal hyphae in spaces under the nail plate[29] may also be relatively refractory to conventional drug therapy. Drug resistance is not thought to be important, though, in determining the outcome of therapy of nail disease.[3] A closer understanding of the factors underlying treatment failure is therefore critical for determining new approaches to treatment. There are other needs, one of the most important of which is not therapeutic: the production of better ways of diagnosing these common infections. To be effective, diagnostic tests should be more accurate than present methods and applicable in different situations from tertiary to primary care settings. It is not clear whether, for example, a simple clinical diagnostic algorithm could be devised or whether the best way forward is through advanced laboratory technology.[30] At present, the diagnostic accuracy for onychomycosis is low and new methods for rapid diagnosis are critical. In some ways in superficial mycoses, as in systemic mycoses, advances in therapy have outstripped current diagnostic methods. This is a deficiency which should be addressed.

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