When the antifungal agent fluconazole reached British pharmacies in 1990, there was a pressing need for effective treatment for oral candidiasis, which was affecting a significant proportion of HIV or AIDS patients, whose prognosis had been newly improved with antiretroviral treatment. In addition, increasing numbers of cancer patients were undergoing intensive bone-marrow suppressing treatments that left them neutropenic and susceptible to life-threatening fungal and other infections.

David Denning, professor of medicine and medical mycology at the University Hospital of South Manchester, recalls that, before fluconazole and itraconazole (which slightly preceded it), the only orally useful antifungal drugs were flucytosine and ketoconazole. But flucytosine was difficult to use because of bone marrow toxicity, nausea and its effects on liver function, and ketoconazole was associated with deaths from liver failure, menstrual disturbance in women and growth retardation in teenagers.

"Fluconazole had fewer drug interactions, was well tolerated and intravenous. It could be used in the intensive therapy unit, in unconscious patients and in those who were vomiting. In its oral form, it was easy to use and quickly became the standard treatment for oral candidiasis in HIV/AIDS patients," explains Professor Denning.

The search for a superiorazole
Fluconazole was developed at the Sandwich laboratories of Pfizer as part of an antifungal programme started in 1978. A member of theazole group of compounds — so-called because of the presence of an imidazole or triazole ring in the chemical structure — its potential was identified on the basis of in vivo rather than in vitro activity. As a 2,4-difluorophenyl analogue of the bis-triazole series, it is structurally simpler than other azoles and easy to make. It was also the only compound to emerge from Pfizer’s research programme that combined good aqueous solubility, a long half-life and a reassuring side effect profile.

Like other azoles, fluconazole works by inhibiting the fungal cytochrome P450 lanosterol 14α-demethylase enzyme needed for production of ergosterol, an essential part of the fungal cell membrane. Also like other azoles, it can affect human CYP450, resulting in drug interactions, notably with the anti-rejection drugs ciclosporin and tacrolimus. Other drugs that fluconazole interacts with include glimepiride, warfarin, cyclophosphamide and other CYP450 associated anticancer drugs.

Thanks to its excellent penetration of the cerebrospinal fluid, fluconazole soon proved useful in the treatment of cryptococcal meningitis, another infection that was problematic for AIDS patients and which had proved hard to treat with other azoles. Its urinary penetration was also welcome in treating urinary candidiasis. But, in contrast to itraconazole, fluconazole lacked clinical activity against aspergillus infection.

Professor Denning explains that the benefits of fluconazole were not immediately apparent at launch because the recommended doses were suboptimal. “Given the toxicity which had occurred with ketoconazole, Pfizer was very cautious with fluconazole and launched it in doses of 50–100mg per day. Today, we use doses of 400–800mg per day, so it wasn’t surprising that the early patients with serious infections didn’t get the benefit which we would have hoped for,” he says.

Increasing reports of resistance to fluconazole and other azoles in AIDS and other patients in the early 1990s also dampened early enthusiasm for fluconazole use in systemic fungal infection.

A change of fortune
Pfizer did not take fluconazole into the fungal nail and skin infection market, but its de-
cision to promote it as a single-capsule treatment for vaginal thrush quickly propelled it ahead of competing antifungal creams and pessaries, which were messy and needed to be taken for up to a week. As toxicity concerns were laid to rest with longer-term experience of the drug, the product moved from prescription only to pharmacy status for vaginal thrush in 1995, and fluconazole joined the elite ranks of blockbuster drugs with billion dollar annual sales.

Next generation azoles
Growing recognition of invasive fungal infection as a major cause of mortality and morbidity in cancer patients undergoing stem-cell transplantation or aggressive chemotherapy led to a resurgence of interest in developing new azoles with activity against aspergillus infection.

By introducing a methyl group next to one of the triazole rings of fluconazole, Pfizer found it could increase potency against *Aspergillus fumigatus* while retaining activity against other fungal organisms. Making one of the triazole rings six-sided and adding other minor changes produced voriconazole, which proved active against a variety of aspergillus species.

Also active against aspergillus infection is posaconazole, developed by Schering-Plough, which has a similar structure to itraconazole.

European guidelines on leukaemia treatment now recommend voriconazole for first-line treatment of aspergillosis, and posaconazole or fluconazole for prophylaxis. Treatment of candidaemia is adapted to the causative species, with fluconazole still recommended for treatment of *Candida albicans*. But it has been superseded by the echinocandins (micafungin, caspofungin and anidulafungin), or liposomal amphotericin B for the non-albicans species, such as *C krusei* and *C glabrata*, which show increasing prevalence in some areas, although they remain considerably less common than *C albicans*.

Despite the increasing focus on echinocandins in fungal infection, triazole research continues, and at least two new agents, ravuconazole and isavuconazole, are in phase III clinical trials.

Golden oldie
Fluconazole continues to repel its upstart offspring in its core indications, and its linear pharmacokinetics makes it easy to use, with little variation in plasma levels between patients. In contrast, there is considerable discussion about the need for therapeutic drug monitoring for itraconazole, voriconazole and possibly posaconazole after studies have shown a failure to reach therapeutic concentrations in some patients on standard doses.

Professor Denning summarises the advantages of fluconazole as lack of toxicity, ease of use and availability of oral and IV formulations:

“Fluconazole has never been superseded for the treatment of oral or oesophageal candidiasis or for vaginal thrush and it is still used for candida prophylaxis in transplant patients. The introduction of the echinocandins, such as anidulafungin, which are slightly more effective than fluconazole in life-threatening candidaemia, has meant that fluconazole has dropped to second-line treatment for those infections. But I’d predict that, even in 20 years’ time, there’ll still be a role for fluconazole.”

References