COMMENTARY

Candida krusei infections and fluconazole therapy

LP Samaranayake

Candida species are by far the most common agents of mucosal fungal infection in man. While _Candida albicans_ is the most notorious pathogen in this group, non-_albicans_ species such as _Candida krusei_ are gradually emerging as pathogens of concern, especially in compromised hosts. It is thought that the wide use of the newer triazole drug, fluconazole, in HIV-infected individuals is contributing to this phenomenon. Studies in both humans and animals have now demonstrated prophylactic and therapeutic failure of fluconazole against _C. krusei_ due to increasing resistance of the organism to this azole. Thus, the indiscriminate use of fluconazole, a drug with relatively minimal toxicity and excellent pharmacokinetics, may lead to the development of widespread resistance to this azole among _Candida_ species.

HKMJ 1997;3:312-4

Key words: Candida krusei; Fluconazole; Drug resistance, microbial; Candidiasis; AIDS-related opportunistic infections; HIV infections

Early reports of *C. krusei* in humans describe the organism as a transient, infrequent isolate of minor clinical significance inhabiting the mucosal surfaces.[1] More recently, it has emerged as a pathogen with biological properties that differ from *C. albicans*[2] and has a spectrum of clinical manifestations such as fungaemia, endophthalmitis, arthritis, and endocarditis, most of which usually occur in compromised patient groups in a nosocomial setting.[3] The widespread use of the newer triazole, fluconazole, to suppress fungal infections in human immunodeficiency virus (HIV) -infected individuals has contributed to a significant increase in *C. krusei* infection.[3]

Fluconazole is active against a variety of pathogens that cause systemic mycoses[4] and is universally accepted as a triazole with unique pharmacokinetics with low molecular weight, good water solubility, weak protein binding, a long half-life, and a high level of cerebrospinal fluid penetration. It is well absorbed orally and has been effective in treating both superficial[5] and systemic *Candida* infections[6] and is the prophylactic drug of choice to prevent oropharyngeal[7] and systemic candidosis[8] in HIV-infected patients. Despite the initial claims of its efficacy in *Candida* infections in general, there are studies both in animals and humans that demonstrate the prophylactic and therapeutic failure of fluconazole against *C. krusei*.[9-17]

Immediately after the approval of its use in early 1990, fluconazole was used as a prophylactic antifungal in recipients of heart and bone marrow transplants.[9,18] In one study conducted by Goodman et al,[18] patients receiving bone marrow transplants were randomly assigned to receive fluconazole (400 mg daily) or placebo. By the end of the treatment period, 28 patients of 177 in the placebo group developed systemic fungal infections, two of which were due to *C. krusei*. In comparison, five of 179 patients who received fluconazole developed systemic fungal infections, of which three were due to *C. krusei*. This study demonstrated that although fluconazole prevents infection with most pathogenic *Candida* species, it does not eradicate *C. krusei*.

In another retrospective study of 463 bone marrow transplant patients and leukaemics, there was a sevenfold greater incidence of blood stream or visceral infection with *C. krusei* in 84 patients who received fluconazole prophylaxis compared with the 355 patients who were receiving other modes of prophylaxis, including amphotericin B, miconazole and ketoconazole, or no prophylaxis.[9]

There are several other reports that have documented the development of resistant strains of *Candida* after use of fluconazole as a prophylactic agent

Faculty of Dentistry, The University of Hong Kong, 34 Hospital Road, Hong Kong
LP Samaranayake, DDS, FRCPath

Correspondence to: Prof LP Samaranayake

or as primary therapy for superficial candidosis.[15-17,19,20] A study by Casanovas et al,[11] also strongly supports these reports and suggests that fluconazole is not the ideal antifungal to prevent *C. krusei* infections. They observed significant (11%) *C. krusei* septicaemia in patients with neutropenia who received fluconazole. Goodman et al,[18] also concluded that fluconazole can be effectively administered to reduce the incidence of systemic mycoses in severely immunosuppressed patients although they noted a tendency towards increased recovery of *C. krusei* during therapy and episodes of candidaemia due to the latter, in patients who received this drug. The foregoing strongly supports the view that the prophylactic use of fluconazole in compromised patients, while decreasing the frequency of *C. albicans* infections may promote the emergence of *C. krusei*.

One major reason for this phenomenon is likely to be the increased resistance of the yeast to azoles. A number of laboratory studies have reported higher minimum inhibitory concentrations (MIC) of fluconazole for *C. krusei* than for other species[21-23] (range, 0.019-100 mg/mL for *C. krusei* compared with 0.019-20 mg/mL for *C. albicans*) although discordant correlations of in vitro testing and in vivo outcome have been observed.[23] For the azole derivatives especially, the results of the in vitro susceptibility tests are profoundly affected by variables such as the methods and media used, endpoint definition, inoculum size, inoculum preparation, and the incubation conditions.[23] Another key problem in interpreting antifungal susceptibility test results is the partial inhibition of growth with azoles. The in vitro activity of fluconazole against *Candida* species appear to be the hardest to determine meaningfully, being heavily dependent on the culture medium used to show the inhibitory activity.[23] Hence, the available data need to be reviewed using a standardised assay method such as the NCCLS (National Committee for Clinical Laboratory Standards) reference method.[24]

Notwithstanding the above problems, there is an emerging consensus that *C. krusei* demonstrate a high level of resistance to fluconazole. Furthermore, the available data strongly suggest that fluconazole therapy (maintenance or intermittent), especially in low doses, as a prophylactic antifungal agent in compromised patients may result in the emergence of resistant *C. krusei* strains. Controlled clinical trials investigating the prophylactic and therapeutic use of triazoles, for either superficial or systemic candidoses, appear to be warranted prior to their widespread recommendation as a primary therapeutic agent. Finally, it should now be routine to identify *Candida* isolates to species level whenever fluconazole is instituted for the treatment of systemic mycoses.

References

1. Samaranayake LP. Introduction and historical aspects. In: Samaranayake LP, MacFarlane TW, editors. Oral candidosis. London: Wright-Butterworth, 1990:1-9.
2. Samaranayake YH, Wu PC, Samaranayake LP, Yuen KY, So M. The adhesion and colonisation of *Candida krusei* on host surfaces. J Med Microbiol 1994;41:250-9.
3. Samaranayake YH, Samaranayake LP. *Candida krusei*: biology, epidemiology, pathogenicity and clinical manifestations of an emerging pathogen. J Med Microbiol 1994;41:295-310.
4. Saag MS, Dismukes WE. Minireview. Azole antifungal agents: emphasis on new triazoles. Antimicrob Agents Chemother 1988;32:1-8.
5. Meunier F, Aoun M, Gerard M. Therapy for oropharyngeal candidiasis in the immunocompromised host: a randomized double-blind study of fluconazole vs. ketoconazole. Rev Infect Dis 1990;12 (3 Suppl):364S-368S.
6. Conti DJ, Tolkoff-Rubin NE, Baker GP Jr, et al. Successful treatment of invasive fungal infection with fluconazole in organ transplant recipients. Transplantation 1989;48:692-5.
7. Samaranayake LP. Oral mycoses in human immunodeficiency virus infection. Oral Surg Oral Med Oral Pathol 1992;73: 171-80.
8. Wheat LP. Diagnosis and management of fungal infections in AIDS. Curr Opin Infect Dis 1993;6:617-27.
9. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 1991; 325:1274-7.
10. Roder BL, Sonnenschein C, Hartzen SH. Failure of fluconazole therapy in *Candida krusei* fungaemia. Eur J Clin Microbiol Infect Dis 1991;10:173-7.
11. Casanovas R, Caillot D, Solary E, et al. Prophylactic fluconazole and *Candida krusei* infections. N Engl J Med 1992; 326:891-2.
12. Akova M, Akalin HE, Uzun O, Gur D. Emergence of *Candida krusei* infection after therapy of oropharyngeal candidiasis with fluconazole. Eur J Clin Microbiol Infect Dis 1991;10: 598-9.
13. Abrahamsen TG, Widing E, Glomstein A, Gaustad P. Disseminated fungal disease resistant to fluconazole treatment in a child with leukaemia. Scand J Infect Dis 1992;24:391-3.
14. Bignardi GE, Savage MA, Coker R, Davis SG. Fluconazole and *Candida krusei* infections. J Hosp Infect 1991;181:326-7.
15. Case CP, MacGowan AP, Brown NM, Reeves DS, Whitehead P, Felmingham D. Prophylactic oral fluconazole and *Candida* fungaemia. Lancet 1991;337:790.
16. McIlroy MA. Failure of fluconazole to suppress fungaemia in a patient with fever and neutropenia. J Infect Dis 1991;163:420-1.
17. Persons DA, Laughlin M, Tanner D, Perfect J, Gockerman JP, Hathorn JW. Fluconazole and *Candida krusei* fungaemia. N Engl J Med 1991;325:1315.
18. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 1992;

326:845-51.
19. Warnock DW, Burke J, Cope NJ, Johnson EM, von Fraunhofer NA, Williams EW. Fluconazole resistance in *Candida glabrata*. Lancet 1988;2:1310-1.
20. Stellbrink HJ, Albrecht H, Fenske S, Koperski K. *Candida krusei* sepsis in HIV infection. AIDS 1992;6:746-7.
21. Morace G, Manzara S, Dettori G. In vitro susceptibility of 119 yeast isolates to fluconazole, 5-fluorocytosine, amphotericin B and ketoconazole. Chemotherapy 1991;37:23-31.
22. Marriott MS, Richardson K. The discovery and mode of action of fluconazole. In: Fromtling RA, editor. Recent trends in the discovery, development and evaluation of antifungal agents. Barcelona: JR Prous Science Publishers, 1994:81-92.
23. Rex JH, Pfaller MA, Rinaldi MG, Polak A, Galgiani JN. Antifungal susceptibility testing. Clin Microbiol Rev 1991;6: 367-81.
24. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing for yeasts: proposed standard M27-P. National Committee for Clinical Laboratory Standards, Villanova, Pa, 1992.