Antifungals in Preventing Oropharyngeal Candidiasis among HIV-Infected Adults

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Oropharyngeal candidiasis (OPC) is attributed to the overgrowth of the commensal fungi, Candida spp., in the mouth and throat. Among HIV-infected adults, there is an increased risk of developing OPC due to the loss of cell-mediated immunity. Fluconazole can be considered as an effective agent with a better safety profile for the prevention of OPC in HIV-infected adults.

Keywords: oropharyngeal candidiasis ; oral candidiasis ; HIV ; antifungal agents ; prevention

1. Introduction

Oropharyngeal candidiasis (OPC) is attributed to the overgrowth of the commensal fungi, *Candida* spp., in the mouth and throat. *Candida* spp. is commonly found in the gastrointestinal tract of humans [1]. OPC is commonly seen in individuals with compromised immune systems, including those with diabetes, HIV infection, or those receiving chemotherapy [2][3][4][5][6].

Among HIV-infected adults, there is an increased risk of developing OPC due to the loss of cell-mediated immunity. Furthermore, HIV-infected patients are also affected by hyposalivation, reduced salivary anticandidal proteins, and other physiological changes that may alter the oral microbiota and increase the risk of OPC [7]. Moreover, multiple deficiencies in the host defense mechanism might also play a major role. The detailed pathogenesis underlying the predisposition of HIV-infected patients for OPC is unclear. The most common forms of OPC in the HIV-infected population include pseudomembranous, erythematous, and angular cheilitis, and it may develop at any point of the disease timeline [6][7][8].

OPC is projected to affect at least one-third of the HIV-infected adults [7][8][9], and 90% of HIV patients will likely experience this opportunistic infection during their period of the illness. An increase in the prevalence of OPC among HIV patients is linked to lower levels of CD4+ cells. However, in the early stages of HV infection, oral *Candida* spp. carriage is greatly enhanced, regardless of the patient's CD4+ cell count [6][7][8]. However, as the condition persists, the frequency of esophageal and pseudomembranous candidiasis has been shown to be increasingly common. It remains the most frequently encountered oral infection in HIV patients [10][11] and negatively impacts the quality of life (QoL) of this population [12]. Prophylaxis for the prevention of opportunistic infections has been suggested as an integral element for the management of HIV-infected adults and has been shown to reduce HIV-associated mortality among patients with low CD4+ counts (<50 cell/cm^3) [13]. Nevertheless, few other investigators have suggested that routine use of secondary prophylaxis for OC is only advised when patients suffer from severe or frequent recurrent infections [14][15][16]. The role of antifungal prophylaxis among immunocompromised patients has been highlighted by Meunier et al. [14]. Few studies have reported the clinical benefits of antifungals in preventing the occurrence of OPC infections among HIV patients [1][3][14][15][16]. Both itraconazole and fluconazole have been found to be effective in preventing the recurrence of OC [14][16]. However, there are currently no available direct comparisons in terms of efficacy between the two drugs. When compared to fluconazole, both nystatin and clotrimazole were found be less effective in preventing OC [14][15][16]. The use of antifungal prophylaxis has been suggested to be considered in the event where the patient suffers from severe and recurrent OPC [17]. There are many available interventions for the prevention of OPC, and choosing a drug is a great challenge in clinical practice.

2. Antifungal Agents in Prevention of Oropharyngeal Candidiasis among HIV-Infected Adults

Due to the different levels of immunodeficiency encountered by HIV patients in their course of disease, determining optimal therapeutic options for secondary infections is difficult. One of the most significant tactics for achieving the

aforementioned goal has always been prevention of secondary infections, which can deteriorate the quality of life and occasionally lead to life-threatening situations.

Even though the prevalence of OPC has dropped off after the introduction of highly active antiretroviral therapy (HAART), it remains a dilemma for clinicians and oncologists. OPC has been suggested as a valuable biomarker for HIV disease progression owing to antiretroviral therapy (HAART) failure as the prevalence of OPC directly correlates with the HIV viral load [18][19]. Within the HIV population, the use of antifungal interventions often helps in reducing clinical symptoms, thereby delivering a transient clinical response by reducing the number of fungi in the affected area [20]. However, complete eradication of the *Candida* spp. can be challenging, and as the HIV infection proceeds, the patients tend to experience more relapses and shorter disease-free intervals. Therefore, for HIV patients with frequent occurrences of OPC, secondary prophylaxis may be beneficial; however, there is concern regarding the issue of azole resistance secondary to long-term exposure to fluconazole.

Itraconazole was found to be not effective in preventing the occurrence of OPC, while fluconazole, on the other hand, was able to achieve a 55% relative risk reduction in OPC episodes when compared to placebo.

Just-Nübling et al. compared two different fluconazole doses (50 and 100 mg) with a control group who did not receive any secondary prophylaxis. The cases included were HIV-infected patients with a CD4 lymphocyte cell count less than 100 cells/mm^2 [21]. The patients who received fluconazole prophylaxis had significantly had fewer relapses of OPC compared to those who did not receive it ($p < 0.01$), and there was no difference in terms of the number of relapses between the two doses of fluconazole [21]. Thus, low-dose fluconazole, 50 mg once a day, could prevent OPC recurrence and be beneficial to HIV-infected patients who are in the advance stages. Another randomized, double-blind placebo study was conducted on 25 patients who were diagnosed with HIV by Stevens et al. to assess the benefit of 100 mg daily of fluconazole in preventing OPC recurrence [22]. Stevens et al. reported no cases of OPC relapse in the arm that received fluconazole as compared to 8 out of 13 patients in the placebo arm for the study duration of 12 weeks [22]. This supported the findings that were published by Just-Nübling et al., although the sample size was small ($n = 25$).

Leen et al. studied the benefits of fluconazole at a dose of 150 mg weekly compared to placebo, and they reported that the majority of those in the weekly fluconazole arm (5 out of 9) were free of OPC relapse for the study duration of 24 weeks, while all 5 of the patients in the placebo group had relapsed [23]. Similar studies were conducted by Marriot et al. [24] and Pagani et al. [25]. These studies compared the effectiveness of a 150 mg weekly dose of fluconazole to that of placebo with a larger sample size than the previous study. Marriot et al. conducted a randomized double-blind study on 84 HIV-infected patients and found that the risk of relapsing was reduced by 56% when compared to the placebo group, and this reduced risk of OPC relapse was significant (95% CI, 0.29–0.66) [24].

Appropriate antiretroviral therapy can prevent the occurrence of OPC [17][26]. Another reason behind the concern of whether to prescribe antifungals for prophylaxis is the emergence of azole resistance. Pagani et al. analyzed the development of resistance to fluconazole among the study participants and reported that weekly doses of fluconazole as secondary prophylaxis did not have any significant impact [25]. A similar study conducted by Revankar et al. also assessed the risk of fluconazole resistance among those who received daily doses of fluconazole along with rate of OPC relapse among HIV-infected patients [27]. They reported that 25% of patients who received fluconazole daily experienced events of OPC relapse as compared to 82% of those who did not; added to that, there was no significant difference in the resistance rates between the two groups, suggesting that daily use of fluconazole as secondary prophylaxis does not increase the risk of developing resistant strains [27].

Fluconazole, which belong to the family of azoles, mainly acts by inhibiting the cytochrome P450 enzyme lanosterol demethylase (14α-demethylase), encoded by *ERG11*, in the ergosterol biosynthesis pathway [26][28]. Ergosterol is an indispensable component of fungal membranes, and cell growth is arrested because of this inhibition of the synthesis. Several resistance mechanisms have been noted in different candidal species, mainly mutations involving *EGR11* and others, loss of heterozygosity, and changes in ploidy. Loss-of-function mutations in *ERG3* in *C. albicans* and *C. dubliniensis* have been associated with drug resistance to azoles [28]. Rosana et al. reported the combined overexpression of *CDR2* and *ERG11* as well as the presence of a mutation in the *ERG11* gene to be associated with fluconazole resistance in *C. albicans* from HIV patients [29]. Evidence with regards to azole resistance in the literature is conflicting as two studies linked the presence of azole-resistant strains of *C. albicans* among HIV patients with low CD4 cell count with prolonged prior exposure to fluconazole [30][31], while other RCTs have shown no significant differences in terms of the emergence of azole resistance when fluconazole was given continuously as prophylaxis as compared to intermittent dosing [25][27].

Fluconazole has been known to be less likely to cause hepatotoxicity and to have better tolerability when compared to itraconazole [32]. Another important aspect to be taken into consideration would be the drug interactions, which are unavoidable in HIV patients owing to the coexistence of epidemics of HIV, tuberculosis, and other opportunistic infections [33]. Most tuberculosis drugs, including rifampicin, are potent inducers of cytochrome P450 enzymes. It has been reported that the concomitant administration of rifampicin with fluconazole modifies the pharmacokinetic factors of fluconazole, including a significant increase in its elimination rate constant resulting in shorter elimination half-life [34]. Moreover, the concomitant use of rifampicin with ketoconazole and itraconazole reduced the serum concentrations of these drugs [35]. Hence, careful consideration is required in such exceptional situations. Moreover, it is important to evaluate and report the prevalence of OPCs in HIV patients regularly, especially in middle- and low-income countries, which will make the decision to use prophylaxis straightforward. A strong and compelling benefit is essential when prophylaxis is weighed against the unavoidable complications with regards to drug interactions and adverse effects [35].

3. Conclusions

Fluconazole is beneficial in the prevention of OPC in HIV-infected adults. However, the use of fluconazole as secondary prophylaxis should be weighed against the cost, possible drug–drug interactions, and drug resistance, which may arise from the routine use of fluconazole as secondary prophylaxis. Further studies should be conducted to identify the optimal parameters for the use of antifungals for the prevention of OPC. High-quality trials are needed to compare fluconazole with relevant new comparators' prevention as well as other outcomes, including adverse effects and quality of life. Future work should also focus on the cost-effectiveness of use of antifungals for the prevention of OPC.

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