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Antifungal prophylaxis in the haematological patient: a practical approach

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ABSTRACT

Antifungal prophylaxis in the haematological patient is currently regarded as the gold standard in situations with a high risk of infection, such as acute leukaemias, myelodysplastic syndromes and autologous or allogenic hematopoietic stem cell transplantation. Over the years, different scientific societies have established a series of recommendations on antifungal prophylaxis based on prospective studies performed with different drugs. However, the prescription of each one of the agents must be personalised, adapted to the characteristics of each patient and to possible interactions with concomitant medication.

Key words: fungal infections, antifungal prophylaxis, haematological patient

Profilaxis antifúngica en el paciente hematológico: una aproximación práctica

RESUMEN

La profilaxis antifúngica en el paciente hematológico es actualmente considerada un estándar de actuación en situaciones de alto riesgo de infección, como las leucemias agudas, los síndromes mielodisplásicos y el trasplante autólogo o alogénico de progenitores hematopoyéticos. Diferentes sociedades científicas han establecido a lo largo de los años una serie de recomendaciones de profilaxis antifúngica basadas en estudios prospectivos realizados con diferentes fármacos. Sin embargo, la prescripción de cada uno de los agentes ha de ser individualizada adaptándose a las características de cada paciente y a las posibles interacciones con la medicación concomitante.

Palabras clave: Infecciones fúngicas, profilaxis antifúngica, paciente hematológico

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INTRODUCTION

Invasive fungal infection is a very frequent complication in patients with hematologic malignancy with regard to prolonged neutropenia and/or immunosuppressive treatment.

Over the years, the different scientific societies have established a series of recommendations on antifungal prophylaxis based on prospective studies performed with different drugs[1-6]. Table 1 summarises these recommendations for the three situations in which fungal infection is most frequent: acute leukaemias, myelodysplastic syndromes and autologous and allogenic hematopoietic stem cell transplantation. As can be seen, each one of them includes most of the drugs currently marketed.

The objective of these recommendations is to establish an individualised prescription guideline according to each patient's characteristics.

CHOICE OF ANTIFUNGAL AGENT FOR PROPHYLAXIS

The antifungal agent of choice for the prophylaxis of invasive fungal infection is a triazole (voriconazole or posaconazole)[7-10]. Itraconazole in oral solution is not considered due its bad digestive tolerance[11]. However, there is a series of possible metabolic interferences with other drugs that render the use of triazoles unadvisable if there is concomitant treatment with:

1) Chemotherapy drugs such as vincristine[12]
2) Immunosuppression such as sirolimus or cyclosporin[13-19]
3) QT-prolonging drugs (table 2)[20,21]
4) CYP3A4 activity-inducing drugs (table 2)[22,23]

Another situation in which a triazole may not be the best alternative is the existence of liver function alterations defined by transaminases 5 times the normal value[24,25].

A triazole is the first prophylactic alternative in the absence of any of these circumstances. Posaconazole has scant bioavailability and high interindividual variability. In clinical practice, with the

Table 1 Main indications of antifungal prophylaxis in haematological patients. Antifungal agents recommended, and duration of prophylaxis according to the recommendations of the main scientific societies[1-6].

Haematological disease	Situation	Recommendation of prophylaxis	Duration
AML	Induction or consolidation chemotherapy	Posaconazole	Until the resolution of the neutropenia
MDS		Itraconazole sol.	
ALL		Fluconazole	
		IV or aerosolized liposomal amphotericin B + fluconazole	
		Voriconazole	
Autologous HSCT	Particularly in the case of mucositis	Fluconazole	Until the resolution of the neutropenia
		Micafungin	
Allogenic HSCT	Neutropenia phase	Fluconazole	Until day +75/100 days
		Micafungin	
		Voriconazole	
		Posaconazole	
		IV Itraconazole	
		IV or aerosolized liposomal amphotericin B + fluconazole	
	With GVHD	Posaconazole	Until the resolution of the GVHD or for the duration of the immunosuppression
		Voriconazole	
		Fluconazole	
		IV or aerosolized liposomal amphotericin B + fluconazole	
		Echinocandins	

ALL: acute lymphoblastic leukaemia. AML: acute myeloid leukaemia. MDS: myelodysplastic syndrome. HSCT: hematopoietic stem cell transplantation. GVHD: graft-versus-host disease

dose of 200 mg/8 h, more than half of the patients do not reach the serum concentration of 700 ng/ml, which is regarded as prophylactic[26-29]. Therefore, it is convenient to make sure that there are no additional complications that could worsen absorption, such as mucositis, diarrhoea or treatment with antacids or proton pump inhibitors. Moreover, the drug should be given with food, preferably with a high fat content, and carbonated drinks should be avoided[30-33]. If these requirements are not met, voriconazole should have priority. If there is any doubt regarding the absorption of posaconazole and its use is regarded as necessary, serum concentration should be measured on the third day. A value of >350 ng/ml predicts a serum concentration of >700 ng/ml on the 7th-10th day. If the concentration is <350 ng/ml, it is important to emphasise that the patient should eat fat-rich food and increase the dose to 200 mg/6 hours or 400 mg/12 hours[29,34].

Oral voriconazole presents better bioavailability. In a treatment study, a dose of 200 mg/12 hours yields serum levels >1.5 mg/L in 49% of patients, which increases to 87% with 300 mg[35]. Occasionally, it may also be necessary to measure the serum concentration of this antifungal agent.

If for any of the above reasons (impaired liver function or metabolic interference with other drugs), because the serum

Table 2 Drugs that significantly prolong QT or induce CYP3A4[20-23].

QT-prolonging drugs	CY3A4-inducing drugs
Citalopram	Aprepitant
Diphenhydramine	Bosentan
Escitalopram	Carbamazepine
Fluoxetine	Phenytoin
Foscarnet	Phenobarbital
Granisetron	Panobidara
Macrolides	Rifabutin
Metronidazole	Rifampin
Nortriptyline	
Ondansetron	
Pentamidine	
Sunitinib	

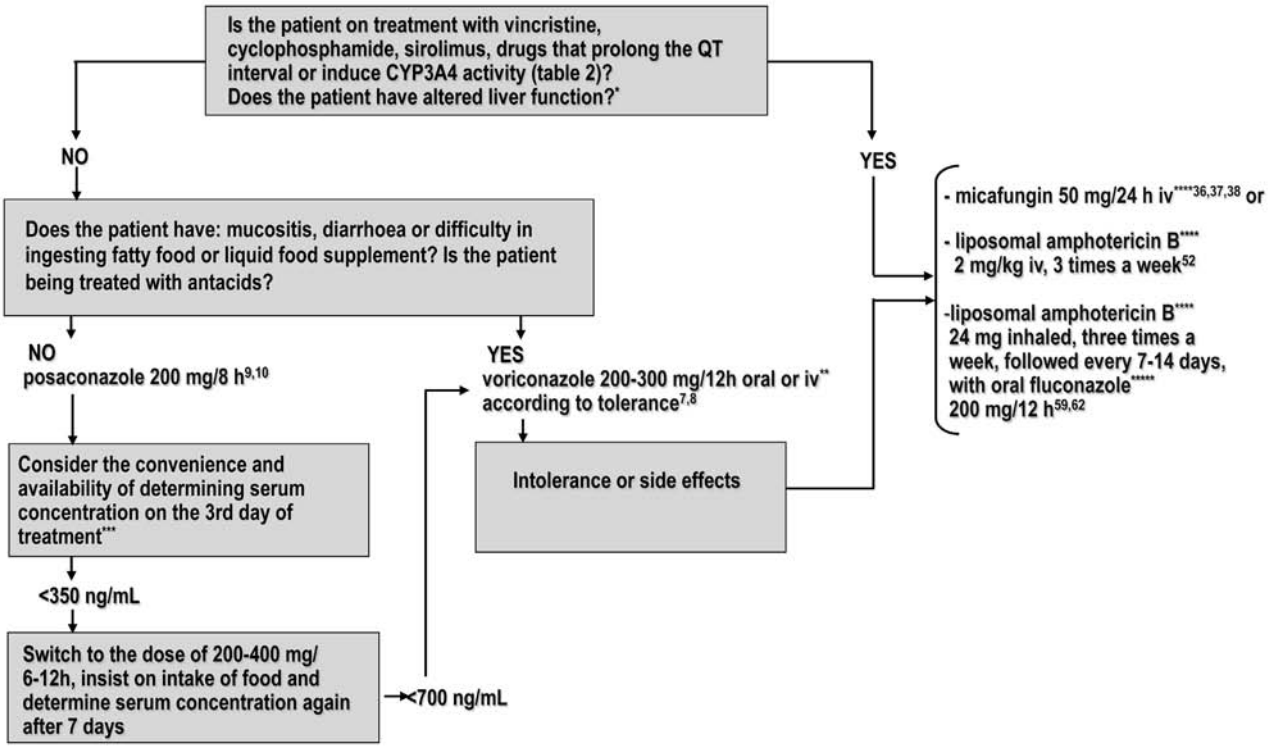

Figure 1 | **Choice of antifungal agent for phophilaxis of infection by filamentous fungi.**

*Increase in transaminases or alkaline phosphatase 3-5 times the normal value

**Itraconazole 200 mg/12 h can also be used iv

***Consider the determination of serum concentration if in doubt with regard to the intake of food together with the suspension of posaconazole

****The decision on the choice of micafungin or liposomal amphotericin B depends on the possibilities of each centre and patient characteristics

*****It has drawbacks similar to the other azoles, although to a less extent (hepatic metabolism 10%)

concentrations associated with efficacy are not reached or due to the patient's intolerance of the antifungal agent, the alternative is micafungin or liposomal amphotericin B.

Micafungin is currently the only echinocandin indicated in the prophylaxis of the haematological patient[36]. In two prospective, randomised and double-blind studies comparative studies with fluconazole and itraconazole, micafungin at a dose of 50 mg/day was significantly more efficacious than fluconazole (p=0.03) and better tolerated than itraconazole in the prevention of infection by *Candida* spp. and *Aspergillus* spp[37,38]. Some authors have used higher doses of 100-150 mg/day[39-41]. Nevertheless, two recent studies, published in abstract form, found no differences in dose-related efficacy[42,43]. Micafungin has a high concentration in the alveolar macrophage, which might explain the efficacy of the dose of 50 mg/day[44]. From the pharmacokinetic, experimental and clinical standpoint, data are available indicating the possibility of giving doses of 150 mg on alternating days, 200 mg every 72 hours and 300 mg two or three days a week[45-50].

Liposomal amphotericin B, either intravenously or inhaled, has been used in prophylaxis. Given intravenously as a daily dose (1 mg/kg/day)[51] or every other day (2 mg/kg three times a week versus placebo[52], 3 mg/kg three times a week versus oral itraconazole and fluconazole[53], 50 mg every other day versus placebo[54] and 7.5 mg/kg once a week versus other anti-fungal agents[55]), it has shown, in several prospective randomised and retrospective studies, a significant reduction in colonisation, delaying its reappearance, the incidence of invasive fungal infection and even mortality. Its tolerance is good[51-57], unlike what has been observed with amphotericin B in lipid complex, that in a study (7.5 mg/kg a week versus posaconazole) more patients doubled their serum creatinine (53%) necessitating discontinuation of the study drug[58].

Liposomal amphotericin B given by inhalation delivers very high levels in bronchial secretion and in the alveolar macrophage[59]. However, as the drug is not absorbed, systemic

activity is practically null, hence oral fluconazole has to be added for prophylaxis against *Candida* spp. Its use in prophylaxis, in different forms of application (two or three times a week) has been well tolerated[60-63] and has been shown to ha significantly superior to placebo ($p<0.005$)[62], and similar to historic controls in the prevention of fungal infections. Nevertheless, in a subgroup of acute myeloid leukaemia, the survival of patients given amphotericin B in aerosol was significantly greater ($p<0.01$), although other factors may have been involved[63].

Fluconazole has drawbacks similar to those outlined above for the other azoles, although to a lesser degree, since its hepatic metabolism (CYP3A4) is only 10%[23,64]. Concomitant use with cisapride, astemizole, pimozide and terfenadine (in the last case if the dose of fluconazole is ≥400 mg/day) is contraindicated[64]. It also increases serum levels of cyclosporine and sirolimus significantly, and this may also occur with vincristine[65,66].

Figure 1 shows a decision algorithm for the choice of antifungal prophylaxis according to the different situations commented.

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