

Novel preventative strategies against invasive aspergillosis

ELPIS MANTADAKIS* & GEORGE SAMONIS†

Departments of *Pediatric Hematology/Oncology, and †Internal Medicine, University Hospital of Heraklion, Heraklion, Crete, Greece

Invasive fungal infections, such as invasive aspergillosis (IA) represent a major threat to immunocompromised patients, especially patients with hematological malignancies or who receive hematopoietic stem cell transplantation. Hence, prevention of IA is a critical strategy that requires a clear understanding of the mould's environmental sources and how it is transmitted to immunocompromised patients. Knowledge of the exposure, mechanisms of transmission, and host susceptibility to IA are vital in selecting appropriate preventive strategies to those settings where infection is more likely to occur. Among the strategies to reduce the incidence of IA is the maintenance of high quality air, i.e. air with low spore counts in hospital areas visited by patients at risk. Housing patients in laminar airflow facilities with high-energy particulate air-filtered rooms helps prevent IA, but it is only realistic and cost-effective for the highest-risk groups and for limited time periods. Air filtration is a costly preventive strategy of questionable value when done with portable filtration units. Moreover, air control measures outside the hospital are extremely difficult to implement and this is important since the majority of cases of IA after allogeneic stem cell transplantation occurs during the post-engraftment period. For these reasons, targeted antifungal prophylaxis remains the most promising of the potential prevention strategies against IA. Many older and newer antifungal agents have been used for this purpose. Amphotericin B, being the oldest and most widely used antifungal, has been used prophylactically in various doses and schedules, but has largely been replaced by its lipid and liposomal formulations that have improved safety profile. Although prophylactic fluconazole prevents candidiasis, this drug has no activity against moulds, including *Aspergillus* spp. On the other hand itraconazole appears to prevent IA in those patients who can tolerate the drug, since its poor tolerability limits its use. The newer extended spectrum triazole posaconazole has been used in prophylactic trials with encouraging results in selected populations of patients at risk. Voriconazole, another extended spectrum triazole that has emerged as the treatment of choice for IA has been used as secondary prophylaxis in immunocompromised patients with history of IA. Echinocandins, such as caspofungin and micafungin appear to be extremely safe and effective for primary and secondary prophylaxis of IA. Patients undergoing transplantation for hematological malignancies from mismatched or unrelated donors are clearly at higher risk of IA compared to patients undergoing autologous transplantation, since among other risk factors they frequently receive moderate doses of corticosteroids for extended periods for Graft vs. Host Disease (GvHD), a well-known risk factor for IA.

Correspondence: George Samonis, Professor of Internal Medicine and Infectious Diseases, The University of Crete, Division of Medicine, PO Box 2208, 710 03 Heraklion, Crete, Greece. Tel: +30 2810 392426; Fax: +30 2810 392802; E-mail: georgsec@med.uoc.gr

Hence, results of studies in specific populations should be analyzed with caution and prophylaxis should be applied to similar patients, because antifungals are not devoid of side effects and overuse selects for resistant fungi. In conclusion, more studies are clearly needed to better define patient populations who will clearly benefit from prophylactic antifungal therapy against IA.

Keywords Invasive aspergillosis, chemoprophylaxis, hematopoietic stem cell transplantation

Introduction

Invasive fungal infections, particularly invasive aspergillosis (IA), represent a major threat to immunocompromised patients, especially those with hematological malignancies or who receive hematopoietic stem cell transplantation (HSCT) [1,2]. Other risk factors include cancer, AIDS, intensive care unit hospitalization, extreme age (premature neonates or elderly patients), and finally use of broad-spectrum antibiotics and corticosteroids [3]. Hence, prevention of IA could be a potentially beneficial strategy that however requires a clear understanding of the mould's environmental sources and how it is transmitted to immunocompromised patients [4]. Knowledge of the exposure, mechanisms of transmission, and host susceptibility to IA are vital in selecting appropriate preventative strategies to those settings where infection is most likely to occur.

Risk factors for IA

One of the best-characterized risk factors of IA is prolonged neutropenia. Neutropenic patients require careful barrier nursing and strict hygienic practices for healthcare workers and visitors. Meticulous attention should be paid to hand washing, efficient air filtration, positive room pressure and maintenance of well-sealed rooms. Patients at risk should be advised to avoid plants, raw vegetables, pepper and places contaminated by animal droppings [5].

One of the most important strategies to reduce the incidence of IA is the maintenance of high quality air, i.e. air with low conidia counts in hospital areas housing immunocompromised or visited by patients at risk. For example, 20 years ago Sherertz *et al.* [6] showed that the risk of nosocomial *Aspergillus* infection in bone marrow transplant recipients can be virtually eliminated by using high-efficiency particulate air (HEPA) filters with horizontal laminar air flow (LAF). These techniques reduced the number of *Aspergillus* organisms in the air to 0.009 cfu/m³,

which was significantly lower than in all other areas of the hospital leading to total protection against nosocomial *Aspergillus* infection in 39 BMT recipients who resided in HEPA-LAF environment vs. 14 cases in 74 BMT recipients housed elsewhere ($P < 0.001$). HEPA filters are protective in controlling outbreaks due to air contamination with *Aspergillus* conidia, as shown in a retrospective cohort study [7] in the hematology-oncology unit of a comprehensive cancer centre in 91 patients admitted for ≥ 4 consecutive days. This study showed that HEPA filters were protective in the setting of an outbreak due to high counts of *Aspergillus* conidia in the non-bone marrow transplant wing of the hospital. Unfortunately, nobody knows the lowest threshold of conidia spores allowed in the air of rooms housing immunocompromised patients, and such information is difficult or even impossible to gather. However, housing patients in LAF facilities with HEPA filters is only realistic and cost-effective for the highest-risk groups and for limited time periods. Air filtration is a costly preventive strategy of questionable value when done with portable filtration units.

A major problem is the exposure to *Aspergillus* conidia during in-hospital construction and the increased likelihood of acquiring the mould during transportation from rooms equipped with HEPA filters and horizontal LAF to hospital areas that do not have such equipment. This is a common scenario; since the recipients of HSCT are frequently sick enough to require in-hospital diagnostic or invasive procedures in potentially contaminated environments. Moreover, nowadays, the majority of cases of IA in HSCT recipients occur in the post-engraftment period [8–13], when patients are more mobile and likely to visit unprotected environments. Finally, air control measures outside the hospital, e.g. in the patient's residence are difficult to implement, although common sense measures such as using masks and avoiding places with high-humidity and dust are warranted.

Antifungal chemoprophylaxis

Targeted antifungal prophylaxis remains the most promising of the potential prevention strategies against IA. Adults with leukemia undergoing intensive chemotherapy have a 24% incidence of proven/probable invasive fungal infections (IFIs) without prophylaxis and a 40–70% mortality rate. Almost 60 clinical trials of antifungal prophylaxis with more than 7000 randomized patients have not demonstrated an overall survival benefit for prophylaxis, partially due to methodological issues related to power, design, patient selection, and end point definitions. Despite that, prophylactic use of antifungals, i.e. the primary prevention of invasive yeast/mould infections has more or less become standard practice of care in neutropenic cancer patients and HSCT recipients and endorsed by the Infectious Diseases Society of America, the Center for Disease Control and the American Society for Blood and Marrow Transplantation.

Primary prophylaxis

Many older and newer antifungals have been used for prophylaxis. Amphotericin B, being the oldest and most widely used antifungal, has been used prophylactically in various doses and schedules, but has largely been replaced by its lipid and liposomal formulations that have improved safety profile. Although prophylactic fluconazole prevents candidiasis, this drug has no activity against moulds, including *Aspergillus* spp. On the other hand itraconazole appears to prevent IA in those patients who can tolerate the drug, since its poor tolerability limits its use. A recent meta-analysis showed that itraconazole in sufficient dose is superior to fluconazole and is the drug of choice for prophylaxis of systemic fungal infections in intensively treated patients with hematological malignancies, especially those receiving allogeneic HSCT [14]. Another meta-analysis of 13 randomized, controlled studies using itraconazole antifungal prophylaxis in 3597 neutropenic patients with hematological malignancies showed that itraconazole reduced the incidence of IFIs (mean relative risk reduction, $40\% \pm 13\%$, $p = 0.002$), and the mortality from IFIs (mean, $35\% \pm 17\%$, $p = 0.04$) [15]. Interestingly, the incidence of IA was only reduced in trials using the itraconazole cyclodextrine solution (mean $48\% \pm 21\%$, $p = 0.02$) and not itraconazole capsules (mean $75\% \pm 73\%$ increase, $p = 0.3$), since the latter have erratic absorption. The overall mortality was unchanged. The effect of prophylaxis was clearly associated with a higher bioavailable dose of itraconazole, hence adequate doses of the oral itraconazole

cyclodextrine solution (at least 400 mg/d) or intravenous (IV) formulation (200 mg/d) are necessary for effective prophylaxis [15]. Mattiuzzi *et al.* [16] determined whether IV itraconazole reduced the incidence of probable/ proven fungal infections in patients with acute myelogenous leukemia (AML) and high-risk myelodysplastic syndromes (MDS) by comparing them to a historic control group treated with fluconazole plus itraconazole capsules. Patients undergoing induction chemotherapy received 200 mg of IV itraconazole every 12 h during the first two days followed by 200 mg given IV once daily. One hundred patients were enrolled, 96 of whom were evaluable. Approximately 48% of the patients in the group of IV itraconazole and in the oral fluconazole plus itraconazole control group completed prophylaxis. Nine patients (9%) in the study group developed proven/probable fungal infections compared with three patients (4%) in the historic control group. After adjusting for relevant prognostic factors, there were no significant differences between the two groups with regard to development of proven/probable fungal infections and to survival. Hence, in that study there was no evidence that IV itraconazole is superior to itraconazole capsules.

The newer extended spectrum triazole posaconazole has been used in prophylactic trials with encouraging results in highly selected populations of patients at risk. Trials using echinocandins as prophylaxis have also started to emerge. Despite the above, more studies are clearly needed to better define patient populations who will clearly benefit from prophylaxis. For example, patients undergoing transplantation for hematological malignancies from mismatched or unrelated donors are clearly at higher risk compared to patients undergoing autologous transplantation, since among other risk factors they frequently receive moderate doses of corticosteroids for extended periods for Graft vs. Host Disease (GvHD), a well-known risk factor for IA [17]. Hence, results of studies in specific populations should be analyzed with caution and prophylaxis should be applied to similar patients, because antifungals are not devoid of side effects and overuse selects for resistant fungi. In the following paragraphs we summarize recent studies on primary and to a lesser extend on secondary antifungal prophylaxis.

Penack *et al.* [18] in a prospective, randomized, open-label study compared low dose liposomal amphotericin B (50 mg every second day) to no antifungal prophylaxis in 231 patients with hematological malignancies following chemotherapy and autologous HSCT with expected neutropenia ≥ 10 d. Prophylaxis with liposomal amphotericin B started one to two days before onset of neutropenia. IFIs occurred significantly

less often in patients receiving prophylaxis (4.6% vs. 20.2%; $P=0.001$). Pneumonia of unknown origin and use of antifungals was significantly lower in patients receiving prophylaxis (5.5% vs. 25.7%, 22% vs. 59%, respectively; $P<0.001$). Death rates were comparable in both arms (3.7% for liposomal amphotericin B vs. 8.2% for no prophylaxis). Glasmacher *et al.* [19] compared a group of patients with acute leukemia receiving standard or high-dose chemotherapy without systemic antifungal prophylaxis with another group of patients who received itraconazole capsules (400 mg/d or 600 mg/d). Itraconazole led to a significant decrease in mortality from IFIs from 8.8 to 0.9% ($p=0.005$), although a considerable number of patients did not reach the desired serum trough therapeutic concentrations of the drug (500 ng/ml). Morgenstern *et al.* [20] randomized adults with hematological malignancies receiving chemotherapy or bone marrow transplants to itraconazole solution 5 mg kg⁻¹ d⁻¹ (288 episodes) or fluconazole suspension 100 mg/d (a rather low dose) (293 episodes) from before the onset of neutropenia until neutrophil recovery or suspected fungal infection. Significantly more deaths of presumed fungal origin occurred in the fluconazole arm (7 vs. 0, $p=0.024$). In an underpowered study Winston *et al.* [21] compared IV and oral itraconazole (200 mg IV every 12 h for two days followed by 200 mg IV every 24 h or a 200 mg oral solution every 12 h) to IV and oral fluconazole (400 mg IV or *per os* every 24 h) for prophylaxis of fungal infections in 140 patients undergoing allogeneic HSCT. Both drugs were administered from day one until day 100 after transplantation. Proven invasive fungal infections occurred in six of 71 itraconazole recipients (9%) and in 17 of 67 fluconazole recipients (25%) during the first 180 days after transplantation ($p=0.01$). Except for more frequent gastrointestinal side effects in patients given itraconazole, both drugs were well tolerated. The overall mortality rate was similar in each group (45% in the itraconazole vs. 42% in the fluconazole arm, $p>0.2$), but fewer deaths were related to invasive fungal infection in patients given itraconazole (9%) than in patients given fluconazole (18%) ($p=0.13$). Very recently, Glasmacher *et al.* [22] reported the results of an open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis in patients with hematological malignancies and profound neutropenia. No difference in efficacy (itraconazole 1.6% vs. fluconazole 2% for IFIs, itraconazole 0.8% vs. fluconazole 1.2% for aspergillosis) or safety was seen.

Ullmann *et al.* [23] compared in a randomized, double blind study posaconazole to fluconazole in 600 allogeneic HSCT recipients with GvHD. Posaco-

nazole was given at 200 mg tid, fluconazole at 400 mg/d. Patients receiving posaconazole had a lower incidence of IFIs during the study period (2% vs. 7%, $P=0.006$) and fewer breakthrough infections by *Aspergillus* spp. (1% vs. 6%, $P=0.001$). The overall mortality rate, safety, and tolerability were similar. A more appropriate study, however, would have compared posaconazole with itraconazole because the latter has activity against aspergillosis while fluconazole has not. Another large study on posaconazole prophylaxis compared its oral suspension 200 mg tid ($n=304$) to either fluconazole 400 mg once per day or itraconazole solution 200 mg orally bid ($n=298$) in patients with AML or high-risk MDS. A total of 116 deaths occurred during the study period (49 in the posaconazole arm). Kaplan-Meier analysis of time to death 100 days post randomization showed a significant survival benefit in favor of posaconazole ($P=0.035$). Moreover, among the 21 deaths deemed fungal-related, only five occurred in posaconazole recipients ($P=0.013$) [24].

Mattiuzzi *et al.* [25] in a small study compared caspofungin 50 mg IV vs. itraconazole 200 mg IV in patients undergoing induction chemotherapy for AML or MDS. A total of 99 patients completed antifungal prophylaxis. Among them, 12 developed documented invasive mycoses, five in the itraconazole (one *Aspergillus* pneumonia) and seven in the caspofungin arm (two *Aspergillus* pneumonia). Two patients in the itraconazole group and four in the caspofungin group died of fungal infection ($p=0.57$). In that study caspofungin and itraconazole provided similar protection against IFIs.

Van Burik *et al.* [26] compared micafungin 50 mg (1 mg/kg for patients weighing <50 kg) IV to fluconazole 400 mg (8 mg/kg for patients weighing <50 kg) IV administered once daily through the end of therapy and for four weeks after therapy in a double-blind, randomized, comparative phase-III trial of 882 children and adults. Success was defined as absence of suspected, proven, or probable IFIs using criteria consistent with the definitions of the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer, and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (USA). The overall efficacy of micafungin was 80% vs. 73.5% of fluconazole (difference, 6.5%; 95% confidence interval, 0.9–12%, $p=0.03$). The treatment difference was consistently in favor of micafungin across all major patient subgroups. Time to treatment success was significantly shorter for micafungin, fewer episodes of IA occurred among patients receiving micafungin and the need for empirical antifungal therapy was reduced.

Secondary prophylaxis

Few data exist regarding secondary prophylaxis against aspergillosis, i.e. prevention of disease recurrence or reactivation. Cornely *et al.* [27] reported results from a multinational case registry of caspofungin use as secondary antifungal prophylaxis for prevention of breakthrough fungal infections in 31 patients with proven or probable pulmonary IFIs. Prior IFIs were probable in 24 patients and proven in seven (aspergillosis in six). Most patients (87%) had AML. Administered therapy was chemotherapy only in 49%, allogeneic transplantation in 48% and autologous transplantation in 3%. The overall incidence of breakthrough IFIs was 19% and the overall mortality was 16% (five deaths, but only one attributed to IFI). Cordonnier *et al.* [28] studied the use of voriconazole as secondary prophylaxis in 11 leukemics and HSCT recipients with previous invasive *Aspergillus* ($n = 10$) and *Candida* ($n = 1$) infections. Voriconazole was administered at 400 mg/d IV or *per os* for between 44 and 245 days. Nine patients were scheduled for allogeneic HSCT, and two for consolidation therapy for acute leukemia. None of the patients had a relapse of the fungal infection, while scheduled treatment was delayed only once.

Conclusions

The cumulative experience to date suggests that long-term antifungal chemoprophylaxis is feasible and effective in patients at high risk for systemic fungal infections. However, the choice of the most appropriate drug for antifungal prophylaxis is a matter of debate and should be individualized by efficacy, safety, and drug-related issues including acquisition cost, toxicity, interactions, and local epidemiology. Since valid concerns about selection of resistant moulds among long-term recipients of antifungal prophylaxis exist [29], chemoprophylaxis should be applied only in well-defined circumstances and after all necessary measures have been taken to minimize environmental exposure to moulds.

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