Meeting the challenge of invasive fungal infections: part 2

Johan Maertens*¹ & Sue Lyon²

¹Department of Haematology, Universitaire Ziekenhuizen Campus Gasthuisberg, KU Leuven, Leuven, Belgium

²A Writer's Touch Medical Communications, 3 Bray Crescent, Rotherhithe, London SE16 6AN, UK

*Author for correspondence: johan.maertens@uzleuven.be

The 23rd European Congress of Clinical Microbiology and Infectious Diseases 2013

Berlin, Germany, 27–30 April 2013

This second and final installment of the report on the 23rd European Congress of Clinical Microbiology and Infectious Diseases follows on from Part 1, published in the September 2013 (volume 8, issue 9) issue of *Future Microbiology*. Invasive fungal infections (IFIs) are a well-recognized complication in immunocompromised patients, with neutropenic patients with leukemia and hematopoietic stem cell transplant recipients at especially high risk. Early diagnosis of IFIs is essential, since delaying the initiation of adequate antifungal therapy increases the risk of death. The rapid diagnosis, and effective treatment and prophylaxis of IFIs were among the topics discussed during the 2013 conference of the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2013).

Conference Scene Future Microbiology

Diagnosis & treatment of invasive fungal infections

When speaking at a satellite symposium held during ECCMID 2013, Claus-Peter Heussel (Ruprecht-Karls-University, Heidelberg, Germany) emphasized the importance of same-day imaging in patients with suspected pulmonary mould infections. Although a chest x-ray is cheap and straightforward to use as an imaging modality, it lacks sufficient sensitivity to visualize early infiltrates of pulmonary aspergillosis in an immunocompromised patient. Heussel recommended using high-resolution or thin-section (1 mm) computed tomography (CT), since it is able to identify pulmonary infiltration patterns typical of invasive fungal infection (IFI) at an early stage.

On CT scan, the halo sign – a macronodule surrounded by ground-glass opacity – is an early sign of invasive pulmonary aspergillosis, and is one of the clinical criteria for probable and possible invasive fungal disease included in the revised EORTC/MSG consensus definitions [1]. However, according to Heussel, the halo sign by itself has insufficient diagnostic specificity in high-risk patients, since it can also be found when imaging patients with other infectious and noninfectious diseases.

Sequential CT can also be used to systematically monitor response to antifungal therapy; however, Heussel warned delegates against assuming lack of response if lesions continue to grow after initiation of treatment. He explained that it is usual for lesions to continue to grow on CT in treated patients with invasive fungal disease,

and that it may take some time before significant lesion regression is visible on imaging.

Heussel concluded that the rapid diagnosis of IFIs depends on multidisciplinary teamwork between hematologists and radiologists. This is especially important in high-risk neutropenic hemato-oncology patients, and should involve discussion of each case to ensure the exchange of detailed clinical information on the treatment history and underlying disease of each patient.

IFIs are also a cause for concern in non-neutropenic patients, commented Matteo Bassetti (San Martino Hospital and University of Genoa, Italy). Furthermore, although the risk of candidemia and its associated high mortality are well recognized in non-neutropenic patients in the intensive care unit, the infection in fact occurs more frequently in patients in the internal medicine department and its incidence is increasing [2,3]. The explanation may be that, compared with intensive care unit patients, internal medicine patients are older, have higher Acute Physiology and Chronic Health Evaluation (APACHE) scores, have longer lengths of hospital stay, are more likely to be treated with antibiotics, have a solid tumor or central venous catheter, or undergo abdominal surgery [3].

Bassetti *et al.* recommended against waiting for blood culture results, because delay in initiating antifungal therapy increases the risk of death in non-neutropenic patients with suspected candidemia [3]. Fluconazole remains the most frequently prescribed pre-emptive antifungal treatment in non-neutropenic patients [4]; however, the epidemiology of *Candida* infection is changing,

Keywords

■ antifungal prophylaxis
■ antifungal therapy ■ early diagnosis ■ invasive fungal infections

Future
Medicine part of

Non-*Candida albicans* species, especially *Candida glabrata*, are now responsible for more cases of candidemia than *C. albicans* [5]. There is also evidence of increasing resistance to fluconazole, particularly in *C. glabrata* isolates [6]. Since echinocandins are associated with lower mortality, guidelines now strongly recommend that targeted initial treatment in non-neutropenic adult patients with candidemia should be with an echinocandin rather than fluconazole [7].

Antifungal prophylaxis

Speaking during the satellite symposium, Rafael de la Cámara (Hospital de la Princesa, Madrid, Spain) noted that the challenges of ensuring timely diagnosis and treatment of IFIs mean that antifungal prophylaxis has become a priority for hematologists. Guidelines now recommend antifungal prophylaxis for high-risk hemato-oncology patients, defined as leukemia patients undergoing induction chemotherapy and allogeneic hematopoietic stem cell transplant (HSCT) recipients, both during the initial neutropenic phase and in graft versus host disease [8].

In recent years, posaconazole has replaced fluconazole as the agent of choice for antifungal prophylaxis in neutropenic patients with acute myeloid leukaemia or myelodysplastic syndrome and in allogeneic HSCT patients with graft versus host disease. de la Cámara accepted that posaconazole may have higher acquisition costs, but reported that the drug has in fact been shown to be cost effective, and possibly cost saving, compared with fluconazole or itraconazole when used as antifungal prophylaxis for high-risk neutropenic patients [9].

Randomized clinical trials have demonstrated posaconazole's efficacy in prophylaxis when compared with other commonly used antifungal agents [10,11]. However, the lack of placebo-controlled studies may be a barrier to the drug's adoption in countries where antifungal prophylaxis is not yet standard practice in patients with hematological malignancies. A study presented during ECCMID 2013 aimed to address this evidence gap through an indirect treatment comparison of randomized, controlled trials of posaconazole, fluconazole and itraconazole [12].

The meta-analysis included ten studies involving a total of 2826 patients, 83% of whom received cytotoxic chemotherapy. A Bayesian random effects model found that, compared with no prophylaxis, using posaconazole for antifungal prophylaxis reduced the number of episodes of proven/probable IFI by 76% in neutropenic chemotherapy recipients. According

to the researchers, this study offers a potential framework to compare clinical efficacy of drugs used for antifungal prophylaxis where head-to-head data are not available, and provides information for use in health technology assessment and formulary decision-making [12].

Posaconazole is currently available as an oral suspension that is taken three-times daily when used as an antifungal prophylaxis. Each dose should be taken during or immediately after a meal (or a nutritional supplement in patients who cannot tolerate food) to enhance oral absorption and to ensure adequate exposure. Careful adherence is therefore critical to ensure adequate exposure to posaconazole, as highlighted by French researchers during ECCMID 2013.

The study included 70 adult patients, 95% of whom were receiving posaconazole as antifungal prophylaxis. In these patients, significant risk factors for low posaconazole plasma concentration (defined as trough level <0.5 mg/l) were nausea or vomiting ($p = 0.001$), diarrhea ($p = 0.002$) and poor adherence including fasting posaconazole intake ($p = 0.002$), low dosage intake ($p = 0.006$) and the number of missed doses being >10% ($p = 0.003$). Only fasting posaconazole intake and the number of missed doses being >10% predicted undetectable plasma concentrations [13].

In the French patients, directly observed therapy provided by a nurse in the stem-cell transplant department predicted adequate posaconazole plasma concentrations. The researchers suggest that directly observed therapy may therefore be helpful when using posaconazole in antifungal prophylaxis, [13]; however, this approach is unlikely to be practical for all patients, especially those who continue to receive antifungal prophylaxis as outpatients. An alternative, and more feasible, strategy may be for hemato-oncology departments to provide personalized education to each patient given antifungal prophylaxis.

During ECCMID 2013, a single-center Austrian study reported that structured, brief (5–10 min) personal advice about intake of posaconazole (e.g., information about intake with food and the importance of maintaining plasma concentrations) improved posaconazole plasma concentrations in patients with previously sub-optimal levels. No patient experienced adverse effects attributed to posaconazole, and there were no cases of breakthrough IFI. This was, however, a small study, and the researchers recommend that larger trials should be undertaken to confirm their findings [14].

A late-breaking study presented at ECCMID 2013 suggests that in the future it may be more straightforward to achieve adequate plasma concentrations of posaconazole. This pivotal study was designed to investigate the pharmacokinetics and safety of a 300 mg posaconazole tablet, which combines the active drug with a pH-dependent polymer with the aim of eliminating the need for multiple daily dosing with food [15].

Following a twice-daily loading dose given on the first day of therapy, the once-daily tablet (taken with or without food for 28 days) achieved steady-state predicted average posaconazole concentration (lower and upper exposure target limits of ≥ 500 and < 3750 ng/ml) in 99% of 210 patients with acute myeloid leukaemia, myelodysplastic syndrome or HSCT. Overall, the once-daily tablet had a safety profile similar

to that previously reported for the oral suspension, the most commonly reported treatment-related adverse effects being nausea (reported by 11% patients) and diarrhea (8% patients) [15]. Marketing authorization applications for the new tablet have been submitted to regulatory authorities in Europe and the USA.

Financial & competing interests disclosure

S Lyon's attendance at ECCMID and her contribution to the writing of the report were supported by MSD. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial involvement in the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- De Pauw BD, Walsh TJ, Donnelly P *et al.* Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin. Infect. Dis.* 46(12), 1813–1821 (2008).
- Bassetti M, Taramasso L, Nicco E *et al.* Epidemiology, species distribution, antifungal susceptibility and outcome of nosocomial candidemia in a tertiary care hospital in Italy. *PLoS ONE* 6(9), e24198 (2011).
- Bassetti M, Molinari MP, Mussap M *et al.* Candidaemia in internal medicine departments: the burden of a rising problem. *Clin. Microbiol. Infect.* 19(6), e281–e284 (2013).
- Bassetti M, de Gaudio R, Mazzei T *et al.* A survey on infection management practices in Italian ICUs. *Critical Care* 16, R221 (2012).
- Horn DL, Neofytos D, Anaissie EJ *et al.* Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin. Infect. Dis.* 48, 1695–1703 (2009).
- Arendrup MC, Dzajic E, Jensen JH *et al.* Epidemiological changes with potential implication for antifungal prescription recommendations for fungaemia: data from a nationwide fungaemia surveillance programme. *Clin. Microbiol. Infect.* 19(8), e343–e353 (2013).
- Cornely OA, Bassetti M, Calandra T *et al.* ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin. Microbiol. Infect.* 18(Suppl. 7), 19–37 (2012).
- Maertens J, Marchetti O, Herbrecht R *et al.* European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3–2009 update. *Bone Marrow Transplant.* 46(5), 709–718 (2011).
- Grau S, de la Cámara R, Sabater FJ *et al.* Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among high-risk neutropenic patients in Spain. *BMC Infect. Dis.* 12, 83 (2012).
- Cornely OA, Maertens J, Winston DJ *et al.* Posaconazole versus fluconazole or itraconazole prophylaxis in patients with neutropenia. *N. Engl. J. Med.* 356, 348–359 (2007).
- Ullman AJ, Lipton JH, Versole DH *et al.* Posaconazole or fluconazole in severe graft versus host disease. *N. Engl. J. Med.* 356, 355–347 (2007).
- Chuang L, Treur M, Yang X *et al.* Efficacy of posaconazole against placebo as antifungal prophylaxis for neutropenic chemotherapy recipients: an indirect treatment comparison. Presented at: *European Congress of Clinical Microbiology and Infectious Diseases 2013*. Berlin, Germany, 27–30 April 2013 (Poster P1012).
- Cambier C, Lafaurie M, Ribaud P *et al.* Poor adherence: main risk factor for posaconazole low plasma concentration. Presented at: *European Congress of Clinical Microbiology and Infectious Diseases 2013*. Berlin, Germany, 27–30 April 2013 (Poster P1017).
- Duettmann W, Wagner J, Huber-Krassnitzer B *et al.* Impact of structured personal on-site patient education on low posaconazole plasma concentrations: a cohort study. Presented at: *European Congress of Clinical Microbiology and Infectious Diseases 2013*. Berlin, Germany, 27–30 April 2013 (Poster P1015).
- Cornely OA, Duarte RF, Haider S *et al.* Phase 3 pharmacokinetics (PK) and safety study of posaconazole (POS) tablet in patients at risk for invasive fungal infection. Presented at: *European Congress of Clinical Microbiology and Infectious Diseases 2013*. Berlin, Germany, 27–30 April 2013.