Journal of Infection (2012) 64, 424—429

BIAM British Infection Association

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Breakthrough invasive mould infections in patients treated with caspofungin

Katy-Anna Phai Pang [a], Cendrine Godet [b], Arnaud Fekkar [c], Julie Scholler [a], Yasmine Nivoix [a], Valérie Letscher-Bru [d], Laurent Massias [e], Catherine Kauffmann-Lacroix [f], Antoine Elsendoorn [b], Madalina Uzunov [g], Annick Datry [c,h], Raoul Herbrecht [a,*,i]

[a] *Pôle d'Oncologie et d'Hématologie, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, 1 Avenue Molière, 67098 Strasbourg, France*
[b] *Service des Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de Poitiers, 86000 Poitiers, France*
[c] *Service de Parasitologie Mycologie, Hôpital Pitié-Salpêtrière (AP-HP), 75651 Paris Cedex 13, France*
[d] *Institut de Parasitologie et de Pathologie Tropicale, Faculté de Médecine, 67085 Strasbourg, France*
[e] *Laboratoire de Toxicologie-Pharmacocinétique, Hôpital Bichat-Claude-Bernard, Assistance publique — Hôpitaux de Paris, 75018 Paris, France*
[f] *Service de Parasitologie Mycologie Médicale, Centre Hospitalier Universitaire de Poitiers, 86000 Poitiers, France*
[g] *Service d'Hématologie clinique, Hôpital Pitié-Salpêtrière (AP-HP), 75651 Paris Cedex 13, France*

Accepted 22 December 2011
Available online 29 December 2011

KEYWORDS
Caspofungin;
Invasive pulmonary aspergillosis;
Mucormycosis;
Fusarium;
Haematopoietic stem cell transplantation;
Acute leukaemia

Summary *Objectives:* To describe and estimate the rate of breakthrough invasive mould diseases (IMD) in patients receiving caspofungin.
Methods: Retrospective, non-interventional study conducted in three University Hospitals.
Results: Nineteen breakthrough infections have been identified including 13 aspergillosis, 2 mucormycosis, a fusariosis, a *Hormographiella aspergillata* infection and 2 possible IMD. Cases were equally distributed between the centres. Fourteen patients had a haematologic malignancy, four were transplant recipients (allogeneic haematopoietic stem cells in three, liver in one) and one had hepatic cirrhosis. Caspofungin has been prescribed as prophylaxis ($n = 3$), empirical therapy ($n = 9$) or directed therapy for candidemia ($n = 5$) or aspergillosis ($n = 2$). *Aspergillus* galactomannan was positive in serum or in bronchoalveolar lavage fluid in 10 of the 13 aspergillosis. Median duration of caspofungin treatment before breakthrough IMD was 15 days. Nine patients died within twelve weeks. Rate of breakthrough IMD in onco-haematology patients has been estimated to 7.3% for all mould infections and to 4.2% when restricted to documented aspergillosis.

* Corresponding author. Tel.: +33 388 12 76 88; fax: +33 388 12 76 81.
E-mail address: raoul.herbrecht@chru-strasbourg.fr (R. Herbrecht).
[h] Annick Datry has been consultant or member of speaker's bureau for Astellas, Gilead, Merck, Pfizer, Schering-Plough.
[i] Raoul Herbrecht has been consultant or member of speaker's bureau for Astellas, Basilea, Gilead, Merck, Pfizer, Schering-Plough.

doi:10.1016/j.jinf.2011.12.015

Conclusions: Our data call for *Aspergillus* galactomannan monitoring and close clinical and radiological examination in case of persistence or recurrence of infection signs in high-risk patients receiving caspofungin.

Introduction

Caspofungin, the first available echinocandin, has antifungal activity against yeasts (with the exception of *Cryptococcus* spp. and *Trichosporon* spp.), as well as against some filamentous fungi, including *Aspergillus* spp.[1] Caspofungin has been approved for the treatment of invasive Candida infections, second line therapy of invasive aspergillosis and empiric therapy of persistent fever in neutropenic patients. However, breakthrough invasive mould diseases (IMD) such as aspergillosis have been reported in patients receiving caspofungin.[2–6] We reviewed 19 cases of breakthrough IMD in patients treated with caspofungin observed in three French hospitals. Rate of these breakthrough infections has been estimated in an oncology and haematology department.

Patients and methods

A retrospective, observational, non-interventional, multicentre study was conducted in three French university hospitals (Strasbourg, Poitiers and Pitié-Salpêtrière, Paris) from March 2002 to September 2009. Patients were included for analysis if they have been treated with caspofungin and had developed a breakthrough invasive filamentous fungal infection.

According to Madureira et al., infections had to occur at least 6 days following the start of caspofungin or within 6 days after the discontinuation of caspofungin therapy.[5] Patient characteristics, risk factors for fungal infection, dose and duration of caspofungin therapy, type of breakthrough infection, modification in therapy and outcome including survival were recorded.

Rate of breakthrough IMD in an oncology and haematology department (University Hospital of Strasbourg) has been estimated based on data from all consecutive caspofungin treatments given in this department during the same period of time.

Aspergillus galactomannan detection test were performed in serum and in bronchoalveolar lavage (BAL) fluid in each institution using the Platelia Aspergillus test (Biorad, Marnes-la-Coquette, France). Samples have been collected as a routine surveillance twice a week in high-risk patients or when a fungal infection was suspected. Cut-off of 0.5 has been accepted for both serum and BAL fluid samples. Moulds were identified in each centre based on macroscopic and microscopic aspects on culture or on molecular biology results when conventional tests were not conclusive.

Caspofungin serum levels have been monitored in two patients using high-performance liquid chromatography with a quantification limit of 0.5 μg/mL. Measurements have been performed by the Laboratoire de Toxicologie-Pharmacocinétique, Hôpital Bichat, Paris.

Episodes were categorized as possible, probable or proven IMD according to the updated European Organisation for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) international consensus criteria.[7] Response to treatment (complete, partial, stable or progression) was assessed according to Segal et al.[8] Six and twelve-week survival was estimated using the Kaplan–Meier method. Cause of death was attributed according the definition of Nivoix et al.[9]

Results

Nineteen patients (7 in Strasbourg and Poitiers and 5 in Paris), developed a breakthrough IMD: aspergillosis in 13, mucormycosis in two, fusariosis in one, *Hormographiella aspergillata* infection in one and possible IMD in 2 (Table 1). Underlying conditions were acute leukaemia ($n = 10$), chronic leukaemia ($n = 4$), allogeneic haematopoietic stem cell transplantation ($n = 3$), liver transplantation ($n = 1$) and liver cirrhosis ($n = 1$). Additional risk factors for fungal infection or significant comorbidities included broad spectrum antibiotic therapy ($n = 18$), neutrophil count $<500/\mu L$ ($n = 16$), steroids or T-cell suppressor administration ($n = 7$), diabetes ($n = 4$) and mechanical ventilation ($n = 1$). At onset of breakthrough IMD, 9 patients were still neutropenic.

Median duration of caspofungin treatment before breakthrough IMD was 15 days (range 7–58 days). Reason for caspofungin therapy included empiric therapy in nine patients, candidemia in five, prophylaxis in three and invasive aspergillosis in two. The latter two patients developed a non-*Aspergillus* mould breakthrough infection. All patients received appropriate loading and maintenance dose of caspofungin, in accordance with the labelling.

Breakthrough IMD treatment was voriconazole monotherapy in nine patients, a lipid formulation of amphotericin B in three, and a combination therapy in 4. Three patients died before any switch to another antifungal therapy could be performed.

Complete response was observed in nine (47%) of the breakthrough IMD including five invasive aspergillosis, two possible IMD, one mucormycosis and the *H. aspergillata* infection. All other breakthrough infections progressed (Table 1). Six and twelve-week survival rates were 63% and 42% respectively. Nine patients died from their IMD and two died from their underlying condition following complete remission from the breakthrough IMD.

Rate of breakthrough IMD in the oncology and haematology department in Strasbourg has been estimated at 7.3% (7 episodes in 96 patients receiving caspofungin therapy), while the rate of documented breakthrough aspergillosis has been estimated at 4.2% (4 episodes). In all cases, caspofungin was administered as either empirical or directed therapy of fungal infection, as no prophylaxis with caspofungin is used in this department.