Diagnostic Microbiology and Infectious Disease 88 (2017) 141–144

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Clinical Studies

No evidence of increased ocular involvement in candidemic patients initially treated with echinocandins

P. Muñoz [a,b,c,d,*], A. Vena [a,b,*], B. Padilla [a], M. Valerio [a], M.I. Sanchez [e], M. Puig-Asensio [f], J. Fortún [g], M. Fernández-Ruiz [h], P. Merino [i], J.E. Losa [j], A. Loza [k], R.A. Rivas [l], E. Bouza [a,b,c,d], for the CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPI [1]

[a] Clinical Microbiology and Infectious Disease Division, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[b] Instituto de Investigación Sanitaria Hospital Gregorio Marañón, Madrid, Spain
[c] CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058), Madrid, Spain
[d] Medicine Department, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain
[e] Hospital Majadahonda, Madrid, Spain
[f] Hospital Universitario Vall D' Hebron, Barcelona, Spain
[g] Hospital Ramón y Cajal, Madrid, Spain
[h] Hospital Universitario 12 de Octubre, Madrid, Spain
[i] Hospital Clínico, Madrid, Spain
[j] Hospital de Alcorcón, Madrid, Spain
[k] Hospital Universitario Virgen de Valme, Sevilla, Spain
[l] Hospital de Galdakano, Bilbao, Spain

ARTICLE INFO

Article history:
Received 23 November 2016
Received in revised form 7 February 2017
Accepted 21 February 2017
Available online 27 February 2017

Keyword:
Candida endophthalmitis
Echinocandins
Initial antifungal therapy

ABSTRACT

Candins are commonly used as initial therapy in patients with candidemia and are known to diffuse poorly into ocular tissue. The aim of our multicenter study was to assess whether eye involvement was more common in patients initially treated with echinocandins. We performed a post hoc analysis of a prospective, multicenter, population-based candidemic surveillance program implemented in Spain during 2010–2011 (CANDIPOP project).
Eye involvement was detected in 13 of 168 patients with candidemia (7.7%) who underwent ophthalmoscopy. Two patients had endophthalmitis, while the remaining patients had chorioretinitis. The frequency of ocular candidiasis was similar in patients receiving initial therapy with candins (3/56; 5.4%) or with other regimens (10/112; 8.9%). At multivariate analysis, risk conditions for eye involvement were dialysis after candidemia (OR, 19.4; 95% CI, 1.7–218.4) and involvement of organs other than the eye (OR, 5.4; 95% CI, 1.1–25.7). In conclusion, eye involvement was not found to be more frequent in patients receiving initial therapy with echinocandins than in patients receiving other drugs.

1. Introduction

Candida endophthalmitis is a significant complication in patients with candidemia because of its potentially devastating consequences (Riddell et al., 2011).

Fluconazole has good intraocular penetration but a limited spectrum of anti-*Candida* activity. In contrast, echinocandins diffuse poorly into the vitreous humor and are not recommended in patients with ocular involvement (Pappas et al., 2016). Data on the rate and outcome of ocular candidiasis in patients initially treated with echinocandins are very scarce and conflicting (Gauthier et al., 2005; Mochizuki et al., 2011; Sarria et al., 2005).

We used the database of a large multicenter study of candidemia carried out in Spain to assess the impact of using echinocandins as initial antifungal therapy on the presence of ocular lesions.

2. Materials and methods

2.1. Study setting

The findings reported here derive from a post hoc subanalysis of the CANDIPOP study, a prospective, multicenter, population-based program for the surveillance of candidemia implemented from May 2010 to April 2011 in 29 hospitals of Spain. The inclusion criteria, study population, main definitions, microbiological studies, and outcomes have been extensively described elsewhere (Puig-Asensio et al., 2014).

* Corresponding authors. Tel.: +34-91-58-68-453; fax: +34-91-50-44-906.
E-mail addresses: pmunoz@micro.hggm.es (P. Muñoz), anton.vena@gmail.com (A. Vena).

[1] GEIH-GEMICOMED, Grupo de Estudio de Infección Hospitalaria-Grupo de Estudio de Micología Médica; REIPI, Red Española de Investigación en Patología Infecciosa; SEIMC, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica.

http://dx.doi.org/10.1016/j.diagmicrobio.2017.02.014
0732-8893/

During the study period, patients were managed according to routine clinical care, and no specific recommendations were provided regarding treatment and microbiological follow-up. According to guidelines, systematic dilated fundoscopy was recommended at baseline for all patients included in the study, but only positive results suggesting *Candida* ocular involvement were recorded in the general database.

For the purpose of this study, we asked the 29 participating hospitals to recheck if an ophthalmoscopy had been performed in the each adult (age > 16 years) patients included in the CANDIPOP study (585 patients), and 11 hospitals complied with our request. Overall, among the 365 patients attended at these 11 hospitals, 168 had an ophthalmoscopy performed and are the objective of the present study (rate of ophthalmological assessment (46%).

A visual field examination and visual acuity tests were performed when requested by the attending physician. Patients were followed during the whole hospital admission.

2.2. Definition and study collection

A standardized case report form was used to record ocular involvement as proven, probable, or possible *Candida* chorioretinitis or endophthalmitis, as previously described by Oude Lashof et al. (2011). Initial antifungal therapy was defined as the first systemic antifungal drug administered after positive blood cultures drawn from a peripheral vein and yielding *Candida* spp. Two categories of initial antifungal therapy were established: echinocandin-based and non–echinocandin-based, which included amphotericin B and azoles. An episode of candidemia was defined as persistent when patients had positive follow-up blood cultures performed according to IDSA guidelines (Pappas et al., 2016). The outcome of ocular candidiasis was considered successful when follow-up fundoscopy revealed disappearance of the retinal lesion or of active inflammation within the eye.

2.3. Statistical analysis

Fisher exact test was used to compare categorical variables; continuous variables were compared using the Mann–Whitney or a two-tailed t test. Risk factors for *Candida* eye involvement were detected using backward stepwise logistic regression. Associations are given as odds ratio (OR) with the 95% confidence interval (95% CI). Statistical significance was established at $p < 0.05$.

3. Results

Overall, 168 patients with candidemia who had an ocular examination performed were included in the study. Patients were classified according to the antifungal therapy received as echinocandin-based (56 patients, 33.3%) and non–echinocandin-based (112 patients, 66.6%).

3.1. Frequency of ocular candidiasis according to initial antifungal therapy

Thirteen of the 168 patients (7.7%) had fundoscopic abnormalities suggestive of *Candida* eye involvement that were categorized as *Candida* endophthalmitis in 2 patients and probable or possible chorioretinitis in 8 and 3 cases, respectively.

As shown in Table 1, the diagnosis of ocular candidiasis was similar in non-echinocandin and echinocandin groups (10 of 112 [8.9%] vs. 3 of 56 [5.4%], $P = 0.54$). Patients who received initial echinocandin-based therapy were more likely to have a higher median Pitt score, had been more commonly exposed to previous antifungal agents and to immunosuppressive therapy, including corticosteroids.

3.2. Risk conditions predisposing to Candida eye involvement

The median time to performance of first ophthalmological examination was 5 days (IQR 3–6 days) after blood cultures withdrawal, with no differences between patients with and without eye involvement ($P = 0.45$). The initial antifungal class administered did not predict eye involvement neither in univariate nor in multivariate analysis. In the multivariate analysis, the only independent risk conditions for eye involvement were: hemodialysis after candidemia (OR, 19.4; 95% CI, 1.7–218.4) and involvement of other organs different from the eye (OR, 5.4; 95% CI, 1.1–25.7).

3.3. Clinical outcome according to antifungal therapy

Overall, information on the evolution of ocular candidiasis was available in 7/13 patients (53.8%), since 5 patients died and fundoscopy follow-up data were not available for 1 patient. All but one patient had a favorable clinical outcome. However, the 3 patients who received initial echinocandin therapy had their treatment switched to fluconazole after ophthalmological assessment with complete resolution of the disease in all evaluable patients. Accordingly no patient with ocular candidiasis was definitively treated with an echinocandin only.

4. Discussion

The issue of whether initial treatment of candidemia with echinocandins is associated with a higher rate of ocular complications is controversial. To our knowledge, the present study is the first to suggest that initial therapy with echinocandins does not increase the frequency of ocular involvement in patients with candidemia. This finding could be related to the greater fungicidal activity of echinocandins that would shorten the duration of candidemia and thus the risk of metastatic lesions.

The use of echinocandins in clinical practice has greatly increased during recent years, mainly due to the higher success rate compared to azoles (Reboli et al., 2007), a broader spectrum of activity (including fluconazole-resistant *Candida*), potent fungicidal activity (Pfaller et al., 2005), and its excellent safety profile (Dowell et al., 2007; Hebert et al., 2005).

Thus it is not uncommon for clinicians to start with an echinocandin and then streamline therapy according to the microbiological results or the clinical manifestation of the infection. Several studies have demonstrated an excellent distribution of echinocandins in most body tissues, but not into ocular fluids (Gauthier et al., 2005; Mochizuki et al., 2011; Sarria et al., 2005). Our results indicate that there are no differences in the diagnosis of ocular candidiasis between patients whose initial therapy was with echinocandins (5.4%) and those who received other antifungals (8.9%). Based on these results, the potential impact of initial therapy on the development of ocular candidiasis should not condition the choice of antifungal agent.

Besides, ocular candidiasis evolved favorably in all except one of our evaluable patients. This result is interesting especially given that historically, endogenous *Candida* endophthalmitis has been reported to be a potentially devastating consequence of candidemia (Binder et al., 2003). This favorable outcome is consistent with the observations of Oude Lashof (Oude Lashof et al., 2011), who reported an unfavorable outcome in only 3% of all evaluable cases.

Our study is subject to a series of limitations. First, in this real life experience, only 46% of the cohort candidemic patients had a fundoscopic examination and could be thus included in this analysis. Accordingly, we cannot exclude that the real rate of ocular involvement could be different. Second, the number of patients with ocular involvement is relatively low. However, our report is the largest experience specifically focusing on initial echinocandin therapy in candidemic patients. It includes a large population who was prospectively followed by an infectious disease specialist. Finally, we acknowledge that early ophthalmoscopies may reflect pre-treatment events and we cannot exclude that some of the patients developed late ocular lesions after discharge.

In conclusion, our study suggests that initial treatment with echinocandin therapy does not imply a higher risk of *Candida* eye involvement in candidemic patients.