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Efficacy and safety of anidulafungin in elderly, critically ill patients with invasive *Candida* infections: a post hoc analysis☆

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ABSTRACT

Post hoc analysis of a non-comparative, prospective, multicentre, phase IIIb study was performed to compare efficacy and safety of anidulafungin in elderly (≥65 years) versus non-elderly (<65 years) Intensive Care Unit (ICU) patients with candidaemia/invasive candidiasis (C/IC). Adult ICU patients with confirmed C/IC meeting ≥1 of the following criteria were enrolled: post-abdominal surgery; solid tumour; renal/hepatic insufficiency; solid organ transplantation; neutropenia; age ≥65 years. Patients received anidulafungin (200 mg on Day 1, 100 mg/day thereafter) for ≥10 days followed by optional azole step-down therapy for a total treatment duration of 14–56 days. The primary efficacy endpoint was global (clinical and microbiological) response at the end of all therapy (EOT). Primary efficacy analysis was performed in the modified intent-to-treat (mITT) population ($n = 170$), excluding unknown and missing responses. In total, 80 patients (47.1%) were aged ≥65 years and 90 (52.9%) were aged <65 years; the mean age difference between the two groups was 21.9 years. Global success at EOT in mITT patients was similar in elderly (68.1%) and non-elderly (70.7%) patients ($P = 0.719$). However, global success rates were significantly lower in elderly versus non-elderly patients at 2 and 6 weeks after EOT ($P = 0.045$ and $P = 0.016$, respectively). Ninety-day survival was significantly lower ($P = 0.006$) for elderly (42.8%) versus non-elderly patients (63.3%). The incidence and profile of adverse events were similar in elderly and non-elderly patients. Anidulafungin was effective and safe for treatment of C/IC in elderly ICU patients, despite higher baseline severity of illness scores.

1. Introduction

Candidaemia and other forms of invasive candidiasis remain a significant clinical problem in Intensive Care Unit (ICU) patients and are associated with considerable morbidity and mortality [1,2]. A recent report from the international Extended Prevalence of Infection in the ICU (EPIC) II study showed that patients with candidaemia had higher crude ICU mortality rates and longer ICU stays than patients with bacterial bloodstream infections [1].

Prompt initiation of antifungal therapy is essential for the effective management of candidaemia/invasive candidiasis (C/IC). Treatment guidelines recommend that initial antifungal therapy should be selected on the basis of the infecting organism and local susceptibility patterns [3]. Whilst fluconazole is generally effective for C/IC, its use may be limited by the increasing prevalence of *Candida* spp. with acquired or intrinsic resistance to fluconazole [4]. Depending on which guidelines are referred to, echinocandins are

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now recommended as first-line treatment for C/IC in all patients [5] or, more specifically, in haemodynamically unstable patients (moderately severe to severely ill), those with prior azole exposure and for invasive infections caused by *Candida krusei* or *Candida glabrata* [3] owing to their excellent activity against invasive *Candida* spp., including azole-resistant strains [6].

Due to more frequent and prolonged treatment in hospital, especially in the ICU, elderly patients are at a greater risk for opportunistic *Candida* infections [7,8]. Over the past two decades, the number of elderly patients admitted to ICUs has increased [9]. A recent, relevant longitudinal study reported that among middle-aged and older adults, patients aged ≥65 years accounted for almost 60% of ICU admissions [10]. In addition, elderly ICU patients are more likely than younger patients to have co-morbid conditions [11,12], particularly renal dysfunction [13], which is associated with increased mortality in the ICU [14]. Co-morbidities, together with age-associated physiological changes and immunosenescence, make the elderly vulnerable to infection [15].

Although the number of elderly patients admitted to ICUs is increasing [9], our understanding of their treatment needs remains limited. To our knowledge, no studies have specifically evaluated the efficacy of an antifungal agent in elderly ICU patients compared with patients <65 years old. A recent phase IIIb trial showed that anidulafungin was both safe and effective for the treatment of C/IC in selected populations of ICU patients [16]. Given the paucity of data in the elderly, a post hoc analysis of this trial was conducted to evaluate the efficacy and safety of anidulafungin in elderly (aged ≥65 years) versus non-elderly (aged <65 years) ICU patients with C/IC. The two age groups were also compared with respect to baseline demographics, clinical characteristics and infecting pathogens in order to better characterise elderly patients with C/IC.

2. Materials and methods

2.1. Trial design

This was a prospective, phase IIIb, exploratory, open-label, non-comparative, multinational trial. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by all appropriate institutional review boards and ethics committees. All patients were required to provide written informed consent prior to study inclusion. The trial was registered on ClinicalTrials.gov (identifier NCT00689338).

2.2. Patient population

Adult ICU patients were eligible if they met the following criteria: confirmed C/IC within 96 h before to 48 h after initiation of study treatment; signs and symptoms of acute fungal infection within 48 h prior to initiating study treatment; and an Acute Physiology and Chronic Health Evaluation (APACHE) II score of <25. Patients were also required to belong to at least one of the following subpopulations: post-abdominal surgery; solid tumour; renal insufficiency; hepatic insufficiency; solid organ transplantation; neutropenia; and/or aged ≥65 years. Patients who had received antifungals for ≤48 h prior to study entry (with up to one echinocandin dose) were eligible, but only if no improvement had been recorded. As part of the pre-specified study design, the presence of renal/hepatic insufficiency was determined by the investigator according to local guidelines; there were no pre-specified protocol definitions.

The key study exclusion criteria were: suspected *Candida* osteomyelitis, endocarditis, meningitis and/or endophthalmitis; poor venous access; or known hypersensitivity or contraindications to anidulafungin, fluconazole or voriconazole. The *Candida* score was calculated according to previously published methods [17], both at study entry or at the time when the first blood sample was withdrawn for blood culture and at the end of all therapy (EOT). In short, the *Candida* score was obtained by assessing specific risk factors and assigning a total point value according to the following scoring system: clinical sepsis (2 points); surgery (i.e. recent surgery requiring post-operative management; 1 point); total parenteral nutrition (1 point); and multifocal colonisation (1 point).

2.3. Treatment

Patients received intravenous (i.v.) anidulafungin (200 mg on Day 1, 100 mg/day thereafter) for 10–42 days. After completing a minimum of 10 days of treatment, patients could be switched to oral voriconazole or fluconazole provided they had two consecutive negative blood cultures and resolution of signs and symptoms of acute invasive fungal infection (IFI). The azole dosage was chosen by the investigator according to local practice. Treatment (with anidulafungin or step-down azole) was continued for ≥14 days after the last positive blood/tissue culture and resolution/significant improvement of IFI signs and symptoms. The total maximum treatment duration was 56 days. All patients, including those who failed therapy, were required to return for follow-up visits at 2 weeks and 6 weeks after EOT.

2.4. Endpoints

The primary efficacy endpoint was global response at EOT in the modified intent-to-treat (mITT) population. Global success was defined as clinical (i.e. cure or significant improvement of C/IC signs and symptoms) and microbiological success (i.e. eradication or presumed eradication of *Candida* spp.). The mITT population was defined as all patients with a confirmed diagnosis of C/IC who had received at least one dose of anidulafungin. Global response was reported as 'unknown' or 'missing' in patients with an unknown or missing clinical response, respectively, and any microbiological response except failure. Clinical response was defined as 'unknown' in non-evaluable patients [i.e. death (not caused by C/IC), loss to follow-up or received less than three anidulafungin doses]. Unless otherwise stated, unknown and missing responses were excluded from the analysis of global response.

Secondary endpoints included: global response at the end of i.v. therapy (EOIVT) and at 2 weeks and 6 weeks post EOT; survival at Day 90; and the incidence of adverse events (AEs) in the safety population (i.e. patients who received at least one dose of anidulafungin).

Antifungal susceptibility testing for baseline isolates was conducted according to standard Clinical and Laboratory Standards Institute (CLSI) methods and breakpoints [18] (i.e. anidulafungin non-susceptibility, >2 μg/mL; fluconazole resistance, ≥64 μg/mL; and voriconazole resistance, ≥4 μg/mL).

2.5. Data analysis

For this post hoc analysis, patients were divided into elderly (aged ≥65 years) and non-elderly (aged <65 years) cohorts. An exact two-sided 95% confidence interval (CI) was calculated for the success rate at each time point in each age group. A two-sided *Z*-test was used to determine whether the proportion of successes differed significantly between age groups. The same test was used to compare both the incidence of deep-tissue *Candida* infection at baseline and the incidence of renal insufficiency/failure/dialysis at baseline between groups. Age group comparisons of continuous variables were mostly performed using the two-sample *t*-test. The Wilcoxon rank-sum test was used to compare the use of