Title

A Retrospective Cohort Study of the Risk of Severe Hepatotoxicity in Hospitalized Patients Treated with Echinocandins

Mei Sheng Duh, MPH, ScD, Analysis Group, Inc, and Harvard T.H. Chan School of Public Health, Boston, Massachusetts

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Keywords

Echinocandin; Anidulafungin; Caspofungin; Micafungin; Severe hepatotoxicity.

Rationale and Background

Anidulafungin, caspofungin, and micafungin are echinocandins used for treating invasive candidiasis. Among these, anidulafungin is the only echinocandin that is not metabolized by the liver and does not require dose adjustment in patients with severe hepatic impairment.

Research Question and Objectives

1. To estimate the unadjusted and adjusted risk of severe hepatotoxicity in patients treated with anidulafungin, caspofungin, and micafungin

2. To evaluate clinical and demographic features associated with the type of echinocandin received

3. To estimate the unadjusted and adjusted risk ratios of severe hepatotoxicity in patients treated with anidulafungin versus those in patients treated with caspofungin or micafungin

Study Design

A retrospective observational cohort study.

Setting

Hospitalized patients treated with anidulafungin, caspofungin or micafungin identified in hospital-based electronic medical records (EMR) data in the United States (US).

Subject and Study Size, Including Dropouts

Patients ≥18 years of age receiving ≥1 intravenous infusion of echinocandins during the hospitalization were included in the study (N = 12,678). The date of the treatment initiation was defined as the index date. The baseline period included the time between the hospital admission date and the index date, inclusive, and the observation period included the time from the index date until the earliest event of severe hepatotoxicity, hospital discharge or death. Patients were required to have liver function test (LFT, ie, aspartate transaminase [AST], alanine aminotransferase [ALT], total bilirubin) values both in the baseline and observation periods. LFTs were graded per modified Clinical Islet Transplantation study - Terminology Criteria for Adverse Events in trials of adult pancreatic islet transplantation (CIT-TCAE). Severe hepatotoxicity was defined as the first occurrence of a Grade ≥3 LFT in the observation period.

Variables and Data Sources

Data were obtained from two US-based hospital EMR databases, Humedica and Cerner Health Facts, pooled into a single dataset. Exposure to echinocandins among hospitalized patients was identified using Healthcare Common Procedure Coding System and National Drug Codes in the EMR data.

For Objective 1, the unadjusted absolute risk (ie, cumulative incidence) of severe hepatotoxicity was calculated as the number of patients with severe hepatotoxicity divided by the total number of patients exposed to each type of echinocandin. The unadjusted incidence rate for each echinocandin group was calculated as the number of patients with severe hepatotoxicity divided by the total person-days of observation in that group, and reported per 30 person-days. Adjusted absolute risk and incidence rate of severe hepatotoxicity in each echinocandin group were computed using regression-based indirect standardization methodology. For Objective 2, factors associated with the type of echinocandin that patients received were identified from multivariate logistic regression models. For Objective 3, relative risks (RRs) and incidence rate ratios (IRRs), used to measure the association between the echinocandin and severe hepatotoxicity, were estimated for anidulafungin versus caspofungin and anidulafungin versus micafungin using log binomial (for RRs) and negative binomial (for IRRs) regressions, adjusting for demographic, baseline LFT (except for the subgroup analysis on patients with normal LFT at baseline), other labs, and clinical covariates.

Several sensitivity and subgroup analyses were conducted for Objective 3: (1) inclusion of patients without baseline LFT values, (2) patients with normal, or mildly or moderately elevated LFT at baseline (ie, Grade 0-2, and Grade 0), (3) Cerner sub-sample, and by baseline LFT grades and treatment duration, (4) Humedica sub-sample, and by baseline LFT grades and integrated delivery network, (5) severe hepatotoxicity outcome defined based on the first occurrence of an event of Grades ≥4, and (6) severe hepatotoxicity outcome defined based on the occurrence of an event of Grade 5.

Results

A total of 12,678 eligible patients were identified (anidulafungin: 1700; caspofungin: 4431; micafungin: 6547), among whom 9161 patients had normal to moderately elevated LFT at baseline (anidulafungin: 1012; caspofungin: 3281; micafungin: 4868). At baseline, compared to patients receiving caspofungin and micafungin, anidulafungin patients had statistically significantly more elevated LFT (proportion LFT Grade ≥3, 40.4% vs 25.9% and 25.6%), critical care admissions (75.3% vs 52.6% and 48.6%), surgeries (41.1% vs 33.7% and 27.1%), use of central venous catheters (43.8% vs 13.3% and 19.3%) and immunosuppressive drugs (14.6% vs 4.4% and 5.9%), and higher rates of comorbidities (eg, organ failures: 69.4% vs 46.7% and 51.5%; sepsis or septic shock: 68.5% vs 46.9% and 47.9%; cardiovascular disease (CVD): 71.1% vs 42.1% and 49.8%; kidney disease: 40.2% vs 17.5% and 21.2%). All comparisons yielded p-values less than 0.05.

In Objective 1 analyses, the unadjusted absolute risk of severe hepatotoxicity was 37.2% (95% CI: 34.3-40.1), 22.4% (95% CI: 21.0-23.8), and 23.3% (95% CI: 22.1-24.4) in the anidulafungin, caspofungin and micafungin groups, respectively. After adjustment, the absolute risk of severe hepatotoxicity decreased to 25.7% (95% CI: 24.7-26.7) in the anidulafungin group, and increased to 24.3% (95% CI: 23.4-25.2) and 24.8% (95% CI: 23.9-25.6) in the caspofungin and micafungin groups, respectively. A similar trend was observed in incidence rates after adjustment. The adjusted incidence rate of severe hepatotoxicity was 0.47 (95% CI: 0.44-0.51) in the anidulafungin group, 0.41 (95% CI: 0.38-0.44) in the caspofungin group, and 0.45 [95% CI: 0.43-0.48] in the micafungin group.

In Objective 2 analyses, baseline clinical features found to be significantly associated with an increased probability of receiving anidulafungin vs caspofungin or micafungin, included higher grade of baseline bilirubin, use of extended-spectrum azoles, having ≥2 fungal infection sites, having critical care admission, using immunosuppressive therapy, using antiretroviral drugs known to have hepatotoxic effects, using central venous catheter, and the presence of comorbid CVD, hypertension, kidney disease, endocarditis, sepsis or septic shock. Clinical features associated with decreased probability of receiving anidulafungin vs caspofungin or micafungin included emergency admission to the index hospitalization, use of antibiotics known to have hepatotoxic events and the presence of comorbid gastro-oesophageal reflux disease.

Table 1 below summarizes the main results from Objective 3 analyses. The adjusted RRs and IRRs are presented for both the main study sample and the subgroup of patients with baseline LFT Grade ≤2. The LFT Grade ≤2 subgroup was chosen for the summary of results because this group excluded patients who had severe hepatotoxicity pre-treatment, allowing the assessment of newly developed severe hepatotoxicity during treatment. The results showed no statistically significant differences in severe hepatotoxicity between anidulafungin and caspofungin/micafungin in the majority of the analyses. The only statistically significant effect was observed in the IRR model for the anidulafungin versus caspofungin comparison in the main study sample (IRR 1.43, 95% CI 1.14-1.79). All subgroup analyses on patients with baseline LFT Grade ≤2 were not statistically

significant. In particular, the IRR for the anidulafungin versus caspofungin was no longer statistically significant (IRR 1.46, 95% CI 0.91-2.37).

Table 1. Adjusted Relative Risks and Incidence Rate Ratios of Severe Hepatotoxicity Between Anidulafungin and Caspofungin or Micafungin

	Anidulafungin vs Caspofungin	Anidulafungin vs Micafungin
Main Study Sample		
Adjusted RR (95% CI)	1.07 (0.95-1.20)	1.03 (0.93-1.15)
Adjusted IRR (95% CI)	1.43 (1.14-1.79)*	1.19 (0.92-1.54)
Baseline LFT Grades 0-2 Subgroup		
Adjusted RR (95% CI)	1.11 (0.88-1.41)	1.08 (0.87-1.34)
Adjusted IRR (95% CI)	1.46 (0.91-2.37)	1.62 (0.95-2.77)

* $p < 0.05$.
CI = confidence interval; IRR = incidence rate ratio; LFT = liver function test; RR = relative risk.

Similarly, the majority of sensitivity analyses for Objective 3 yielded adjusted RRs and IRRs estimates that were not statistically different from 1 (ie, no difference in risk between anidulafungin and the comparison echinocandin). The exception included the adjusted RRs and IRRs for the anidulafungin versus caspofungin comparison in the Humedica subsample, and the adjusted RR for the anidulafungin versus micafungin comparison in the sensitivity analysis for Grade 5 hepatotoxicity events, which suggested higher risk of severe hepatotoxicity in anidulafungin patients. Among patients with Grade 5 events, those in the anidulafungin group had significantly worse prognosis for death at baseline than those in the caspofungin and micafungin groups: 86.0% were admitted to critical care (vs 59.6% [$p < 0.001$], 58.0% [$p < 0.001$]), 61.3% had surgeries (vs 34.0% [$p < 0.001$], 35.4% [$p < 0.001$]), 90.7% had organ failures (vs 66.7% [$p < 0.001$], 71.7% [$p < 0.001$]) and 92.0% had sepsis or septic shock (vs 64.5% [$p < 0.001$], 70.4% [$p < 0.001$]).

Discussion

Based on real-world hospital practice data, the majority of the current study analyses showed that adjusted RRs and IRRs estimates were not statistically different from 1, suggesting that anidulafungin was not associated with a statistically significantly higher absolute risk or incidence rate for severe hepatotoxicity, as compared to caspofungin and micafungin. In the IRR comparison to caspofungin, however, there was a statistically significantly higher incidence rate in anidulafungin in the main study sample, although the statistical significance was not present in the subgroup of baseline LFT Grades 0-2.

It is important to note that the baseline data demonstrated the channelling of anidulafungin treatment towards patients with impaired liver function and higher mortality prognosis based on comorbidity profiles; this is especially notable among patients with Grade 5 hepatotoxicity events. This confounding by indication bias is well-known in epidemiology literature and adjustment is methodologically challenging. Attempts to control for differences in the severity profile of patients in the current study were limited to the information available in the databases. Thus, residual confounding due to unobserved factors is possible. In subgroup analyses on patients with normal or mildly/moderately elevated LFT at baseline (Grades 0-2), which used restriction as a method to homogenize the baseline LFT risk across the treatment groups, no evidence was found to indicate significant differences in the risk of severe hepatotoxicity between patients treated with anidulafungin and patients treated with caspofungin or micafungin.

Marketing Authorization Holder (s)

Pfizer Ltd

Names and Affiliations of Principal Investigators

Name, degree(s)	Title	Affiliation
Mei Sheng Duh, MPH, ScD	Managing Principal and Chief Epidemiologist Visiting Scholar	Analysis Group, Inc Harvard T.H. Chan School of Public Health
Lisa Weiss, PhD, MPH	Director, Epidemiology	Pfizer Inc
Francis Vekeman, MA	Vice President	Groupe d'analyse, Ltée
Wendy Cheng, MPH, MPhil	Manager	Analysis Group, Inc
Raluca Ionescu-Ittu, PhD	Economist	Groupe d'analyse, Ltée
Yongling Xiao, PhD	Economist	Groupe d'analyse, Ltée
Rachel Bhak, MS	Analyst	Analysis Group, Inc