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BRIEF REPORT

Game Changer or More of the Same? A Comparative Meta-analysis of Rezafungin and Caspofungin in Treating Candidemia and Invasive Candidiasis

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Abstract

This meta-analysis assesses the recent Food and Drug Administration (FDA)-approved antifungal, rezafungin, for treating candidemia and invasive candidiasis— both are significant health concerns with limited treatment options. Two randomized controlled trials comparing rezafungin to caspofungin were meta-analyzed, revealing no significant differences in global cure rates and 30-day all-cause mortality. While rezafungin's unique attributes, like a novel mechanism and once-weekly dosing, may enhance patient adherence, concerns arise about its clinical relevance given the substantial investment. The study emphasizes the need for ongoing research, post-marketing surveillance, and real-world data to determine rezafungin's true value in managing these life-threatening fungal infections. Despite FDA approval, further investigation is warranted for a comprehensive understanding of rezafungin's efficacy and safety.

Keywords: Rezafungin, Candidemia, Invasive candidiasis, Meta-analysis, Antifungal therapy

1. Background

Invasive fungal infections, particularly candidemia and invasive candidiasis, are critical issues affecting global health and community well-being, leading to substantial morbidity and mortality in affected patients. These conditions can lead to severe complications such as retinitis,[1] which can impair vision; endocarditis, which involves the infection of the heart's inner lining and is notably associated with high mortality rates; and hepatic and splenic abscesses, where abscesses form in the liver or spleen due to the systemic spread of the fungus.[2] Additionally, Candida species are capable of infecting surgical hardware, such as artificial joints, complicating post-operative recovery and potentially leading to further invasive procedures. The mortality rates associated with these infections range from 10% to 47% depending on the patient's overall health and the presence of underlying conditions.[3] Specifically, Candida endocarditis has an even higher mortality rate, reported at 59%, emphasizing the lethal potential of these infections.[4] However, survival rates significantly improve with timely and appropriate treatment.

The U.S. FDA approved the antifungal rezafungin for the treatment of candidemia and invasive candidiasis on 22nd March, 2023; this is the first therapy to be approved for the condition in over ten years.[5] The FDA approval of rezafungin has generated excitement due to its front-loaded dosing regimen (i.e., a higher dose of the drug is administered initially, followed by lower or standard doses in subsequent treatments) which may offer early treatment advantages for candidemia and invasive candidiasis. The debate centers on

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concerns about the development of resistance to existing echinocandins like caspofungin, which has documented resistance issues in *Candida albicans* due to mutations in conserved regions. Additionally, there are discussions around the potential of rezafungin to address these resistance challenges given its new pharmacological profile. While rezafungin is seen as an important advancement in the treatment of severe fungal infections, questions about its cost and distribution also play a critical role in its integration into clinical practice. Table 1 provides a direct comparison of the two drugs, highlighting the longer half-life and less frequent dosing requirements of Rezafungin compared to Caspofungin, alongside their similar mechanisms of action but different pharmacokinetic profiles.[6]

The primary aim of this meta-analysis is to evaluate the comparative efficacy of rezafungin versus caspofungin in the treatment of candidemia and invasive candidiasis, examining global cure outcomes and all-cause mortality.

2. Methods

To conduct our literature search, we systematically reviewed PubMed/MEDLINE, Scopus, and Web of Science databases up until June 5, 2024. An additional search of two engines − Google Scholar and ClinicalTrials.Gov. Two investigators (Z.S. and F.J.) reviewed electronic records, using a combination of the following keywords: rezafungin, candidiasis, and/or candidemia. The Boolean logic was applied (and/or). We only included randomized controlled trials (RCTs). The findings from these RCTs were tabulated and discussed the findings to synthesize the current understanding of rezafungin's effectiveness in treating candidiasis and/or candidemia. A meta-analysis was conducted for outcomes of global cure at 14 days and 30-day all-cause mortality were meta-analyzed for risk difference (RD) applying 95% confidence intervals (CI). The software used for this study was Review Manager (RevMan, v.5.4, Cochrane).

3. Results

The results of the meta-analysis, including the characteristics and outcomes of the included RCTs, are summarized in Table 2.[7,8] Each study evaluated the efficacy and safety of rezafungin compared to existing treatments, focusing on key endpoints such as global and overall cure rates and all-cause mortality.

Two RCTs were meta-analyzed.[7,8] The global cure meta-analytical findings for rezafungin versus caspofungin showed a risk difference of −0.01 [95% CI: −0.10, 0.08], with a test for overall effect: $Z = 0.13$ ($P = 0.90$). This result suggested no significant difference in the global cure rates between rezafungin and caspofungin. Additionally, the 30-day all-cause mortality meta-analysis findings for rezafungin versus caspofungin showed a risk difference of −0.00 [95% CI: −0.07, 0.07], with a test for overall effect: $Z = 0.07$ ($P = 0.94$). This result also indicated no significant difference in the 30-day all-cause mortality rates between rezafungin and caspofungin (Fig. 1).

The ongoing RCT, registered under NCT04368559, is investigating the efficacy of rezafungin compared to standard antimicrobial regimens in preventing invasive fungal diseases in adults undergoing allogeneic blood and marrow transplantation.[9] This multicenter phase 3 study aims to evaluate fungal-free survival rates, the incidence of treatment-emergent adverse events, and overall mortality among participants across multiple countries, with a projected enrollment of 462 individuals (Table 3). The study's outcomes are expected to provide critical data on rezafungin's effectiveness and safety in a high-risk patient population.

Table 1. Pharmacokinetics and pharmacodynamics of rezafungin and caspofungin.

Parameter	Rezafungin	Caspofungin
Mechanism of Action	Inhibits 1,3-β-D-glucan synthase, disrupting fungal cell walls	Inhibits β-(1,3)-D-glucan synthesis in fungal cell walls
Pharmacodynamics	Concentration-dependent fungicidal activity	Inhibits cell wall synthesis, potential for resistance development
Absorption	Not applicable (intravenous only)	Not applicable (intravenous only)
Distribution	Volume of distribution: 67 L	Tissue distribution within 36–48 h, higher protein binding (97%)
Protein Binding	87.5% to >98.6%	97%
Metabolism	Minimal metabolism, not via CYP450 enzymes	Slow metabolism by hydrolysis and N-acetylation
Half-Life	152 h	9–11 h
Excretion	Mainly fecal, some renal as inactive metabolites	Approximately equal fecal and renal excretion
Administration Frequency	Once weekly	Daily
Clinical Use	Treatment of candidemia and invasive candidiasis in adults	Treatment of esophageal candidiasis, invasive aspergillosis, and other fungal diseases

Table 2. Characteristics of included RCTs.

Author, Year	Study Type	Intervention	N	Endpoints	Age	Efficacy	Safety
Thompson, 2023	Double-blind, double-dummy, randomized phase 3 trial; NCT03667690	IV rezafungin once a week (400 mg in week 1, followed by 200 mg weekly, for a total of two to four doses)	199 (n = 100 in rezafungin group)	- Global cure (consisting of clinical cure, radiological cure, and mycological eradication) at day 14 - 30-day all-cause mortality	61 ± 15.2	- 55/93 had a global cure at day 14 - 22/93 died or had unknown status at day 30	89 (91%) of 98 patients had TEAEs in the rezafungin group
Thompson, 2021	Phase 2, Randomized Double-blind Study; NCT02734862	Rezafungin 400 mg once a week, on week 1 then 200 mg weekly (400/200 mg)	207 (n = 138 in rezafungin group)	- Overall cure (resolution of signs of candidemia/IC + mycological eradication) at day 14 - Investigator-assessed clinical response at day 14 - 30-day all-cause mortality	59 ± 16	Overall cure rates: - 46/76 for the 400 mg ITT arm - 35/46 for the 400/200 mg ITT arm 30-day all-cause mortality: - 12/76 for the 400 mg ITT arm - 2/46 for the 400/200 mg arm	87.7% in the RZF 400 mg group and 92.5% in the RZF 400/200 mg group experienced at least 1 TEAE

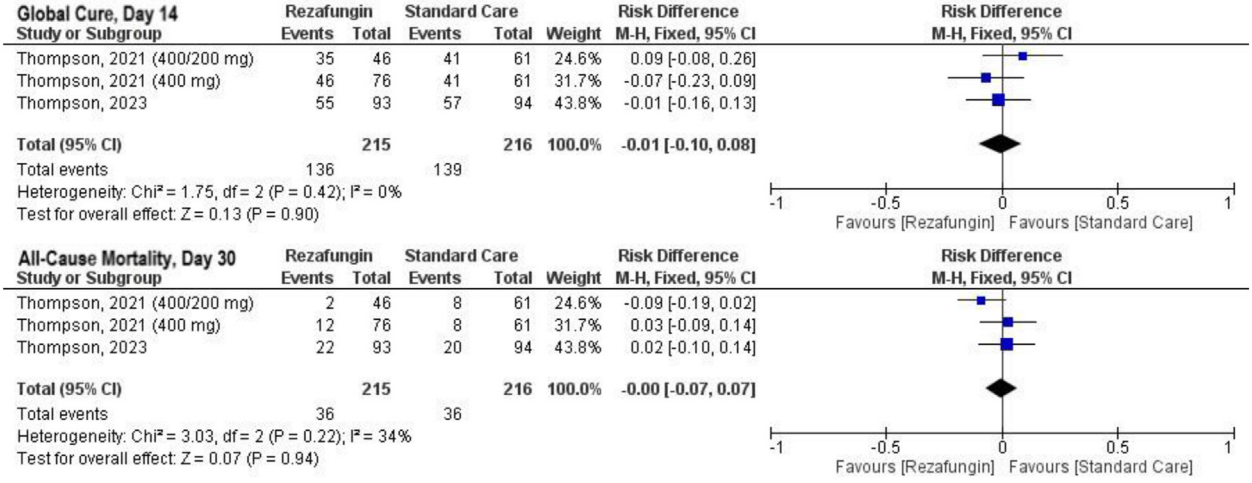

Fig. 1. Forest plots depicting risk difference, 95% CI for global cure at day 14 and all-cause mortality at day 30.

4. Discussion

Proponents of rezafungin may posit that its novel mechanism of action and once-weekly dosing regimen offer advantages over current echinocandins, potentially improving patient adherence and reducing the likelihood of antifungal resistance development.[10] Furthermore, the drug's approval by the FDA was based on positive data from phase 3 clinical trials, indicating its non-inferiority to caspofungin as a standard of care.[11]

On the other hand, our meta-analysis findings reveal no significant differences in global cure rates and all-cause mortality between rezafungin and caspofungin. These results raise concerns about the clinical relevance of rezafungin's introduction, considering the substantial investment and resources required for its development and distribution.[12] Additionally, according to the FDA's report dated 22 March 2023, the approval of rezafungin (Rezzayo) for the treatment of candidemia

Table 3. Characteristics of the ongoing RCT.

NCT Number	Study Title	Study Status	Conditions	Interventions	Primary Outcome Measures	Secondary Outcome Measures	Sex	Ages	Phases	N	Study Type	Study Design	Start Date	Primary Completion Date	Locations
NCT04368559	Study of Rezafungin Compared to Standard Antimicrobial Regimen for Prevention of Invasive Fungal Diseases in Adults Undergoing Allogeneic Blood and Marrow Transplantation	Ongoing	Candidemia; Invasive Candidiasis; Invasive Fungal Disease; Prophylaxis of Invasive Fungal Infections; Fungal Infections	(1) Rezafungin for Injection, (2) Posaconazole, (3) Fluconazole, (4) Trimethoprim-sulfamethoxazole (TMP/SMX), (5) Intravenous/Oral Placebo	1. Noninferior Fungal-Free Survival (US FDA): Number of subjects achieving fungal-free survival, Day 90 (±7 days). 2. Noninferior Fungal-Free Survival (US FDA): Percentage of subjects achieving fungal-free survival, Day 90 (±7 days). 3. Superior Fungal-Free Survival (EMA): Number of subjects achieving fungal-free survival, Day 90 (±7 days). 4. Superior Fungal-Free Survival (EMA): Percentage of subjects achieving fungal-free survival, Day 90 (±7 days).	1. Discontinuation for Toxicity or Intolerance: Number of subjects discontinuing Rezafungin vs. SAR due to toxicity/intolerance, Day 90 (±7 days). 2. Discontinuation for Toxicity or Intolerance: Percentage of subjects discontinuing Rezafungin vs. SAR due to toxicity/intolerance, Day 90 (±7 days). 3. Proven and Probable IFD: Number of subjects with proven/probable IFD including infections from Candida spp., Aspergillus spp., and Pneumocystis jirovecii, Day 90 (±7 days). 4. Proven and Probable IFD: Percentage of subjects with proven/probable IFD including infections from Candida spp., Aspergillus spp., and Pneumocystis jirovecii, Day 90 (±7 days). 5. Fungal-Free Survival (with/without Clinically Significant GVHD): Number of subjects with fungal-free survival, with/without clinically significant GVHD, Day 90 (±7 days). 6. Fungal-Free Survival (with/without Clinically Significant GVHD): Percentage of subjects with fungal-free survival, with/without clinically significant GVHD, Day 90 (±7 days). 7. Time to IFD or Death: Time to IFD (proven/probable) or death, comparing Rezafungin vs. SAR, Day 90 (±7 days). 8. Mortality Comparison: Evaluate overall and attributable mortality, adjusted for comorbidities, comparing Rezafungin vs. SAR, Day 1 to follow-up (Day 120). 9. Incidence of Treatment Emergent Adverse Events: Number of subjects with treatment emergent adverse events based on labs, vital signs, physical exams, and ECG, Day 1 to follow-up (Day 120).	All	Adults, Older Adults	Phase 3	462	Interventional	Randomized, Parallel, Quadruple (Participant, Care Provider, Investigator, Outcomes Assessment), Preventive Trial	5/11/2020	2024-08	United States, Canada, France, Germany, Italy, Spain, Switzerland, Turkey, United Kingdom

and invasive candidiasis in adults was based on a single adequate and well-controlled phase 3 study.[12] This study, designed with a day 30 all-cause mortality primary endpoint and a 20% non-inferiority margin, demonstrated that rezafungin is noninferior to the comparator echinocandin.[12] It is important to note that nonclinical studies in nonhuman primates identified a neurotoxicity safety signal, although rezafungin's safety profile in completed clinical studies was similar to other FDA-approved echinocandins.[12]

There is a need for continued research into more efficacious antifungal agents and the importance of assessing the long-term safety and effectiveness of rezafungin in real-world settings.[13-15] The FDA's detailed review process for rezafungin emphasized the flexibility of the development program intended to expedite the availability of antimicrobial therapies for patients with limited treatment options, highlighting the balance between rapid approval and comprehensive efficacy and safety assessments.[12]

In this context, the debate surrounding the introduction of rezafungin as a treatment option for candidemia and invasive candidiasis highlights the complex interplay between scientific discovery, clinical implementation, and the need for continuous evaluation of novel therapeutic interventions. Ultimately, further research and post-marketing surveillance will be crucial in determining the true value of rezafungin in the management of these life-threatening fungal infections.[16]

In this context, the debate surrounding the introduction of rezafungin as a treatment option for candidemia and invasive candidiasis highlights the subtleties between scientific discovery, clinical implementation, and the need for continuous evaluation of novel therapeutic interventions. Ultimately, further research and post-marketing surveillance will be crucial in determining the true value of rezafungin in the management of these life-threatening fungal infections.

In conclusion, this study has critically assessed the effectiveness of rezafungin compared to caspofungin, primarily within in-hospital settings where management of complications like retinitis, endocarditis, and hepatosplenic abscess is crucial. Despite rezafungin's FDA approval and its distinct pharmacokinetic advantages, our analysis found no significant differences in global cure rates or all-cause mortality between the two drugs. While rezafungin introduces a new therapeutic option with potential logistical benefits due to its dosing regimen, its practical impact and safety profile in the acute management of severe fungal infections warrant further investigation through extensive clinical trials and real-world application.

Ethics information

No patient data was collected during the course of this analysis. While an ethical approval was sought, it was not deemed necessary given the nature of the study.

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No funding was obtained for this study.

Conflict of interest

The authors declare they have no conflict of interest.

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