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Rezafungin: A Brief Notes to Know

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Short Communication

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Abstract:

Rezafungin is a novel long-acting echinocandin licensed by the US Food and Drug Administration for the treatment of invasive candidiasis and candidaemia. A novel inhibitor of -glucan synthase, rezafungin possesses a chemical relationship with anidulafungin. It is regarded as the original echinocandin molecule of the current generation. With improved tissue penetration, better pharmacokinetic, phamacodynamic (PK/PD) pharmaco-metrics, and an excellent safety profile, it offers a number of advantages over the FDA-approved echinocandins. Hypokalemia, pyrexia, diarrhea, anemia, vomiting, nausea, hypomagnesemia, stomach pain, constipation, and hypophosphatemia are the most frequent side events of this medicine (incidence 5%). Because of its remarkable half-life, rezafungin is a promising new addition to the antifungal toolbox that may be used as prophylaxis in immunocompromised patients and early hospital discharge for stable patients. This study provides a brief description of the mechanism of action, target, side effect, and metabolism data on rezafungin.

Key Words: Pharmacokinetic; Candidaemia; Metabolism; Echinocandins.

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INTRODUCTION:

In the setting of healthcare, invasive candidiasis and candidemiaemia are significant causes of morbidity and mortality [1 – 6]. Although the causal pathogen varies greatly by region, Candida albicans is the most frequently implicated species in candidaemia and invasive candidiasis in the majority of clinical situations. However, nonalbicans species (*Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, and *Candida auris*) are steadily increasing in prevalence [1]. It is particularly challenging to treat C glabrata, C parapsilosis, and the newly discovered species C auris due to resistance. In the USA and Europe, echinocandins are the first-line treatment [7, 8].

Rezafungin is a recently approved echinocandin by the US Food and Drug Administration. It shares structural similarities with the other three approved echinocandins and has a well-established mechanism of action, but its stability and pharmacokinetics enable front-loaded dosing and once-weekly intravenous administration [9, 10]. A population pharmacokinetic study of rezafungin in patients with fungal infections found that, despite correlations between rezafungin pharmacokinetics and body surface area, infection status, serum albumin, hepatic function, and sex, this interindividual variability is unlikely to be clinically meaningful. This is because modern drug delivery systems are so sophisticated [11, 12]. This note provides a brief description of the mechanism of action, target, side effect, and metabolism data on rezafungin.

PROPERTIES:

In order to avoid many of these pharmacological and stability issues, rezafungin is currently being developed. It is anidulafungin's structural analogue. They have a very similar cyclic core, with a choline aminal ether substituting for the hemiaminal region at the echinocandin cyclic nucleus (C5 ornithine residue). They also have the same side chain. This alteration makes anidulafungin more stable and soluble by decreasing the chemical degradation that takes place at the hemiaminal region of the compound [13]. The half-life of rezafungin is longer than that of the other echinocandins (>130 h, >5 times) [14]. Furthermore, when higher dosage regimens were examined, the hepatocytes of rats given high doses of rezafungin showed no signs of toxicity [15].

MECHANISM AND TARGET:

The extracellular matrix that makes up the fungal cell wall is composed of glycoproteins on the outside and carbohydrate polymers on the inside [16]. The main carbohydrates found in the fungal cell wall are chitin and -D-1,3-glucans, which are accompanied by -D-1,6-glucans [17]. The dry weight of this structure is made up mostly of this carbohydrate. Of those glucans, 65–90% are glucan polymers; these glucans with glucose units joined by 1,3 links are called {-D-1,3-glucans} [18]. Rezafungin inhibits the production of cell walls, particularly the synthesis of 1,3-D-glucan. Reduced 1,3-D-glucan levels in the cell wall cause morphological changes in the cells, which lead to osmotic instability and eventual cell death or inhibition [19].

METABOLISM:

Three hydroxylated metabolite isomers of rezafungin are produced when the terphenyl, pentyl ether side chain is hydroxylated: 2'-, 3′-, or 4'-hydroxylpentyl rezafungin. Despentyl-rezafungin is the product of another metabolic process that uses O-dealkylation to remove the pentyl group from rezafungin. The hydroxyl metabolites undergo very little additional conjugation (sulfation) compared this [20]. Rezafungin is not metabolized in the liver and is not expected to be a clinically relevant substrate of CYP450 enzymes [21].

SIDE EFFECTS:

Rezafungin is not expected to be dialyzable due to its high protein binding. Rezafungin did not exhibit any mutagenicity in a standard battery of assays in non-clinical studies. It also had no effect on mating or fertility in male or female rats administered intravenously with up to 45 mg/kg of rezafungin (6 times the clinical exposure) every three days. Male mice showed reduced sperm motility at rezafungin doses greater than or equal to 30 mg/kg; at 45 mg/kg, the mice showed mild to moderate hypospermia and no motile sperm were visible. At the conclusion of the study, male rats receiving 45 mg/kg of rezafungin intravenously every three days for three months displayed minimal tubular degeneration/atrophy in the testes and cellular debris in the epididymides. The carcinogenicity of rezafungin has not been evaluated in non-clinical studies. Rezafungin has an elimination clearance of 0.35 L/hour [21].

CONCLUSION:

Rezafungin is a new-glucan synthase inhibitor that is chemically related to anidulafungin, with better stability, tissue penetration. Rezafungin is an echinocandin that functions similarly to the others in terms of targets and mechanisms of action, but it has a safer profile that makes it possible to administer higher doses. Rezafungin and the more established echinocandins have the same target and resistance mechanisms. Compared to the earlier echinocandins, rezafungin is substantially more stable in solution. This feature is advantageous for manufacturing as well as for storage and dosing flexibility.

Competing interest: None.

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