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New Aminoglycoside on the Block: What role should Plazomicin play in the management of infectious diseases?

Introduction

Plazomicin (Zemdri™) is a new parenteral aminoglycoside that received FDA-approval for treatment of complicated urinary tract infections (cUTI) in adults on June 26th, 2018.[1] In the era of increasing antimicrobial resistance among Gram-negative bacteria, plazomicin may be useful for treating infections when few or no alternative treatment options exist. This newsletter reviews key points about plazomicin including its antimicrobial spectrum, clinical efficacy, safety, and monitoring parameters. We also review its role in the management of infectious diseases in community hospitals.

Antimicrobial Activity

Similar to other aminoglycosides, plazomicin binds to the bacterial 30S ribosomal subunit and interferes with protein synthesis.[2] Plazomicin has *in vitro* activity against Gram-negative (*E. coli*, *K. pneumoniae*, and *Enterobacter spp*., as well as other Enterobacteriaceae) and Gram-positive bacteria (*S. aureus*, including MRSA).[3] Unlike gentamicin, tobramycin, and amikacin, the chemical structure of plazomicin was modified in development to resist aminoglycoside-modifying enzymes (AME) that are often present in carbapenem resistant Enterobacteriaceae (CRE).[4] While this modification makes plazomicin particularly potent against Enterobacteriaceae (including CRE), this advantage comes at an expense. Plazomicin has no *in vitro* activity against streptococci, enterococci, *Stenotrophomonas maltophilia*, and *Acinetobacter spp*., and reduced activity against *Pseudomonas aeruginosa*. **Table 1** outlines advantages and disadvantages of plazomicin spectrum as compared with existing aminoglycosides (gentamicin, tobramycin, amikacin). Plazomicin susceptibility testing materials are currently available through a research use only (RUO) program with overnight shipping. For more information on how to participate in this RUO program, please visit: https://www.zemdri.com/assets/pdf/AST-Info-Sheet.pdf.

Table 1. Comparison of plazomicin's microbiological activity with existing aminoglycosides

Advantages	Disadvantages
• Enhanced activity against CRE, ESBL, and/or aminoglycoside-resistant: ○ *E. coli* ○ *K. pneumoniae* ○ *P. mirabilis* ○ *E. cloacae*	• Less activity against *P. aeruginosa* • No activity against: ○ Streptococci ○ Enterococci ○ *S. maltophilia* ○ *Acinetobacter spp.*

Summary of Clinical Trials

The safety and efficacy of plazomicin for treatment of cUTI, including acute pyelonephritis (AP), was evaluated in one Phase 2 and one Phase 3 trial.[5,6] The EPIC (**E**valuating **p**lazomicin **i**n **c**UTI) study was a Phase 3 trial that randomized 609 patients to receive either plazomicin or meropenem for a minimum of 4 days with the option to transition to oral levofloxacin 500mg daily for a total duration of 7-10 days.[6] The primary endpoint was a composite cure endpoint, defined as achieving both microbiological eradication and clinical cure at day 5 and test of cure (TOC) (defined as both microbiological eradication and complete resolution of signs and symptoms of infection at day 15-19). Baseline characteristics between groups were similar; 42% had AP and less than 15% had concomitant bacteremia. This study showed that plazomicin was non-inferior to meropenem for composite cure at day 5 (88% vs 91.4%) and superior to meropenem at TOC (81.7% vs 70.1% (95% CI: 2.7, 20.3).

Plazomicin was also evaluated for treatment of bloodstream infections (BSI), hospital-acquired bacterial pneumonia (HABP), and ventilator associated

pneumonia (VAP) in a randomized, open-label, Phase 3 clinical trial.[7] The CARE (**C**ombating **A**ntibiotic-**r**esistant **E**nterobacteriaceae) study randomized 39 patients to receive either plazomicin (n=18) or colistin (n=21) in combination with meropenem or tigecycline. The primary endpoint was all-cause mortality or significant disease-related complications (SDRCs) at day 28. Overall, this study showed that plazomicin treatment was non-inferior to colistin in regards to all-cause mortality or SDRCs at day 28 (23.5% vs 50%) (95% CI: -5.8% to 55.3%) in patients with BSI, HABP, and VAP. However, in the subset of patients with BSI, plazomicin (n=14) was associated with reduced mortality or SDRCs as compared with colistin (n=15) (14.3% vs 53.3%, p=0.033). There are several notable limitations worth discussing. First, this trial was stopped early, which resulted in limited enrollment and significant disparities in important characteristics between treatment arms. Second, due to limited enrollment, this trial was likely underpowered to detect a meaningful difference in treatment groups. Third, randomization occurred up to 96 hours after empiric treatment was initiated; therefore, it is possible patients were already significantly treated and/or improving prior to starting study therapy. On the basis of these limitations, the FDA rejected the request for plazomicin approval for treatment of BSIs.[1] Therefore, plazomicin is only FDA-approved for treatment of cUTI.

Safety

All aminoglycosides, including plazomicin, have FDA-issued black box warnings for nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm. In all clinical trials to date, 590 patients received at least one dose of plazomicin. The most common adverse events reported in the EPIC study are shown in **Table 2**.

In the EPIC study, serum creatinine increases of 0.5 mg/dL or more above baseline occurred in 7% (21/300) and 4% (12/297) of plazomicin- and meropenem-treated patients, respectively.[6] Adverse events related to renal function were more common in patients with an estimated creatinine clearance (CrCl) of 30 – 60 mL/min, and all adverse events were more common in plazomicin-treated patients 65 years-of-age or older.

Table 2. Adverse reactions occurring in more than 1% of patients in the EPIC study[6]

Adverse Reactions	Plazomicin (N=303) n (%)	Meropenem (N=301) n (%)
Decreased renal function	11 (3.6)	4 (1.3)
Diarrhea	7 (2.3)	5 (1.7)
Hypertension	7 (2.3)	7 (2.3)
Headache	4 (1.3)	9 (3.0)
Nausea	4 (1.3)	4 (1.3)
Vomiting	4 (1.3)	3 (1.0)
Hypotension	3 (1.0)	2 (0.7)

Dosing and Therapeutic Drug Monitoring

The recommended dose of plazomicin for treatment of cUTI requires adjustment for renal impairment (**Table 3**.) All doses are infused over 30-minutes.[2]

Table 3. Plazomicin dosage regimens[2]

Estimated CrCl	Dosage	Dosing Interval
≥ 60 mL/min	15 mg/kg	Every 24 hours
30 – 59 mL/min	10 mg/kg	Every 24 hours
15 – 29 mL/min	10 mg/kg	Every 48 hours

Calculate dosage using total body weight (TBW) in normal weight patients. For patients with TBW greater than ideal body weight (IBW) by 25% or more, use adjusted body weight (AdjBW): AdjBW = IBW + 0.4 x [TBW – IBW].

Therapeutic drug monitoring is recommended to ensure plasma trough concentrations remain below 3 mcg/mL.[2] It is recommended to measure plazomicin trough levels approximately 30 minutes prior to the second dose. The dose should be adjusted by extending the dosing interval by 1.5-fold (e.g., from every 24 hours to every 36 hours) for patients with trough concentrations greater than 3 mcg/mL. For information regarding plazomicin assays, visit: https://www.thermofisher.com/us/en/home.html.

Plazomicin is available as a solution of 500 mg/10 mL for injection that is stable for 24 hours in 0.9% Sodium Chloride Injection, USP and Lactated Ringer's Injection, USP. A standard patient with normal renal function (e.g., 70 kg, CrCl >60 mL/min) would require 1,050 mg of plazomicin (three vials). No pricing data are available at this time.

What is the Role of Plazomicin in Therapy?

In the era of increasing antimicrobial resistance, a new agent is always welcome to our diminishing armamentarium of antibiotics. Plazomicin is a new parenteral aminoglycoside approved for treatment of cUTI in adults, but its role in use for community hospital patients is limited. We agree with the FDA's statement "plazomicin should be reserved for use in patients who have limited or no alternative treatment options."[1] Plazomicin is particularly potent against CRE *in vitro*, but clinical experience treating cUTI caused by CRE with plazomicin is lacking. CRE UTI patients were excluded from the EPIC trial. Further, inability to obtain susceptibility testing data for clinical isolates will limit its utility in clinical medicine in the near term. Cost information is also unavailable at this time but will impact future formulary decisions for community hospitals.

In the future, we believe plazomicin will be best utilized as targeted therapy in patients with cUTI caused by Gram-negative enteric pathogens resistant to existing aminoglycosides and beta lactams. Plazomicin might also be considered for treatment of cUTI in patients that cannot tolerate beta-lactams due to severe allergy when other aminoglycosides or fluoroquinolones are not an option due to resistance. Plazomicin should not be used for empiric treatment of cUTI due to its limited activity against *Pseudomonas aeruginosa.*

Take Home Points:

1. Plazomicin (Zemdri™) is a new aminoglycoside recently approved for treatment of complicated urinary tract infections (cUTI) in adults.
2. The safety profile of plazomicin is similar to existing aminoglycosides which have renal toxicity.
3. Plazomicin is more active against CRE but less active against *Pseudomonas aeruginosa* as compared with existing aminoglycosides.
4. Susceptibility tests and cost information for plazomicin are unavailable at this time.
5. Plazomicin may be considered for targeted therapy in patients with cUTI caused by bacteria that are resistant to existing aminoglycosides. Its use should be limited to scenarios where alternative agents cannot be used (e.g., confirmed severe allergy or concern for serious adverse events).

References:

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