What’s inside this fall issue?

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- OFID podcast interview
- Keynote speaker for 2019
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- CE Article

MAD-ID Proud Supporter of New Global initiative to fight antibiotic resistance

U.S. Challenges World to Intensify Global Fight against Antibiotic Resistance

‘AMR Challenge’ calls for more action to save lives from one of the greatest threats to public health

Will you fight or fuel antimicrobial resistance (AMR)?

One of the greatest global health issues of modern time is threatening our progress in healthcare, food production, and life expectancy. How will you lead?

This unprecedented challenge, led by the U.S Department of Health and Human Services (HHS) and Centers for Disease Control and Prevention (CDC), charges pharmaceutical and health insurance companies, food animal producers and purchasers, medical professionals, government health officials, and other leaders from around the world to work together to address antibiotic resistance by:

- reducing antibiotics and resistance in the environment (e.g. in water and soil);
- improving antibiotic use, including ensuring people can access these medicines when they are needed;
developing new vaccines, drugs, and diagnostic tests
improving infection prevention and control
enhancing data sharing and data collection

HHS Secretary Alex Azar announced the challenge at a U.S. event co-hosted by the Bill & Melinda Gates Foundation, the Pew Charitable Trusts, the United Nations Foundation, Wellcome Trust, and the CDC Foundation. Secretary Azar unveiled the first commitments from more than 100 organizations intent on building on progress against one of the greatest global public health threats. MAD-ID is proud to step up and contribute to this global initiative.

"Untreatable infections are the reality for too many families around the world—and in the U.S." says HHS Secretary Alex Azar. "We’ve had some success fighting antibiotic resistance but, if we don’t all act fast together, we will see global progress quickly unravel. Antibiotic resistance isn’t slowing down. Every country and industry has to step up."

The U.S. government’s Antimicrobial Resistance (AMR) Challenge is a yearlong effort to accelerate the fight against antimicrobial resistance across the globe. The AMR Challenge is a way for governments, private industries, and non-governmental organizations worldwide to make formal commitments that further the progress against antimicrobial resistance. The challenge starts Sept 25, 2018 and encourages a One Health approach, recognizing that the health of people is connected to the health and animals and the environment.

MAD-ID has signed on as an organization committed to this cause. We encourage MAD-ID members to use the hashtag #GlobalAMRChallenge in their tweets. The mission of MAD-ID is to provide education, in the form of traditional continuing education, skills training, and other life-long learning methods, to health care professionals concerning the prevention and treatment of infectious diseases in general, and antimicrobial stewardship specifically.

The goals of MAD-ID’s AMR challenge commitment are:
• Increase the number of trained professionals in antimicrobial stewardship in developing nations and underserved areas of the United States
• Fund research that aims to directly impact antimicrobial resistance development
• Engage additional healthcare professionals in committing to actions that will reduce resistance, consistent with the goals of the AMR challenge

Many useful tools and brochure (see below) are available free on the CDC website. Here is a link to the program

Antibiotic Resistance: The U.S. Is Fighting Back

Each year in the United States, at least 2 million people get infections caused by antibiotic-resistant (AR) germs. At least 23,000 people die as a result and the global burden is unknown.

**Detect, Respond To, & Contain AR**
- Strengthening ability to track changes in resistance in healthcare, agriculture, and animal health
- Rapidly identifying new threats with a national AR lab network, and improving response
- Leveraging international partnerships to improve surveillance practices and enhance coordination
- Providing incentives for healthcare facilities to report resistant germs and infections

**Prevent Infections & Improve Antibiotic Use**
- Advancing prevention of healthcare-associated and community infections
- Supporting antibiotic stewardship programs and actions wherever antibiotics are used
- Implementing national educational efforts to improve antibiotic use in human medicine, and improving the use of antibiotics in animals by food producers and veterinarians
- Developing international collaborations to improve understanding of resistance drivers and identifying evidence-based interventions

**Stay Ahead of Emerging Threats**
- Investing millions of dollars to support drug, diagnostic, and vaccine innovations
- Driving public health and clinical research to enhance drug and diagnostic discovery, improve healthcare practices, and find new ways to protect people
- Using new technologies, like whole genome sequencing, to better understand threats and help stop spread
- Expanding AR isolate collections to accelerate research and help build solutions

**Antibiotic Resistance**
when germs are no longer killed by the drugs designed to kill them

- 2+ MILLION infections annually
- AT LEAST 23,000 deaths annually

Commit to action
Deliver results
Combat antibiotic resistance
#GlobalAMRChallenge

Fighting antibiotic resistance starts with you
#GlobalAMRChallenge

www.mad-id.org

MAD-ID
537 Calico Retreat
Mt. Pleasant, SC 29464-2765
Three Pharmacist TEDx Speakers

MAD-ID member Ravina Kullar PharmD, MPH is a 2018 TEDx Detroit speaker on the topic of antibiotic resistance. This is her second TEDx invited talk on this topic. On Sept 26th Ravina returned to Detroit MI where she completed her infectious disease fellowship training under the leadership of Mike Rybak PharmD, MPH. Several MAD-ID members were in the audience to cheer her on.

Debbie Goff PharmD gave a TEDx talk Nov 2016 titled antibiotics “just-in-case” viewed by over 12,600 people to date https://www.youtube.com/watch?v=ALryAB_AYiA
Diane Ashiru PhD, PharmD from the UK leads the Antibiotic Guardian public health initiative in England. She gave her talk “keep antibiotics working-it’s your business” in Aug 2018.

Please help spread these TEDx talks on antibiotic resistance by sharing the YouTube link on social media or with colleagues via email or newsletters. Dr’s. Kullar and Ashiru’s talks will be posted in a few weeks.

Susan Davis PharmD and MAD-ID board member was invited to do a podcast interview with Paul Sax MD with the new journal Open Forum Infectious Diseases (OFID). The podcast can be found at this link https://academic.oup.com/ofid/pages/Podcasts

**OFID Podcasts**

*Open Forum Infectious Diseases* provides free podcast interviews with experts in the field, keeping you up to date with the latest research on your computer or on the go. Now available on iTunes or via your favorite podcast service.

**Podcast 21: An interview with Susan Davis, PharmD**

In this episode, OFID Editor Paul Sax, MD, interviews Susan Davis, PharmD, about the role pharmacists play in improving patient outcomes, why PharmDs may be underutilized in the clinical setting, and ID drugs. They also reference the recent OFID article "A Qualitative Study of the Real World Experiences of Infectious Diseases Fellows Regarding Antibiotic Stewardship."
Keynote Speaker

Tim Jenkins MD

“New Frontiers in Antimicrobial Stewardship”

Dr. Jenkins is co-investigator of the multidisciplinary Colorado’s Statewide Antimicrobial Stewardship (AMS) Collaborative: Facilitating Syndrome-Specific Interventions for Skin and Soft Tissue Infection (SSTI) and Urinary Tract Infection (UTI). Twenty-seven hospitals are participating.

Dr. Jenkins is currently the Director of the Antimicrobial Stewardship Program at Denver Health. Research interests include the treatment of skin and soft tissue infections, interventions to optimize antibiotic use in health care settings and the community, use of short-course antibiotic therapy for common infections, and the management Staphylococcus aureus bloodstream infections. Dr. Jenkins has NIH K23 funding to study the problem of antibiotic overuse in patients hospitalized with skin and soft tissue infections.

The MAD-ID planning committee is busy selecting topics and speakers for 2019 conference. The meeting will be held in Orlando FL. May 8-11, 2019. We are planning on 8 hands on workshops with a variety of cutting edge topics. MAD-ID is the ONLY meeting dedicated to antibiotic stewardship. The multidisciplinary faculty includes physicians, pharmacists and nurses. Mark your calendar!

Patient Advocate Speaker

MAD-ID has a tradition of inviting a patient or a patient advocate to share their story of how antibiotic resistance, or how an adverse reaction to antibiotics impacted them or someone near to them. At the 2018 meeting Christian Lillis gave a compelling talk about his mother who lost her life as a result of developing C. difficile infection (CDI) after taking a course of clindamycin. Watch for an announcement on the www.mad-id.org website for the 2019 speaker.
ASP Basic or Advanced Registration Waivers

Remember to check the MAD-ID website (www.MAD-ID.org) for registration waivers for either the basic or advanced ASP training for MAD-ID members who practice in a healthcare setting. These are awarded on a first-serve basis and available depending on current funding. These waivers are provided by the generous support from the rapid diagnostic companies OpGen and Cepheid. Both have been long time supporters of MAD-ID.

MAD-ID NEWSLETTER CONTINUING EDUCATION ARTICLE

The self-assessment quiz which can be found at the end of this article can be completed for 1 CEU of Continuing Pharmacy Education credit. The quiz may be completed online at (http://mad-idtraining.org/newsletter/) at no cost for MAD-ID members. Non-members should print and mail the completed quiz, along with a $15.00 check made payable to MAD-ID to: MAD-ID, 537 Calico Retreat, Mt. Pleasant, SC 29464-2765. Your CE credit will be reported on CPE monitor within 4 weeks of receipt.

ACPE UAN# 0485-000-18-021-H01-P

Knowledge-based activity. Target audience: pharmacists and other healthcare providers (expires10/30/19)

MAD-ID is accredited by the Accreditation Council for Pharmacy Education as the provider of continuing pharmacy education.
Plazomicin: Making Aminoglycosides Great Again

Jacinda C Abdul-Mutakabbir, PharmD, Razieh Kabriaei, PhD, and Sarah CJ Jorgensen, PharmD, BCPS, AAHIVP

Learning Objectives:
At the end of this activity, learners will be able to:
1). State plazomicin’s spectrum of activity; and indications for use
2). Describe the necessary modifications to sisomicin implemented into plazomicin’s chemistry
3). Determine the appropriate use of plazomicin based upon possible mechanisms of resistance
4). Given a specific patient case, select the most appropriate dose for plazomicin

Disclosures: The authors have no conflicts of interest to disclose related to this learning activity.

Overview:
The emergence of Gram-negative, multi-drug resistant, organisms has become a dire worldwide health concern. Gram-negative bacteria such as Enterobacteriaceae (Klebsiella pneumoniae, E. coli, Shigella spp.,) Acinetobacter spp., and Pseudomonas aeruginosa have rendered most antibiotics useless, leaving aminoglycosides and polymyxins. Plazomicin (formerly ACHN-490), is a neoglycoside developed to mitigate the lack of antibiotics available to eradicate resistant Gram-negative organisms. ACHN-490 was recently approved by the US Food and Drug Administration for the treatment of complicated urinary tract infections (cUTIs) caused by MDR enterobacteriaceae. In this era highlighting the prevalence of gram-negative resistance, it is imperative to describe potential antimicrobials that have the capacity to change the course of therapy. The purpose of this article is to discuss available data detailing plazomicin’s biochemistry, pharmacokinetic/ pharmacodynamics characteristics, in vitro activity, as well as a review of its progress in clinical trials performed to affirm its position as a new treatment against multi-drug resistant (MDR) Gram-negative bacteria.

Introduction:
Multidrug-resistance (MDR) among Gram-negative pathogens represents an urgent public health threat that continues to escalate as bacteria relentlessly evolve and acquire new resistant determinants.[1] The global dissemination of beta-lactam resistance among Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter spp. has forced clinicians to resort to last-line agents such as tigecycline and colistin, of which lack robust efficacy and safety data, have poorly defined pharmacokinetic/pharmacodynamic (PK/PD) targets, as well as significant toxicity. [2] Plazomicin (formerly ACHN-490), a semisynthetic next generation aminoglycoside has demonstrated activity against Gram-negative bacterial isolates expressing an immense range of resistance mechanisms. [3] Aminoglycosides (AGs) are broad spectrum, bactericidal, antibiotics; utilized empirically for treating complicated urinary tract infection, nosocomial respiratory tract infections, and septicemia. [4] Similar to other classes of antibiotics, resistance to AGs has emerged in the most recent 50 years; with over 30% of Enterobacteriaceae
portraying a reduced response to gentamicin, tobramycin, and amikacin. [5,6] The cessation of available antibiotics, to mitigate serious MDR infections, demonstrates the necessity in the integration of novel therapeutics, such as plazomicin.[7,8]

Chemistry and Mechanism of Action:

Aminoglycosides act primarily by impairing bacterial protein synthesis, through binding to the A-site of the 16S ribosomal RNA (rRNA); functionally known as the decoding center of the 30s ribosome. The passage of these highly polar molecules, across the outer membrane of Gram-negative bacteria, is an energy-dependent process involving the drug-induced disruption of Mg$^{2+}$ bridges between adjacent lipopolysaccharide molecules. The unique combination in the uptake of AGs, as well as the inhibition of bacterial protein synthesis, aid in producing the concentration dependent killing exhibited by this class of antimicrobials. [9]

AG resistance develops through several mechanisms that can coexist simultaneously within the same isolate. Mechanisms of resistance include modification of the target site through the mutation of the 16S rRNA or ribosomal proteins, methylation of 16S rRNA, reduced permeability by modification of the outer membrane, or the enzymatic inactivation of the antibiotic molecule through the development of AG specific transferases. Noted in several Enterobacteriaceae organisms, resistance to aminoglycosides is caused primarily due to aminoglycoside modifying enzymes (AMEs), either alone or in combination. [10] AMEs are defined by various transferases including those that inactivate aminoglycosides by N-acetylation (AG acetyltransferase [AAC]), O-adenylation (AG-nucleotidytransferase [ANT]), or O-phosphorylation (AG-phosphotransferases [APH]). These enzymes can be present in the transferable elements or chromosomally of the bacteria. Transferases are diverse in respect to the positions of the AG scaffold that they attack; as well as the genes that encode them. [5,11]

Plazomicin, C25H48N6O10, was synthetically derived from sisomicin through appending a hydroxyamino butyric acid substituent at position 1 and a hydroxyethyl substituent at position 6’. Synthesized in an eight-step process, plazomicin was constructed through the basic rendering of sis sulfate; followed by a subsequent reaction with ethyl trifluoroacetate to selectively form the 6’trifluoroacetamide. Due to the natural lack in the 3’-and 4’ – OH groups, obtained from the parent molecule, plazomicin is active against the APH (3’) and ANT (4’) enzymes, of which generate resistance to amikacin. The implementation of the HABA substituent adds additional protection from the AAC (3), ANT (2”), and APH (2”) AMEs; while the addition of the hydroxyethyl group at the 6’ position supplements further protection from the AAC (6’) AME, present in various Enterobacteriaceae. The modifications made to sisomicin, the parent molecule, in the creation of plazomicin allows for it to potentiate potent bactericidal activity against a multitude of AME-expressing strains. [12]
Microbiology:

The in vitro activity of plazomicin and comparator AGs, against a diverse range of Gram-negative and Gram-positive pathogens; including those expressing various AMEs and ESBLs are presented in Tables 1 and 2. Minimum inhibitory concentration (MIC<sub>50</sub> and MIC<sub>90</sub>, range) values are representative of pooled data from studies conducted with plazomicin with preference for studies conducted using isolates collected within the last three years. Standard MIC determination methods were conducted under neutral pH conditions.

<table>
<thead>
<tr>
<th>Species</th>
<th>AG</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (mg/L)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>MIC range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>Plazomicin</td>
<td>0.5</td>
<td>1</td>
<td>0.25–8</td>
</tr>
<tr>
<td></td>
<td>AMK</td>
<td>8</td>
<td>64</td>
<td>1 to &gt;64</td>
</tr>
<tr>
<td></td>
<td>GEN</td>
<td>32</td>
<td>&gt;64</td>
<td>0.5 to &gt;64</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Plazomicin</td>
<td>1</td>
<td>2</td>
<td>0.25 – 4</td>
</tr>
<tr>
<td></td>
<td>AMK</td>
<td>16</td>
<td>&gt;64</td>
<td>0.5 to &gt;64</td>
</tr>
<tr>
<td></td>
<td>GEN</td>
<td>32</td>
<td>&gt;64</td>
<td>0.25 to &gt;64</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>Plazomicin</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>4 to &gt;64</td>
</tr>
<tr>
<td></td>
<td>AMK</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>2 to &gt;64</td>
</tr>
<tr>
<td></td>
<td>GEN</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>2 to &gt;64</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Plazomicin</td>
<td>8</td>
<td>64</td>
<td>0.5 to &gt;64</td>
</tr>
<tr>
<td></td>
<td>AMK</td>
<td>16</td>
<td>&gt;64</td>
<td>1 to &gt;64</td>
</tr>
</tbody>
</table>
## Table 2. Plazomicin and Comparators Activity against AMEs and ESBLs [12,14]

<table>
<thead>
<tr>
<th>Organism Group</th>
<th>Phenotype</th>
<th>AMK</th>
<th>GEN</th>
<th>Plazomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td>ATCC 25992</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ANT(2&quot;)-I</td>
<td>4</td>
<td>&gt;64</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>AAC(6')-I</td>
<td>32</td>
<td>4</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>AAC(3)-II</td>
<td>4</td>
<td>&gt;64</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>APH(3')-Ib</td>
<td>0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>AAC(3)-Iva</td>
<td>4</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>ATCC 29213</td>
<td>4</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ANT(4')-I</td>
<td>&gt;64</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>APH(3')-III</td>
<td>2</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>APH(2&quot;) +</td>
<td>64</td>
<td>&gt;64</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>AAC(6')-I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acinetobacter spp.</strong></td>
<td>APH(3')-VI</td>
<td>&gt;64</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Susceptible</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>ATCC 19606</td>
<td>16</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>AAC(6')-I</td>
<td>32</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>ATCC 27853</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Wild-type pump</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>ΔEfflux pumps</td>
<td>0.5</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td></td>
<td>MexXY up</td>
<td>4</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>ANT (4')-II</td>
<td>32</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>AAC(3)-I</td>
<td>4</td>
<td>64</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>AAC(6')-II</td>
<td>4</td>
<td>32</td>
<td>2</td>
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<tr>
<td></td>
<td>CTX-M ,</td>
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<tr>
<td></td>
<td>AmpC, SHV,</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>TEM</td>
<td>16</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

**ESBLs**
The observed in vitro activity of plazomicin encompasses a variety of AG resistant organisms such as, *Staphylococcus aureus*, members of the *Enterobacteriaceae* family, *P. aeruginosa*, *Acinetobacter spp.*; as well as AMEs and ESBL expressed within the aforementioned organisms. [12-15]

When tested against 493 methicillin resistant *S. aureus* isolates, plazomicin exhibited superior activity against the isolates in comparison to amikacin and gentamicin. The MIC$_{50}$ and MIC$_{90}$ values for plazomicin were 1 and 2 mg/L respectively, in comparison to 32 and > 64 mg/L for gentamicin, and 16 and >64 mg/L for amikacin. [12,13]

Of 407 *A. baumannii* isolates gathered through a surveillance study, high rates of non-susceptibility to the three traditional aminoglycosides was observed. Among the isolates, the plazomicin MIC$_{50}$ was <= 8 mg/L in 80% of the isolates, while 20% had an MIC$_{50}$ of 8-16 mg/L. High level aminoglycoside resistance (HLAR), defined as an MIC$_{50}$ of >64 mg/L, was documented in 21 strains. The PCR of 20 of the strains with HLAR revealed AAC(3)-Ib as the most prevalent AME responsible for the observed resistance. An MIC$_{50}$ of <= 8 mg/L for plazomicin was documented for 4 of the strains presenting with HLAR; for the remaining 16 strains, an MIC$_{50}$ of >16mg/L was observed; similar to that of the traditional aminoglycosides. [13-16]

In *P. aeruginosa*, the activity of plazomicin was similar to amikacin. A plazomicin MIC of <= 16 mg/L was found in 62% of isolates, while 38% had an MIC >= 32 mg/L. Two isolates presented with AAC (3)-Ib; an AME possibly attributable to the documented resistance. The plazomicin MIC for these two strains harboring the AAC (3)-Ib AME was found to be >64 mg/L. [17]

Uptregulation of efflux pumps, most commonly orchestrated through the MexXy efflux pump, compromises the antimicrobial effect of AGs. The presence of the MexXy efflux pump in *P. aeruginosa* and *Acinetobacter spp.*, correlate to plazomicin’s decline in activity amongst these organisms. [12-19]

The most prevalent aminoglycoside modifying enzymes that contribute to AG resistance in *Enterobacteriaceae* are AAC (3)-II, AAC (6’)-I, and ANT (2’’)-I (2,3). As represented in table 2, plazomicin remains highly potent against each of these AMEs. [12,20]

Also represented in table 2 is plazomicin’s activity against common extended spectrum beta-lactamases (ESBLs). While ESBLs do not directly inhibit AG activity, they are frequently plasmid encoded. The encoded plasmids are responsible for carrying aminoglycoside modifying genes; which prohibit AG activity. Nevertheless, plazomicin in vitro activity against (ESBL) producing strains was retained when utilized in 209 isolates in which these enzymes were present. Gentamicin, and amikacin’s MICs were documented as 8 mg/L and 16 mg/L respectively; while plazomicin maintained MICs at <= 1 mg/L for all ESBL producing strains. The following results indicate the superiority of plazomicin against AMEs as well as ESBLs that typically render aminoglycosides ineffective. [12-20]
Pharmacokinetics/Pharmacodynamics:

The pharmacokinetic (PK) properties of plazomicin have been evaluated through two phase 1, randomized, double blind, placebo-controlled studies conducted in healthy human subjects.

Study 1 was a parallel-group design, with escalating single (SD) and multiple doses (MD); while the second study included patients receiving a longer duration of the highest tolerated dose from the first study. [21]

The dosing of traditional aminoglycosides (5-7 mg/kg daily), served as a reference for the dosing of plazomicin utilized in first study. The patient cohorts in study 1 were dosed ascendingly (cohort 1a-4): beginning with 1mg/kg, 4mg/kg, 7mg/kg, 11mg/kg, and concluding with 15 mg/kg respectively. Patients received either a SD or MD of plazomicin, for a descending amount of days (cohort 1b for 10 days, cohort 2 for 10 days, cohort 3 for 5 days, and cohort 4 for 3 days). The subjects that received plazomicin in study 2 received the greatest tolerated dose from study 1, 15 mg/kg once daily for a total of 5 days. [21]

The 28 subjects of study 1 that received the plazomicin injection, were included in the single and multiple-dose pharmacokinetic analyses. The mean peak plasma plazomicin concentration was attained either at or shortly following initiation. Following the single dose administration, the mean + standard deviation Cmax ranged from 8 +0.8 mg/L in the 1-mg/kg group to 144 +/− 45 mg/L in the 15-mg/kg group. Following the conclusion of the infusion, the decline in plazomicin concentrations appeared to be multiphasic, with a decline immediately following initiation, and then a biphasic elimination in the terminal phase; beginning at 16-24 hours. The elimination half-life was measured at 12 hours following the initial dosing. The mean AUC ranged from 15 +/− 1 h x mg/l in the 1 mg/kg group to 246 +/− 39h x mg/L the 15 mg/kg group. Study 1 results for AUC versus dose (mg) and Cmax versus dose (mg), following the initial once-daily 10-min intravenous infusion of the plazomicin injection, were linear and dose proportional. [21]

The mean plasma PK parameters for the patients that received multiple doses in cohorts 1b-4 were generally similar to that of the patients that received single dosing PK for each respective cohort. Elimination half-lives were also similar in both groups across each study, ranging from 3-4 hrs. Steady state volumes were attained following the second dose of plazomicin, with the volume of distribution rates having limited variability across both studies. [21]

Similar PK parameters were also observed in the patients that received 15mg/kg MD daily versus those that received a SD daily of 15mg/kg, for both studies 1 and 2. The Cmax from those patients in study 1 that received multiple doses of plazomicin was documented to be 117 +/− 28, while the Cmax was 113 +/− 17 for those patients that had received 15mg/kg once daily in study 2. The AUC0−24 was 224 +/− 37, and 235 +/− 44 for the 15 mg/kg allocated group in study 1 versus study 2 respectively. The pharmacokinetic profile of the 15 mg/kg once daily group was consistent with the expectations related to aminoglycoside dosing. The high plasma, low trough concentrations, suggests a favorable AUC/MIC ratio indicating success amongst the aminoglycoside class of antibiotics. Despite the AUC being an important indicator in
aminoglycoside efficacy, a higher Cmax is correlated with better tissue penetration which is imperative in terms of preventing adaptive antimicrobial resistance A higher Cmax is achieved through delivering the total daily dose in a single administration, or once daily dosing. [5,22]

Represented in a small randomized, double blind, phase two study conducted a comparing plazomicin 10 mg/kg, 15 mg/kg, and levofloxacin 750mg (each administered daily); plazomicin dosed at 15 mg/kg was shown to be an effective treatment in adult patients diagnosed with a cUTI. The microbiological infection was eradicated in over 85% of the patients that received plazomicin, with 80% of patients that received the 15 mg/kg daily dose of plazomicin being pronounced clinically cured, per the complete resolution of baseline signs and symptoms of infection. In addition, a lower rate of disease recurrence was observed in the 15mg/kg daily plazomicin group in comparison to the levofloxacin group. [23]

Through these various studies; representing the necessity of a higher Cmax, required to achieve AG specific concentration dependent killing, as well the superiority of 15 mg/kg daily to other regimens; there is true justification in the utilization of 15 mg/kg daily dosing of plazomicin in healthy adults. [21,23]

Within the phase 3 trial, Combating Antibiotic Resistant Enterobacteriaceae (CARE); the management of plazomicin through therapeutic drug monitoring (TDM) for 22 patients, noted as being critically ill, was evaluated. Renal function varied in this patient population, ranging from a Crcl of <36 o 224 ml/min. Patient’s received 4-14 days of plazomicin therapy, with therapeutic drug monitoring utilized in each patient to attain an AUC of 262 mg/L for plazomicin. At the conclusion of therapy, 2 patients had creatinine levels that rose above baseline, however the levels did resolve within 48hrs. While a third patient experienced renal decline, the investigators were able to attribute this matter to septic shock unrelated to the plazomicin therapy. These results indicate that for critically ill patients, the institution of therapeutic drug monitoring would be efficacious in producing the required AUC to eradicate infection, while protecting the patient from kidney injury and/or failure. [24]

Resistance:

In vitro studies indicate that the development of resistance to plazomicin is similar to that of the traditional aminoglycosides. The development of plazomicin resistance was evaluated in an in vitro chemostat model, in which exposure to plazomicin was applied to 10 isolates (equal numbers in 1 E. coli and 1. K pneumoniae group) in increasing concentrations. Resistant isolates in this study were defined as those that had with an MIC >4 post-baseline, following a baseline MIC reading of <= to 4. In the strains that developed resistance, per the study definition, an AUC of <= to 66 mg/L was identified. This AUC indicates that the dosing of the isolates was exceedingly below the recommended 15 mg/kg, predisposing the included strains to the development of common aminoglycoside resistance mechanisms. Resistance was not detected in those isolates for which an AUC of >66 mg/L was observed. Despite plazomicin’s success in evading most mechanisms of aminoglycoside resistance; the presence of the New Delhi metallo-beta-lactamases (NDM), in strains of E. coli and K. pneumoniae, did render the drug ineffective. Due to the encoded plasmids of NDM being avid producers of 16S rRNA methylases, the plazomicin associated MICs were > 8mg/L; indicating resistance to this metallo-beta-lactamase. [25,26]
Adverse Effects:

In the conducted plazomicin studies, adverse events generally had a low frequency of occurrence, and were comparable between the plazomicin and comparator groups. The most frequently reported adverse events were gastrointestinal disorders. In general, the adverse events associated with plazomicin were defined as mild; and did not result in mortality nor an escalation in morbidity. Clinical trials did indicate the potential for a rise in baseline serum creatinine, a common adverse event associated with AGs. As observed through the data compiled from various clinical trials, a greater risk for nephrotoxicity was represented in those patients that had a Crcl 16-60 ml/min, or had been treated with plazomicin >/= to 5 days rather than those that had a Crcl >60 ml/min or had been treated for less than 5 days. [1,24,26]

Drug-Drug interactions:
The likelihood of drug-drug interactions with plazomicin was determined following the in vitro testing of plazomicin against a panel of drug metabolizing enzymes as well as drug transporters. Due to plazomicin being 97.5% excreted, unchanged, through the urine; the interaction with drug enzymes is unlikely. Interactions with major drug transporters, such as the p-glycoprotein, was also not observed in plazomicin trials. [23-25]

Clinical Efficacy:
In the EPIC study, a randomized, double blind trial, patients with cUTI including acute pyelonephritis (AP) who required hospitalization and intravenous antibacterial drug were randomized 1:1 to receive either plazomicin or meropenem. The plazomicin was dosed as 15 mg/kg daily while meropenem was dosed at 1g every 8 hours for a total of 4-7 days. The randomization was stratified by infection type (cUTI or AP), with the primary objective of the study being to demonstrate the noninferiority of plazomicin when compared to meropenem. The noninferiority margins was defined as 15%. Plazomicin exhibited highly sustained microbiological and clinical response rates, with 77.0% microbiological eradication vs. 60.4% in the plazomicin and meropenem groups respectively. These results; superior to that of meropenem (regularly used in the treatment MDR cUTI), support plazomicin as a potential antibacterial for cUTI clearance. [27]

Plazomicin efficacy was also evaluated for use in patients with carbapenem-resistant Enterobacteriaceae (CRE), bloodstream infections (BSI). In the Combating Antibiotic-Resistant Enterobacteriaceae (CARE) study, patients were separated into two different cohorts where they were to receive plazomicin (in combination with either meropenem or tigecycline) or colistin (in combination with meropenem or tigecycline). Ultimately, the CARE study supported plazomicin’s use in CRE associated BSI, with a >80% relative reduction in all-cause mortality when compared to colistin therapy. [24]

Conclusion:
The urgent need for new therapeutic options, to address infection caused by Enterobacteriaceae, is due largely to the growing resistance amongst members of this Gram-negative family. Plazomicin retains AG potentiated concentration-dependent bactericidal activity while evading common AMEs. The prolonged antibiotic effect enhances plazomicin’s action against Gram-negative pathogens that render broad-spectrum antibiotics defenseless. An emphasis on the decline of microbiological recurrence as well as the increase of patients capable of participating in late-follow up, indicate plazomicin’s clear benefits as well
as non-inferiority to its comparators. Based upon the attested in vitro spectrum of activity profile, as well as an established PK/PD profile validated by clinical studies, plazomicin has the ability to serve as an efficacious therapy for treating MDR Enterobacteriaceae amid the rise of complicated infections.

References:
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SELF-ASSESSMENT QUESTIONS

(To be completed online (http://mad-idtraining.org/newsletter/) or, in the case of non-MAD members, printed and mailed. You must achieve a grade of 80% of better to receive continuing education credit.)

1. Which of the following organisms are included in plazomicin’s spectrum of activity are the following? (objective 1)
   
   A. E. coli, Streptococcus pneumoniae, Streptococcus viridians  
   B. Serratia spp, Staphylococcus epidermis, Shigella spp.  
   C. E. coli, K. pneumoniae, P. aeruginosa  
   D. P. aeruginosa, Streptococcus viridians, Staphylococcus aureus

2). Which modifications to sisomicin were instituted in the development of plazomicin? (Objective 2)
   
   A. the implementation of a 4’ hydroxyl group; active against the several AMEs  
   B. the addition of a 3’ OH group making plazomicin active against AAC(3)-Ia  
   C. the addition of a 6’ hydroxyethyl group

3). Patient X is admitted to the hospital on 10/5/18, on 10/7/18 his microbiology cultures reveal an E. coli infection. Per a genotyping request, the strain was shown to be NDM-1 positive for resistance. Would plazomicin would be the best antibiotic of choice for the treatment of patient X’s infection? (Objective 3)
   
   A. Yes  
   B. No

4). Which of the following is the recommended dose for plazomicin administration in a healthy adult, with a CrCl > 60ml/min? (Objective 4)
   
   A. 10 mg/kg q 24 h  
   B. 1 mg/kg loading dose x 1, 15 mg/kg q 8h  
   C. 15 mg/kg q 12h  
   D. 15 mg/kg q 24h

5). Patient Y was admitted to the hospital on 10/6/18 with a CrCl of 28 ml/min, however the documents from her long-term care facility stated that she had a baseline CrCl of 78 ml/min, (last documented on 10/3/18). What dosing of plazomicin should you recommend for patient Y? (Objective 4)
A. 10 mg/kg loading dose; and continue at 15 mg/kg q12h
B. 4 mg/kg q24h
C. Dose the patient according to therapeutic drug monitoring to achieve the recommended trough level for eradication
D. Reduce the 10 mg/kg q 24h by half for 2 days; initiate 15 mg/kg q 24h dosing for the remaining duration of therapy

LEARNING ACTIVITY ASSESSMENT

(Please provide your honest assessment of the value of this learning activity so that we can continue to improve our offerings.)

Please indicate your degree of agreement or disagreement with the following statements regarding this learning activity by indicating strong agreement (a), general agreement (b), no opinion (c), mild disagreement (d), or strong disagreement (e):

1. The information presented was relevant to my practice
   a. 
   b. 
   c. 
   d. 
   e. 

2. This program/session met the stated learning objectives
   a. 
   b. 
   c. 
   d. 
   e. 

3. The information was presented in an objective and balanced manner without commercial bias
   a. 
   b. 
   c. 
   d. 
   e. 

4. The information presented will alter/affect my practice (usefulness)
5. The educational materials enhanced my learning
   a. 
   b. 
   c. 
   d. 
   e. 

6. The learning method was effective
   a. 
   b. 
   c. 
   d. 
   e. 

7. The learning assessment activity (self-assessment quiz) was appropriate
   a. 
   b. 
   c. 
   d. 
   e. 

8. The faculty/authors were of appropriate quality
   a. 
   b. 
   c. 
   d. 
   e. 

ABOUT MAD-ID

MAD-ID is incorporated as a non-profit entity [501(c)(3)] in the state of South Carolina. MAD-ID provides continuing professional education in the general area of infectious diseases pharmacotherapy and the specific area of antimicrobial stewardship. Educational initiatives and content are determined by an eight-member Scientific Committee composed of infectious
diseases experts from clinical pharmacy and medicine and are based upon ongoing needs assessments. The main venue for our programming is an annual meeting, which takes place in May of each year. Other MAD-ID initiatives have included regional programs related to specific topics and our Antimicrobial Stewardship Training Programs.

OUR MISSION. The mission/purpose of the Foundation is to provide education, in the form of traditional continuing education, skills training, and other pertinent life-long learning methods, to pharmacists and other healthcare professionals concerning pharmacotherapy as it pertains to the prevention and treatment of infectious diseases and to do all things necessary or convenient to further these goals, with a special emphasis on antimicrobial stewardship.

MEMBERSHIP. Membership in MAD-ID is available to all healthcare providers, including students and post-graduate trainees, interested and/or practicing in the area of infectious diseases. For more information, visit our webpage (www.mad-id.org).

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