

Comparison of the next-generation aminoglycoside plazomicin to gentamicin, tobramycin and amikacin

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Plazomicin (formerly ACHN-490) is a next-generation aminoglycoside that was synthetically derived from sisomicin by appending a hydroxy-aminobutyric acid substituent at position 1 and a hydroxyethyl substituent at position 6'. Plazomicin inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity. Plazomicin demonstrates activity against both Gram-negative and Gram-positive bacterial pathogens, including isolates harboring any of the clinically relevant aminoglycoside-modifying enzymes. However, like older parenteral aminoglycosides, plazomicin is not active against bacterial isolates expressing ribosomal methyltransferases conferring aminoglycoside resistance. Plazomicin has been reported to demonstrate *in vitro* synergistic activity when combined with daptomycin or ceftobiprole versus methicillin-resistant *Staphylococcus aureus*, heteroresistant vancomycin-intermediate *S. aureus*, vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus* and against *Pseudomonas aeruginosa* when combined with cefepime, doripenem, imipenem or piperacillin-tazobactam. After intravenous administration of plazomicin to humans at a dose of 15 mg/kg, the maximum concentration was 113 µg/ml, the area under the curve_{0–24} was 239 h·µg/ml, the half-life was 4.0 h and the steady-state volume of distribution was 0.24 L/kg. Results from a Phase II randomized, double-blind study in patients with complicated urinary tract infection and acute pyelonephritis including cases with concurrent bacteremia comparing plazomicin 15 mg/kg intravenously once daily for 5 days with levofloxacin 750 mg intravenously for 5 days are anticipated in 2012. Human studies to date have not reported nephrotoxicity or ototoxicity, and lack of ototoxicity has been reported in the guinea pig model. Given reported increases in bacterial resistance to current antimicrobial agents and the lack of availability of new agents with novel mechanisms, plazomicin may become a welcomed addition to the antibacterial armamentarium pending positive results from large-scale clinical trials and other required clinical studies.

KEYWORDS: ACHN-490 • aminoglycoside • antibiotic • plazomicin

Aminoglycosides first became available for clinical use in the 1940s (TABLE 1) and were shown to have broad-spectrum activity that included a wide variety of Gram-negative bacilli and many Gram-positive cocci [1]. Aminoglycosides are bactericidal, possess well-defined pharmacokinetic properties and demonstrate synergy when combined with β-lactam antibiotics. Their limitations include the worldwide spread of resistance mechanisms, primarily aminoglycoside modifying enzymes and well-described adverse effects, including ototoxicity and nephrotoxicity [2,3].

Clinical use of aminoglycosides started to diminish in the late 1980s due to the development and increasing use of carbapenems,

fluoroquinolones, extended-generation cephalosporins and β-lactam/β-lactamase-inhibitor combinations, all agents with similar antibacterial spectra to aminoglycosides but with less resistance and fewer adverse effects [4]. However, aminoglycosides continue to be used for a variety of serious systemic infections as short-term or longer-term therapy (with monitoring for adverse effects), particularly in situations where synergy is required [2,4–6]. Recently, clinicians appear to be returning to the use of aminoglycosides as the prevalence of resistance to carbapenems, fluoroquinolones, extended-generation cephalosporins and β-lactam/β-lactamase-inhibitor combinations and multidrug resistance increases [7,8].

Table 1. Year of availability of selected aminoglycosides for clinical use.

Aminoglycoside	Year of availability
Streptomycin	1944
Neomycin	1949
Kanamycin	1957
Paromomycin	1959
Spectinomycin	1961
Gentamicin	1963
Tobramycin	1967
Sisomicin	1970
Amikacin	1976

Despite the obvious need for novel agents, only two new antibiotic classes have been discovered and developed in the past 30 years and neither possess activity against Gram-negative bacilli [9]. The alternative route to novel antimicrobial development is via modification of existing classes to impede known antibiotic resistance mechanisms. Some progress has recently been made against Gram-negative bacilli in this area [10]. Plazomicin (ACHN-490) is a next-generation aminoglycoside synthetically derived from sisomicin [11] that is designed to evade all clinically relevant aminoglycoside-modifying enzymes [12], the main mechanism of aminoglycoside resistance [13]. This article will review the chemistry, mechanisms of action and resistance, microbiology, pharmacokinetics, pharmacodynamics, animal and human efficacy and adverse effects of plazomicin in comparison with the parenteral legacy aminoglycosides: gentamicin, tobramycin and amikacin.

Chemistry

The aminoglycosides are characterized by a central aminocyclitol ring substituted with hydroxyl and amino groups (FIGURE 1). With the exception of spectinomycin, the central ring is also connected to amino sugar substituents via glycosidic bonds [2]. In streptomycin, the aminocyclitol ring is streptamine; in all other parenteral aminoglycosides, it is 2-deoxystreptamine. Aminoglycosides are polar, basic molecules, highly soluble in water and poorly soluble in organic solvents. They are positively ionized at physiological pH and do not easily cross cellular membranes, which explains why they are poorly absorbed from the gastrointestinal tract and do not readily cross the blood–brain barrier. Intravenous or intramuscular administration is necessary for systemic use, and intrathecal administration is necessary to achieve therapeutic concentrations in the CNS [2]. The aminoglycosides are stable over a wide range of temperatures and pH values, although their antimicrobial action is increased in alkaline environments. The cationic nature of aminoglycosides allows them to bond with a variety of negatively charged biomolecules such as membrane lipids, DNA and RNA. This affinity is responsible for the ribosome-targeting action of aminoglycosides and may contribute to their rapid bactericidal activity [2,14].

Sisomicin is an aminoglycoside isolated from the aerobic fermentation of *Micromonospora* spp., first reported in 1970 [15]. Plazomicin (FIGURE 1) is derived from sisomicin using an eight-step synthetic pathway [11] and is named 6'-(hydroxyethyl)-1-(hydroxyaminobutyric acid)-sisomicin or (2S)-4-amino-N-[(1R,2S,3S,4R,5S)-5-amino-4-({2-amino-2,3,4,6-tetradeoxy-6-[(2-hydroxyethyl)amino]- α -D-glycero-hex-4-enopyranosyl}oxy)-2-{{3-deoxy-4-C-methyl-3-(methylamino)- β -L-arabinopyranosyl}oxy}-3-hydroxycyclohexyl]-2-hydroxybutanamide. Appending hydroxy-aminobutyric acid to sisomicin at position 1 and hydroxyethyl group at position 6' yields plazomicin [11]. These substitutions allow the novel molecule to avoid the action of aminoglycoside-modifying enzymes that confer aminoglycoside resistance (FIGURE 2) but do not reduce the molecule's affinity for the ribosomal site of action. The molecular formula of uncharged plazomicin is $C_{25}H_{48}N_6O_{10}$ and its molecular weight is 592.68 Da. Specific chemical data have not yet been reported for plazomicin, but it can be expected that it will display typical aminoglycoside properties.

Plazomicin is similar to gentamicin, tobramycin and amikacin in that it possesses a three-ring structure consisting of 2-deoxystreptamine substituted with 6-membered amino sugars at the 4 and 6 positions (FIGURE 1). Plazomicin is unsaturated at 4' where the comparator molecules are fully saturated. In contrast to amikacin, plazomicin has an amino group in the 2' position instead of a hydroxyl group, providing it with a total of five basic groups compared with amikacin. Plazomicin and amikacin share the hydroxy-aminobutyric acid group at 1 position.

Mechanism of action

In susceptible bacteria, aminoglycosides, including plazomicin, are bactericidal agents whose principle mechanism of action is through inhibition of protein synthesis. Uptake of the aminoglycosides into cells can be observed to have three stages [16]. In Gram-negative bacteria, the first stage involves binding of the polycationic aminoglycoside to anionic lipopolysaccharides, phospholipids and proteins of the outer membrane. This is followed by uptake of the drug across the outer membrane, diffusion across the periplasmic space and adsorption to the cytoplasmic membrane [17]. Outer membrane penetration is due to displacement of divalent cations (which are involved in crossbridging and stabilization of the outer membrane's lipopolysaccharide) [18], leading to disruption of outer membrane stability and increase in its permeability [19]. This increase in membrane permeability, which is the first stage of uptake, is referred to as self-promoted uptake [18]. In Gram-positive bacteria, this first stage involves ionic binding of the polycationic drug to the anionic phospholipids and lipoteichoic acids on the bacteria's surface [17]. For both Gram-negatives and Gram-positives, this stage is rapid, reversible and concentration dependent but not energy dependent [17].

The energy-dependent second and third phases are named energy-dependent Phase I (EDP-I) and energy-dependent Phase II (EDP-II) [17]. Although the precise mechanism is not currently known, EDP-I represents the initial slow uptake of drug into the cell, initial ribosomal binding and the incorporation

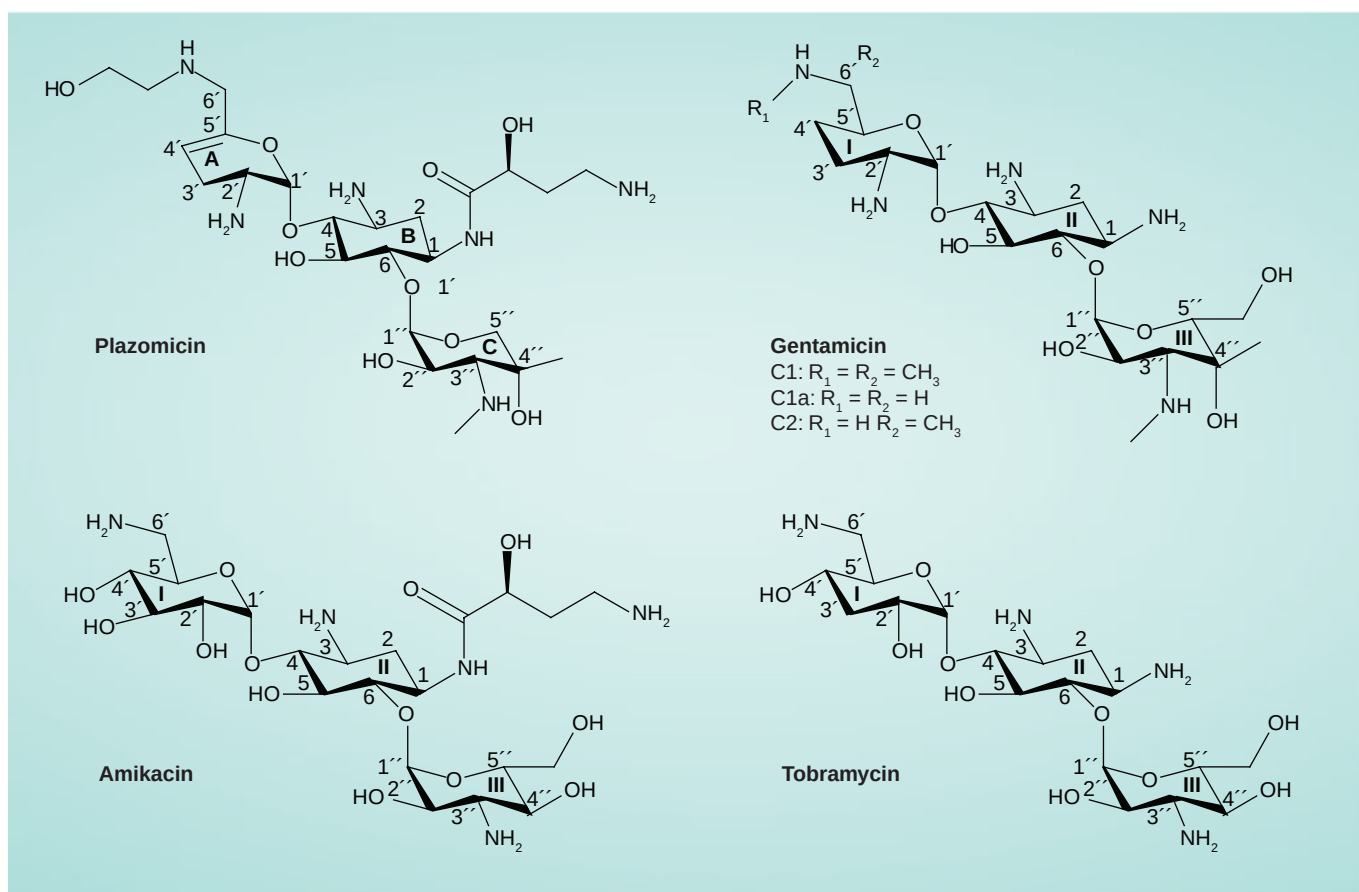


Figure 1. Chemical structures of plazomicin, gentamicin, amikacin and tobramycin. Examples of two-ring numbering systems are illustrated; both are in use interchangeably in the literature.

of misread proteins into the cell wall [20]. EDP-I depends on a minimum threshold membrane potential and a functioning electron transport chain [17]. The duration of EDP-I is also affected by the external aminoglycoside concentration, with sufficiently high concentrations reducing the length of EDP-I almost completely [17]. The incorporation of misread proteins into the cytoplasmic membrane during EDP-I leads to EDP-II, which represents a greatly increased linear rate of drug uptake into the cell and saturated ribosome binding [20]. Like EDP-I, the precise mechanism of EDP-II phase uptake is not known, but EDP-II is dependent on ribosome binding in the EDP-I phase [16], is driven by the membrane electrical potential arising from the electron transport chain or possibly ATP hydrolysis [17] and follows diffusion/electrophoretic kinetics instead of Michaelis–Menton kinetics, which would be expected based on the standard membrane active-transport model [20]. Uptake into the cell is one-way, most likely due to ionic binding of the aminoglycoside with anionic macromolecules inside the cell [20,21]. The dependence of aminoglycoside uptake on membrane potential and cellular respiration explains the sensitivity of aminoglycoside action to pH levels outside the cell and anaerobic environments.

Once inside the cell, aminoglycosides bind to the decoding region aminoacyl-tRNA site (A site) of the 16S rRNA portion of the 30S component of the prokaryotic ribosome [22,23]. This

causes mistranslation of the mRNA codon and inhibits translocation [24,25]. The highly conserved prokaryotic A site only differs from the eukaryotic ribosomal A site by a single base pair – the prokaryotic RNA has an adenosine at 1408 where the eukaryotic RNA has a guanine [26] – but this small change leads to a large difference in aminoglycoside specificity and is the basis for the clinical utility of the aminoglycosides [26,27]. It is not completely clear which component(s) of the aminoglycoside mechanism contribute to the class's bactericidal action. Induction of mistranslation, inhibition of translocation, accumulation of high drug concentrations in the cell and cell membrane disruption all may play a role.

Unpublished data suggest that the mechanism of action of plazomicin will be similar to that of the other members of the aminoglycoside class. This conclusion is indirectly supported by the bactericidal profile plazomicin shares with other members of the aminoglycosides and the role ribosomal mutation plays in conferring plazomicin resistance to bacteria that are otherwise susceptible (see 'Microbiology' section). Further investigation of this area is warranted.

Mechanisms of resistance

Mechanisms of resistance to aminoglycosides can be subdivided into three categories: ribosomal modification, alteration of

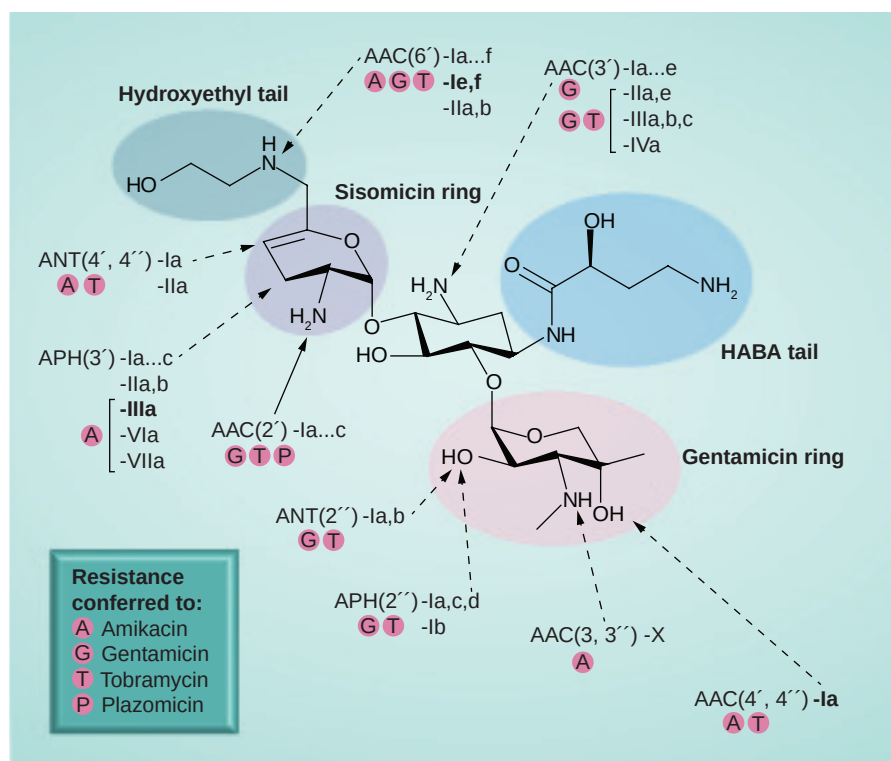


Figure 2. Chemical structure of plazomicin in relation to aminoglycoside-modifying enzyme target sites. Solid arrows indicate that the AME confers resistance against plazomicin and dashed arrows indicate that plazomicin is not a viable target for the AME. Circled letters indicate where resistance to a comparator aminoglycoside is conferred by the AME. The highlighted A ring contains a double bond, which alters the shape of this ring of plazomicin (and the parent, sisomicin) in comparison with other members of the aminoglycoside family. Also highlighted are the hydroxyethyl substituent attached to the nitrogen atom at 6' and the HABA substituent at position 1, identical to the HABA substituent on amikacin.

AAC: Aminoglycoside *N*-acetyltransferase; AME: Aminoglycoside-modifying enzyme; ANT: Aminoglycoside *O*-nucleotidyltransferase; APH: Aminoglycoside *O*-phosphotransferase; HABA: Hydroxy-aminobutyric acid.

uptake/efflux mechanisms and aminoglycoside modifying enzymes [28]. These mechanisms are not mutually exclusive and can coexist in the same bacterial strains [29].

Ribosomal modification confers resistance by reducing aminoglycoside binding affinity to the target site on the ribosome and can take one of two forms: amino acid or rRNA sequence mutations in the ribosome or enzymatic alteration of the ribosome. Mutations of even a single base-pair in the 16S portion of the bacterial ribosome have been shown to confer aminoglycoside resistance to bacteria [30,31]. This mechanism is responsible for streptomycin resistance in strains of *Mycobacterium tuberculosis* [32]. Enzymatic modification of the aminoglycoside target site takes the form of methylation of the nucleotides G1405 or A1408, part of the ribosomal A site [33]. The genes for these enzymes have been discovered on transposons and transferrable plasmids [34,35]. Although target-site modification enzymes were first reported in aminoglycoside producers [36,37], they have now been reported in clinically relevant isolates [38,39] and have become more of a concern [40]. Ribosome mutation has been found to confer broad-spectrum aminoglycoside resistance

[30,40,41], in particular very high resistance against the 4,6-disubstituted deoxystreptamines, including amikacin, gentamicin and tobramycin [31,42]. Enzymatic modification of the target site has also been found to confer a high level of resistance to the 4,6-disubstituted deoxystreptamines [33–35]. Although no susceptibility data have been published regarding the effect of ribosomal mutations against plazomicin, reported data demonstrate that enzymatic modification of the target site increases the minimal inhibitory concentration for plazomicin [11]. The similarity between the effect of ribosome mutation and target-site modification on resistance against current 4,6-disubstituted deoxystreptamines implies ribosomal mutation will also confer resistance to plazomicin.

Uptake and efflux resistance mechanisms inhibit the action of aminoglycosides by preventing a sufficient concentration from accumulating inside the cell. Organisms growing in an anaerobic environment without a functioning electron transport chain [43], and organisms growing in an environment with low pH [16] demonstrate reduced susceptibility to aminoglycosides simply by not providing the conditions required for aminoglycoside uptake (see Mechanism of action section). Efflux mechanisms lower drug concentration in the cytosol by removing drug molecules across the cell membrane (or cell membrane and outer membrane of Gram-

negatives) [44]. A large variety of transmembrane efflux mechanisms, grouped into five families, exist in both Gram-positive and Gram-negative bacteria. Mechanisms that target specific drugs, target specific classes, or can accommodate multiple chemical classes are known in each family. These mechanisms may be encoded chromosomally or on plasmids [44]. Although several of these transmembrane efflux-pump families have members that are able to transport aminoglycosides [45], efflux-based resistance has only been found to confer clinically significant resistance to aminoglycosides in *Pseudomonas aeruginosa* isolates [29,44]. In *P. aeruginosa*, efflux mechanisms contribute to resistance against all legacy aminoglycosides, including amikacin, gentamicin, and tobramycin [44,46]. Results regarding the effect of efflux mechanisms on resistance to plazomicin in *P. aeruginosa* have been mixed [11,12,47].

Aminoglycoside-modifying enzymes are the most widespread and clinically important mechanism of resistance to legacy aminoglycosides [28,48]. Three types of AMEs are known: aminoglycoside *N*-acetyltransferase (AAC), aminoglycoside *O*-nucleotidyltransferase, and aminoglycoside

O-phosphotransferase [8]. These enzymes catalyze covalent bonding of a particular transfer group to a hydroxyl or amino group on the aminoglycoside molecule, as specified in the name. Cofactors are required for the activity of these enzymes: acetyl-CoA for AAC, ATP (the adenylyl group) for aminoglycoside O-nucleotidyltransferase, and ATP (the phosphate group) for aminoglycoside O-phosphotransferase. Bonding of the transfer group to the aminoglycoside reduces the drug's binding affinity for their ribosomal target [49], increasing the drug concentration required for bactericidal action. The genes encoding AMEs may be located on chromosomes but are also widely found on and horizontally transferred by integrons, transposons and plasmids [28]. Under a common nomenclature [8], these enzymes are named by indicating the enzyme type in upper case, the ring carbon to which the targeted functional group is attached and a roman number that specifies the resistance profile. A similar naming scheme is used to name the gene expressing the enzyme, with the enzyme type in lower case and a lower-case letter appended to differentiate multiple genes encoding proteins with identical resistance patterns (FIGURE 2). For example, 'AAC(3)-I' names an *N*-acetyltransferase targeting the amino group attached to carbon 3, and 'aac(3)-Ia' and 'aac(3)-Ib' name two genes capable of expressing that enzyme. An alternate naming scheme, defined as part of a larger plasmid naming scheme, is also in use but not described here [50]. Although no one modifying enzyme provides resistance against the entire aminoglycoside class, all existing aminoglycosides are susceptible to one or more enzyme [48,51]. Amikacin, gentamicin, tobramycin, and sisomicin are all susceptible to several AMEs [48]. By contrast, plazomicin does not function as a substrate for any of the known AMEs except the AAC(2')-I enzyme expressed in *Providencia stuartii* (FIGURE 2). Against organisms resistant to other aminoglycosides due to AMEs, the MICs for plazomicin remain low [11,12,47,52–56].

Microbiology

TABLES 2 & 3 present the *in vitro* activities of plazomicin and comparator aminoglycosides against Gram-negative and Gram-positive pathogens where plazomicin data were available [11,12,47,52–54,57–65]. The values in the tables are modal minimal inhibitory concentration in µg/ml (MIC)₅₀ and MIC₉₀ cited in the literature for each of the aminoglycosides. For plazomicin, the range of reported MICs is also given. All of the studies included in the MIC evaluation adhered to a recognized laboratory standard method (Clinical and Laboratory Standards Institute).

Against Gram-negative enteric bacteria, plazomicin demonstrates more potent *in vitro* activity than amikacin, gentamicin and tobramycin (TABLE 2). Against *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter* spp., *Enterobacter* spp. and *Serratia* spp., the MIC₅₀ and MIC₉₀ for plazomicin were either comparable with or lower than all three comparator aminoglycosides. Plazomicin was less active against *Proteus mirabilis* and indole-positive *Proteus* spp. than it was against other members of the Enterobacteriaceae (TABLE 2). For the nonfermentative Gram-negative bacilli, *Acinetobacter baumannii* and *P. aeruginosa*, plazomicin was less active compared with the Enterobacteriaceae; however, it demonstrated greater activity than amikacin, gentamicin and tobramycin, with twofold- to greater than fourfold lower MIC₉₀ (TABLE 2). Plazomicin also demonstrated potent activity against species of *Staphylococcus* (TABLE 3). Plazomicin demonstrated similar activity to gentamicin (and greater activity than amikacin) against methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible *S. aureus*, coagulase-negative staphylococci and *Staphylococcus saprophyticus* (TABLE 3).

With the exception of AAC(2')-I (reported only in *Providencia stuartii* and some *Mycobacterium* spp. [57]), plazomicin retains activity against both Gram-negative and Gram-positive bacterial strains expressing any of the clinically relevant aminoglycoside-modifying

Table 2. *In vitro* activity[†] of plazomicin and comparator aminoglycosides against Gram-negative aerobes.

Bacteria	Plazomicin			Amikacin		Gentamicin		Tobramycin	
	MIC range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Acinetobacter baumannii</i>	0.12 to >128	8	16	32	>64	64	>64	32	>64
<i>Citrobacter</i> spp.	0.25–4	0.5	1	32	64	>64	>64	ND	ND
<i>Escherichia coli</i>	0.06–16	1	2	2	32	0.5	32	0.5	32
<i>Enterobacter</i> spp.	0.25–64	0.5	1	16	>32	2	>64	32	32
<i>Francisella tularensis</i>	0.03–1	0.5	1	0.25	0.5	ND	ND	ND	ND
<i>Klebsiella pneumoniae</i>	0.12–64	0.5	1	1	32	1	64	32	>64
<i>Proteus mirabilis</i>	1–16	4	8	8	64	32	>64	ND	ND
<i>Proteus</i> , indole-positive	4–16	8	16	8	32	>64	>64	ND	ND
<i>Pseudomonas aeruginosa</i>	0.12–256	8	32	16	>64	8	>64	1	64
<i>Serratia</i> spp.	0.5–4	1	4	8	>64	64	>64	ND	ND
<i>Yersinia pestis</i>	0.12–1	0.5	1	0.5	0.5	ND	ND	ND	ND

[†]MIC₅₀, MIC₉₀ and MIC range values (µg/ml) are modal values derived from a review of all published literature available on plazomicin to date.

MIC: Minimal inhibitory concentration; ND: No data.

Data taken from [11,47,52–54,57–61,63].

Table 3. *In vitro* activity[†] of plazomicin and comparator aminoglycosides against Gram-positive aerobes.

Bacterial species/strain	Plazomicin			Amikacin		Gentamicin		Tobramycin	
	MIC range	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
Methicillin-resistant <i>Staphylococcus aureus</i>	0.12–4	1	2	8	32	0.5	1	≥16	≥16
Methicillin-susceptible <i>Staphylococcus aureus</i>	0.5–2	1	2	4	4	0.5	1	ND	ND
Coagulase-negative Staphylococci	0.5	0.5	0.5	1	4	0.25	>32	ND	ND
<i>Staphylococcus saprophyticus</i>	0.25–1	0.25	0.25	0.5	1	0.12	0.25	ND	ND

[†]MIC₅₀, MIC₉₀ and MIC range values (µg/ml) are modal values derived from a review of all published literature available on plazomicin to date.

MIC: Minimal inhibitory concentration; ND: No data.

Data taken from [11,52,56,60,61].

enzymes (TABLE 4). Aside from AAC(2')-I, no correlation has been reported between the activity of plazomicin and the presence of aminoglycoside-modifying enzymes that impair the activity of amikacin, gentamicin or tobramycin. As with legacy aminoglycosides, the activity of plazomicin is inhibited by ribosomal methyl-transferases (TABLE 4). Like other aminoglycosides, plazomicin activity is reduced by the presence of aminoglycoside efflux pumps (TABLE 4).

Several studies have evaluated the activity of plazomicin against multidrug-resistant Gram-negative bacilli (including *E. coli*, *K. pneumoniae*, *Citrobacter* spp., *Enterobacter* spp., and *Serratia* spp.) expressing extended-spectrum β -lactamase (ESBL) and carbapenemase resistance mechanisms [57,58,61,62,65]. Although resistance mechanisms targeting β -lactam antibiotics would not be expected to alter the activity of aminoglycoside antibiotics, the presence of these resistance phenotypes in Gram-negative bacilli has been associated with concomitant aminoglycoside resistance. This association is due to the frequent presence of aminoglycoside-modifying enzymes in ESBL and carbapenemase-producing clinical isolates [66,67]. With the exception of a case where a carbapenemase was associated with a ribosomal methyl transferase [62], the *in vitro* activity of plazomicin was unchanged in ESBL or carbapenemase-producing organisms. By contrast, the presence of an ESBL or carbapenemase was associated with a general decrease in activity for amikacin, gentamicin and tobramycin with many isolates demonstrating resistance to these agents. Where aminoglycoside-modifying enzymes were reported in conjunction with a β -lactam resistance mechanisms and where a β -lactam resistance mechanism was the only resistance determinant reported, the MIC for plazomicin was most commonly 1–2 µg/ml and did not exceed 4 µg/ml.

Pharmacokinetics

TABLES 5–7 summarize the available pharmacokinetic parameter data for plazomicin, its parent compound sisomicin and comparator aminoglycosides.

Absorption

As a class, aminoglycosides demonstrate poor oral absorption and must be administered parenterally for systemic use [2,68]. The chemical structure of plazomicin provides no reason to suspect that its absorption profile would differ markedly from that of the aminoglycoside class in general. In all reported studies where

plazomicin was administered to human or animal subjects, the administration was intravenous or subcutaneous [64,65,69–73].

Distribution

A population pharmacokinetic analysis [73] was performed on data from a Phase I dose-escalation trial [69] to determine an optimal population pharmacokinetic model for plazomicin. The data fit a three-compartment model with zero-order absorption and first-order distribution which is consistent with that described for other aminoglycosides [2,68]. Steady-state volume of distribution (V_{ss}) for plazomicin was 19.8 l in a population pharmacokinetic model in healthy volunteers [73], 0.20–0.26 ($\pm$ 0.03) l/kg in a Phase I dose-escalation trial [69], and 0.24 $\pm$ 0.04 l/kg in a multidose Phase I trial (TABLE 6) [71]. The reported V_{ss} for plazomicin was consistent with V_{ss} values for comparator aminoglycosides (TABLE 7).

A Phase I dose-escalation study in healthy female and male volunteers from 18 to 55 years of age [101] was performed with plazomicin administered as a single-dose intravenous infusion over 10 min followed by a 7-day washout, and then multiple-dose infusions once daily for 5–10 days (TABLE 5) [69]. Consistent with a linear pharmacokinetic profile, the maximum concentration (C_{max}) and area under the concentration–time curve were dose proportional. Mean C_{max} ranged from 8.1 µg/ml for a 1-mg/kg dose to 144 µg/ml for a 15-mg/kg dose, and the mean area under the curve ranged from 14.5 µg $\times$ h/ml for a 1-mg/kg dose to 246 µg $\times$ h/ml for a 15-mg/kg dose (TABLE 5). The higher C_{max} values compared with those reported for other aminoglycosides with similar V_{ss} values may be explained by the relatively short infusion time of 10 min for plazomicin (TABLE 7).

A second Phase I study in healthy normal weight volunteers (18–44 years) [102] was performed, where subjects received 15 mg/kg of plazomicin as a 10-min infusion once daily for 5 days [71]. Trough concentrations were measured daily, whereas multiple samples for pharmacokinetic analysis were collected after the final dose. The mean pharmacokinetic parameters determined by noncompartmental analysis are shown in TABLE 6. Daily trough values which were only reported in a figure appeared to increase with time, but did not exceed 0.6 µg/ml after 5 days [71].

Plasma protein binding was determined *in vitro* for several animal species via an equilibrium dialysis method [70]. Binding was found to be low, 12% in human plasma (10–18% for other species), and to be independent of plazomicin concentration.

Table 4. *In vitro* activity[†] of plazomicin and comparator aminoglycosides against bacteria expressing specific aminoglycoside-resistance mechanisms.

Species	Resistance phenotype	MIC (µg/ml)			
		Plazomicin	Amikacin	Gentamicin	Tobramycin
<i>Acinetobacter baumannii</i>	Aminoglycoside-susceptible	4	2	1	ND
	ATCC 19606	8	16	16	ND
	AAC(3)-I	16	>64	>64	>64
	AAC(6')-I	32	>64	>64	>64
	ANT(2'')-I	64	>64	>64	>64
	APH(3')-VI	16	>64	>64	>64
<i>Acinetobacter calcoaceticus</i>	AAC(6')-I	2	32	8	ND
<i>Citrobacter freundii</i>	AAC(3)-II	1	4	>16	16
	AAC(6')-I	2	64	1	>16
<i>Enterobacter aerogenes</i>	AAC(3)-II	0.5	1	>64	16
	AAC(6')-I	0.25	32	1	ND
<i>Enterobacter cloacae</i>	AAC(6')-I, ANT(2'')-I	0.5	16	16	16
	AAC(3)-II, APH(3)-I/II	2	8	>16	>16
<i>Escherichia coli</i>	ATCC 25922	0.25	2	0.5	1
	AAC(3)-II	2	4	>64	8
	AAC(3)-IV	1	4	32	ND
	AAC(6')-I	0.25	32	2	32
	ANT(2'')-I	1	4	>64	ND
	APH(3')-I	0.25	0.5	0.25	ND
	AAC(3)-II; ANT(3'')-I	1	4	>32	>32
	AAC(3)-II; AAC(6')-I	2	8	>32	>32
	AAC(3)-II, APH(3)-I/II	1	4	>16	>16
	AAC(6')-I; ANT(3'')-I	1	>32	4	>32
	AAC(6')-Ib; ANT(3')-I	4	>32	>32	>32
	ArmA methylase	>64	>64	>64	ND
	Permeability/efflux	8	32	4	8
<i>Klebsiella oxytoca</i>	AAC(3)-II	0.5	4	>16	16
<i>Klebsiella pneumoniae</i>	ATCC 10031	0.25	0.5	0.125	ND
	AKPN 1073	0.5	>32	>64	ND
	AAC(3)-II	0.5	8	>16	>16
	AAC(6')-I	1	16	4	16
	ANT(2'')-I	1	4	>64	ND
	ANT(3'')-I	2	>32	>32	>32
	AAC(3)-II, AAC(6')-I	0.5–1	>32	>32	>32
	AAC(6')-I, ANT(2'')-I	0.5	32	32	>32
	AAC(6')-I, ANT(3'')-I	1	32	16	≥64
	ANT(2'')-I, APH(3')-I/II	1	2	16	>16
	AAC(3)-IV, AAC(6')-I, APH(3')-I/II	0.5	32	>16	>16
	AAC(6')-I, ANT(2'')-I, ANT(3'')-I	0.25	16	8	32
	AAC(6')-I, ANT(3'')-I, APH(3')-I	2	>32	>32	>32
	AAC(6')-I, ANT(3'')-I, ANT(2'')-I, AAC(6')-33	0.25	32	16	>32

AAC: Aminoglycoside *N*-acetyltransferase; ANT: Aminoglycoside *O*-Nucleotidyltransferase; APH: Aminoglycoside *O*-phosphotransferase; MIC: Minimal inhibitory concentration; ND: No data.

[†]Data taken from [11,53,54,56–59,74].

Table 4. *In vitro* activity[†] of plazomicin and comparator aminoglycosides against bacteria expressing specific aminoglycoside-resistance mechanisms (cont.).

Species	Resistance phenotype	MIC (µg/ml)			
		Plazomicin	Amikacin	Gentamicin	Tobramycin
<i>Morganella morganii</i>	AAC(3)-II	4	16	>16	>16
	AAC(3)-II, APH(3)-I/II	4	4	>16	16
<i>Pseudomonas aeruginosa</i>	ATCC 27853	2	2	1	ND
	AAC(3)-I	16	>64	>64	>64
	AAC(6')-I	>64	>64	>64	>64
	AAC(6')-II	2	4	32	ND
	Wild-type efflux	4	4	1	ND
	Δ efflux	0.125	0.5	0.125	ND
	MexXY upregulated	8	4	2	ND
<i>Proteus mirabilis</i>	AAC(3)-II	4	4	>16	16
	ANT(2'')-I	8	4	16	8
<i>Providencia stuartii</i>	AAC(2')-I	>64	8	>64	ND
<i>Serratia marcescens</i>	AAC(3)-I, AAC(6')-I	1	16	>16	>16
	ANT(2''), AAC(6'')	2	8	4	ND
<i>Staphylococcus aureus</i>	ATCC 29213	1	4	0.5	ND
	ANT(4')-I	1	16	0.5	>16
	APH(3')-III	4	32	1	1
	APH(2')-I + AAC(6')-I	2	64	>64	ND
	AAC(6')-I + APH(2'')-I, ANT(4')-I	1	16	>16	>16
	AAC(6')-I + APH(2'')-I, APH(3')-III	1	>64	>16	>16
	AAC(6')-I + APH(2'')-I, APH(3')-III, ANT(4')-Ia	4	64	16	>16

AAC: Aminoglycoside *N*-acetyltransferase; ANT: Aminoglycoside *O*-Nucleotidyltransferase; APH: Aminoglycoside *O*-phosphotransferase; MIC: Minimal inhibitory concentration; ND: No data.

[†]Data taken from [11,53,54,56–59,74].

Higher plasma protein binding of 25% was reported in one study [73]; however, the method of determination was not described.

Metabolism

Plazomicin is largely unmetabolized in the body. In a Phase I trial, renal clearance of unmetabolized plazomicin was found to be 86.9% [73]. In an *in vitro* study, plazomicin was found to be unaffected by hepatocytes and liver microsomes [70]. These results

are comparable with results reported for the aminoglycoside class in general [2,68].

Elimination

As stated above, plazomicin is primarily eliminated unchanged in the urine [73] with renal clearance (4.19 l/h) accounting for 87% of total clearance (4.81 l/h). Compartmental analysis determined α -, β - and γ -phase half-lives ($t_{1/2}$) of 0.22, 2.33 and 18.9 h, respectively. The β $t_{1/2}$ was reported to best represent

Table 5. Plazomicin pharmacokinetics in normal volunteers.

Variables measured	Plazomicin dose ^{††}				
	1 mg/kg × 1	4 mg/kg q24 h	7 mg/kg q24 h	11 mg/kg q24 h	15 mg/kg q24 h
Duration (days)	N/A	10	10	5	3
C _{max} (µg/ml)	8.1 ± 0.8	43.1 ± 6.5	45.5 ± 6.8	114 ± 26.5	144 ± 45.1
AUC [§] (µg × h/ml)	14.5 ± 1.2	64.8 ± 8.8	88.8 ± 11.2	181 ± 35.6	246 ± 39.2

[†]Intravenous infusion over 10 min.

^{††}Pharmacokinetics based on final dose in multiple-dose studies.

[§]AUC_{0–inf} for single dose and AUC_{0–24} for multiple doses.

q24 h: Every 24 h.

Data taken from [69].

the effective half-life of plazomicin, and this value corresponds well with the known values for the comparator aminoglycosides (TABLE 7). In Phase I trials, plazomicin $t_{1/2}$ was reported between 3.1 h and 4.0 h [69,71].

Pharmacodynamics

In time-kill studies performed on nine *E. coli* clinical isolates [53], plazomicin was bactericidal with $>3 \log_{10}$ reduction in colony-forming units for seven isolates at four-times the MIC. In the same study, plazomicin at four-times the MIC was bactericidal against 15 *K. pneumoniae* clinical isolates studied.

Time-kill studies were also performed on bacterial strains expressing a single aminoglycoside-modifying enzyme phenotype, including an *E. coli* with AAC(3)-IV, *E. aerogenes* with AAC(3)-IIa, *K. pneumoniae* with ANT(2'')-Ia, *S. aureus* with fused APH(2')-I + AAC(6')-I, and one each of *E. coli*, *E. aerogenes* and *K. pneumoniae* with AAC(6')-I [74]. Plazomicin was bactericidal for all isolates at concentrations equivalent to 2-, 4-, 8-, 16- and 32-fold the MIC.

Regrowth was observed in the time-kill studies with concentrations four-times the MIC [53,74]. In one study, plazomicin MICs after regrowth of two isolates were eight and 16-fold higher than pre-regrowth values [53]. These increases were not associated with the AMEs (aac(3)-IIa and ant(3'')-Ia); however, the stability of these changes in MIC were not investigated. One of the isolates had a fourfold reduction in postregrowth MIC with the introduction of an efflux-pump inhibitor. In the other study, MICs of all aminoglycosides (plazomicin, amikacin, arbekacin and gentamicin) for colonies showing regrowth after exposure to plazomicin were four- or eightfold higher than pre-exposure MICs [74]. Based on the uniform increase in MICs against all tested aminoglycosides, this increase was attributed to efflux pump upregulation, although the existence of efflux-pump genes was not confirmed. This type of inducible, adaptive aminoglycoside resistance is well known with legacy aminoglycosides and has been described with various organisms including *P. aeruginosa*, *E. coli* and *S. aureus* [75]. Exposure to one aminoglycoside leads to resistance to all members of the class. The resistance is reversible with activity of the aminoglycoside restored after variable periods following removal of the inducing agent.

Table 6. Plazomicin pharmacokinetics in healthy volunteers receiving 15 mg/kg once daily for 5 days.

Parameter	Mean value $\pm$ SD
C_{max} (μ g/ml) [†]	113 $\pm$ 17
AUC _{0–24} (μ g $\times$ h/ml)	239 $\pm$ 45
C_{min} (μ g/ml)	0.43 $\pm$ 0.14
$t_{1/2}$ (h)	4.0 $\pm$ 1.0
CL _{ss} (l/h/kg)	0.065 $\pm$ 0.011
V _{ss} (l/kg)	0.241 $\pm$ 0.039

[†]Intravenous infusion over 10 min.
AUC: Area under the curve; CL_{ss}: Clearance at steady state; C_{max} : Maximum concentration; C_{min} : Minimum concentration; SD: Standard deviation;
 $t_{1/2}$: Half-life; V_{ss}: Steady-state volume of distribution.
Data taken from [73].

In vivo studies measuring survival as a function of plazomicin concentrations were performed using a murine-septicemia model comparing plazomicin, amikacin and gentamicin [65]. Septicemia was induced in a control and treatment group of ten CD-1 strain mice via intraperitoneal injection of *E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853 at twice the 90–100% lethal dose (LD). Antibiotic doses or vehicle (control) were injected subcutaneously 1 h later and mortality was monitored for 7 days. Exact antibiotic doses were not reported. The control groups demonstrated 100% mortality, whereas plazomicin efficacy was dose-dependent with 100% survival at doses ≥ 1.6 mg/kg for *E. coli* (MIC of 1) and >16 mg/kg for *P. aeruginosa* (MIC of 2). Against *E. coli*, plazomicin demonstrated efficacy similar to that of gentamicin, while 100% survival was observed for amikacin only at the highest dose tested. Although gentamicin was more effective than plazomicin at lower doses against *P. aeruginosa*, plazomicin produced 100% survival when dosed at identical levels to gentamicin. Amikacin showed identical efficacy to plazomicin at lower doses but failed to produce 100% survival at any dose. effective dose₅₀/MIC values were 0.6 for plazomicin, 0.6 for amikacin and 0.7 for gentamicin versus *E. coli*, and 4.2 for plazomicin, 5.2 for gentamicin and 11.2 for amikacin versus *P. aeruginosa*.

The same authors evaluated the efficacy of plazomicin compared with a variety of antibiotics, including gentamicin in

Table 7. Pharmacokinetic parameters for plazomicin compared with other aminoglycosides.

Parameter	Plazomicin	Sisomicin	Amikacin	Gentamicin	Tobramycin
Dose (mg/kg) [†]	15	1	7.5	1	1
C_{max} (μ g/ml)	144 $\pm$ 45.1	4.66 $\pm$ 1.24	37.5 $\pm$ 4.9	3.85 $\pm$ 0.67	4.40 $\pm$ 1.18
AUC _{0–inf} (μ g $\times$ h/ml)	246 $\pm$ 39.2	19.7 $\pm$ 5.8	140.4 $\pm$ 24.3	14.6 $\pm$ 2.7	18.1 $\pm$ 4.6
$t_{1/2}$ (β) (h)	4.0 $\pm$ 1.0	2.03 $\pm$ 0.45	1.90 $\pm$ 0.41	1.6 $\pm$ 0.4	2.01 $\pm$ 0.30
Volume of distribution (l/kg)	0.20–0.26 ($\pm$ 0.03)	0.17 $\pm$ 0.07	0.18 $\pm$ 0.02	0.22 $\pm$ 0.05	0.18 $\pm$ 0.05
Clearance (l/h/kg)	0.080 $\pm$ 0.010	0.084 $\pm$ 0.054	0.095 $\pm$ 0.023	0.136 $\pm$ 0.063	0.092 $\pm$ 0.019
Protein binding (%)	12, 25	<10	<10	<10	<10

[†]Intravenous infusion over 10 min for plazomicin, and 1 h for sisomicin, amikacin, gentamicin and tobramycin.

AUC: Area under the curve; C_{max} : Maximum concentration; $t_{1/2}$: Half-life.

Data taken from [68,69,71,73,77,78].

a murine neutropenic thigh model [65]. Male CD-1 mice were rendered neutropenic and inoculated in the right thigh with an aminoglycoside-susceptible strain (*K. pneumoniae* ATCC 43816, *E. coli* ATCC 25922), a multidrug-resistant strain (*K. pneumoniae* AKPN 1073, *E. coli* AECO 1003), a *K. pneumoniae*-carbapenemase producing strain (*K. pneumoniae* AKPN 1109, *S. marcescens* ASMA 1030) or MRSA strain (ATCC 33591) at levels previously determined to be unlikely to produce mortality. Antibiotic or vehicle (control) was administered at 2 and 14 h, and the mean log CFU/g of thigh was determined at 26 h after bacterial inoculation. The antibiotic dose required to produce bacteriostasis was then calculated. Plazomicin had dose-dependent efficacy against the two aminoglycoside-susceptible strains with a static dose of 11 mg/kg/day for *E. coli* ATCC 25922 and 7.8 mg/kg/day for *K. pneumoniae* ATCC 43816 (static dose/MIC of 11 and 16, respectively) comparable with gentamicin at 7.8 mg/kg/day and 15 mg/kg/day (static dose/MIC of 16 and 30), respectively. Plazomicin retained efficacy against both multidrug resistant strains with static doses of 25 mg/kg/day for *E. coli* AECO 1003 and 12 mg/kg/day for *K. pneumoniae* AKPN 1073 (static dose/MICs of 25 and 24), while gentamicin up to 64 mg/kg/day was unable to prevent bacterial growth. Plazomicin also retained efficacy against both *K. pneumoniae*-carbapenemase-producing strains with static doses of 64 mg/kg/day for *K. pneumoniae* AKPN 1109 (static dose/MIC of 110) and 37 mg/kg/day for *S. marcescens* ASMA 1030 (static dose/MIC of 37), while gentamicin was again ineffective. Plazomicin and gentamicin showed similar efficacy against the MRSA ATCC 33591 strain with static doses of 54 mg/kg/day (static dose/MIC of 14) and 52 mg/kg/day (static dose/MIC of 13).

In vitro synergy testing between plazomicin and daptomycin, ceftobiprole and linezolid was evaluated for 47 isolates of *S. aureus* with a broad range of resistance phenotypes, including hospital-acquired MRSA, Pantone-Valentine leukocidin positive community-acquired MRSA, Pantone-Valentine leukocidin negative community-acquired MRSA, heteroresistant vancomycin-intermediate *S. aureus*, vancomycin-intermediate *S. aureus* and vancomycin-resistant *S. aureus* [76]. Time-kill assays were performed for each drug alone at concentrations equivalent to an eighth, a quarter, a half, and one-, two- and four-times the MIC. Synergy time-kill assays were performed over 24 h using plazomicin with one of the other agents at a half or a quarter of the MIC. Synergy was defined as a 2 log₁₀ or greater reduction in CFU/ml count compared with the most active drug (and at least a 2 log₁₀ reduction in CFU/ml count compared with the initial inoculation), antagonism was a 2 log₁₀ or greater increase in CFU/ml count, and indifference as a reduction or increase in CFU/ml count less than 2 log₁₀. Synergy was observed for plazomicin and daptomycin in 91% of isolates, for plazomicin and ceftobiprole in 36% of isolates, and for plazomicin and linezolid in 13% of isolates. At 24 h, antagonism was only seen for plazomicin and linezolid in 4% of isolates.

An *in vitro* synergy time-kill study of plazomicin with cefepime, doripenem, imipenem and piperacillin-tazobactam was performed

against 25 clinical isolates of *P. aeruginosa* with a range of phenotypes [63]. Definitions of synergy, indifference and antagonism as well as the method of determining synergy were identical to those described for the previous study. At 24 h, synergy was found for plazomicin and cefepime in 80% of isolates, for plazomicin and doripenem in 80% of isolates, for plazomicin and imipenem in 68% of isolates, and for plazomicin and piperacillin-tazobactam in 92% of isolates. No antagonism was observed for the combinations studied.

Animal efficacy

In a study assessing the efficacy of plazomicin against *Yersinia pestis* and *Francisella tularensis* infection in comparison with gentamicin, female BALB/c mice (ten per cohort) were inoculated with aerosol doses of the strain *Y. pestis* CO92 (25 × LD₅₀) or *F. tularensis* Schu S4 (100 × LD₅₀) [59]. Antibiotic treatment commenced 24 h after bacterial inoculation. For *Y. pestis* infection plazomicin was dosed at 48 mg/kg intravenously (iv.) once per day for 3 or 5 days, and for *F. tularensis* infection plazomicin was dosed either 48 mg/kg iv. once per day for 14 days, or 60 mg/kg twice per day for 5, 7 or 10 days. Gentamicin was dosed at 48 mg/kg iv. for 3 or 5 days for *Y. pestis* and for 14 days for *F. tularensis*. Untreated control groups demonstrated 100% mortality by day 3 for *Y. pestis* and day 5 for *F. tularensis*. All dosing regimens in the *Y. pestis* cohorts produced significantly increased survival ($p < 0.05$) compared with the control group (70% survival for plazomicin 3 days, 90% for plazomicin 5 days and gentamicin 3 days and 100% for gentamicin 5 days). In the *F. tularensis* cohorts, the 48-mg/kg/day and 5-day 60-mg/kg/day iv. plazomicin regimens delayed but did not prevent mortality. The 7-, 10- and 14-day plazomicin regimens and the gentamicin regimen all significantly improved mortality ($p < 0.05$) compared with the control group (90% survival for 7-day plazomicin and 100% survival for the rest).

A murine urinary tract infection efficacy model comparing plazomicin, gentamicin and levofloxacin was performed where female C3H/HeJ mice (with diuresis induced 6 days before the beginning of and maintained during the course of the study) were inoculated transurethrally with 8.8 log₁₀ CFUs of *E. coli* ATCC 700336 [64]. All three agents were administered subcutaneously twice per day with doses ranging from 0.125 to 8 mg/kg for plazomicin, and 0.125 to 2 mg/kg for gentamicin, and with doses of 0.125 and 0.5 mg/kg for levofloxacin. Treatment began 4 days after bacterial inoculation and lasted for 3 days. Urine, bladders and kidneys were collected 18 h after the final dose. Compared with controls, a reduction in CFUs was observed for all doses of plazomicin (2.4–4.5, 0.4–4.1 and 0.2–4.5 mean log₁₀ CFU reduction in the kidneys, bladder and urine, respectively) gentamicin (3.7–4.4, 2.1–2.5 and 0.8–3.6 mean log₁₀ CFU reduction in the kidneys, bladder and urine, respectively), and levofloxacin (2.1–3.7, 1.5–2.9 and 0.5 mean log₁₀ CFU reduction in the kidneys, bladder and urine, respectively); however, no statistical differences between agents were reported.

Clinical trials

Plazomicin clinical efficacy data are limited to a single Phase II trial, which is currently underway [103]. This is a multicenter, multinational, randomized, double-blind, comparator, controlled study in patients with complicated urinary tract infection and acute pyelonephritis including cases with concurrent bacteremia. Plazomicin dosed iv. 15 mg/kg once daily for 5 days is being compared with levofloxacin 750 mg also administered intravenously for 5 days. This study is currently enrolling patients with an expected completion date in early 2012.

Adverse effects

Aminoglycosides as a class are known for their ototoxic and nephrotoxic adverse effects [5]. In a Phase I dose-escalation study [74,101], the safety of plazomicin was assessed in 39 healthy volunteers divided into five groups (4, 7, 11 or 15 mg/kg plazomicin, placebo control) [69]. A single test dose of 4, 7, 11 or 15 mg/kg was administered, a 7-day washout period followed, then the same dosage was administered once daily for 10, 5 or 3 days, respectively [69]. Renal safety was monitored by daily testing of serum BUN and creatinine concentrations, creatinine clearance measurement by 24-h urine collection, and glomerular filtration rate measured by iothalamate clearance. No evidence of nephrotoxicity was found during the study. To assess cochlear effects, audiometry testing with bone conduction over 2–20 kHz and daily otoacoustic emission testing was performed. Vestibular function was monitored using electronystagmography and daily dynamic visual acuity tests. Cochlear and vestibular function remained normal in test subjects. Tinnitus was reported by one subject in the 11-mg/kg group and one in the 15-mg/kg group, but both events were reported before the multidose phase of the trial commenced and were determined to not be drug related. Both subjects were found to have normal cochlear and vestibular function. Dizziness was reported by one or two subjects in each cohort but each reported that the event resolved rapidly with no lasting effects. Treatment emergent adverse events were reported across all dose cohorts including the placebo group; all events were mild or moderate.

In another Phase I study, eight healthy volunteers received iv. 15 mg/kg plazomicin or placebo once per day for 5 days [75,102]. BUN and serum creatinine measurements were performed daily during the study to monitor renal function. Cochlear and vestibular function was monitored using four types of tests (pure tone audiometry, otoacoustic emissions testing, electronystagmography, and modified Romberg testing), assessed at baseline (predosing), daily during the dosing period for otoacoustic emissions testing and modified Romberg testing, and at 1 week after dosing for pure tone audiometry and electronystagmography. Subjects were monitored for renal and ototoxic effects for 6 months. Drug-related treatment emergent events were reported in all subjects in both cohorts and were mild to moderate in the drug group and mild in the placebo group. All events were reported as transient with no lasting effects. No evidence of cochlear/vestibular toxicity or renal toxicity was observed during the drug-administration period or the subsequent 6-month

monitoring period. Electrocardiograms were performed 10 and 30 min after the first dose in the series. Cardiac monitoring showed no QT interval increase greater or equal to 30 s and no QTc in excess of 450 ms.

The ototoxicity potential of plazomicin was compared with gentamicin and amikacin in a guinea pig model [72]. Plazomicin (8, 30 and 80 mg/kg/day), gentamicin (25, 50, 80 and 100 mg/kg/day), amikacin (75, 150 and 300 mg/kg/day) and a control were administered subcutaneously once daily for 14 days. Hearing loss was assessed via auditory brainstem response with threshold values measured at 4, 10 and 20 kHz before the dose series and again 14 days after administration of the final dose. Auditory brainstem response testing showed significant hearing loss with gentamicin 80 mg/kg at 4 kHz ($p < 0.05$), 10 kHz ($p < 0.001$) and 20 kHz ($p < 0.001$) gentamicin 100 mg/kg at 20 kHz ($p < 0.001$) amikacin 150 mg/kg at 20 kHz ($p < 0.05$) and amikacin 300 mg/kg at 4 kHz ($p < 0.001$), 10 kHz ($p < 0.001$) and 20 kHz ($p < 0.001$). By contrast, no significant hearing loss was reported with any dose of plazomicin. At the end of the study period, hair-cell damage was assessed in the dissected cochleae of each animal via microscopic histological examination. Animals receiving gentamicin, and animals receiving amikacin, displayed aminoglycoside dose-related hair-cell loss with and without associated hearing loss. In contrast, there were no reports of aminoglycoside associated hair-cell loss in the plazomicin group. Mild hair-cell loss not consistent with expected aminoglycoside-induced cell damage was observed at 30 and 80 mg/kg doses of plazomicin but was attributed to the animal model and not distinguishable from hair-cell loss in the control group.

At this time, animal and Phase I studies with plazomicin suggest no oto- or nephrotoxicity; however, further clinical studies are required to fully elucidate the adverse effect profile of plazomicin.

Drug interactions

Similar to other aminoglycosides, plazomicin is primarily eliminated renally with minimal hepatic clearance [69]. In an *in vitro* study [70], human cytochrome P450 (CYP450) isoforms 1A2, 2C9, 2C19, 2D6 and 3A4 and fluorescent probe substrates were incubated in the presence of 25 μ M plazomicin and fluorescent inhibition was measured. Plazomicin was found to have no inhibitory effect on the examined cytochrome enzymes and is thus not expected to interact with drugs that are CYP450 substrates, inhibitors or inducers.

Conclusion

Plazomicin is a next-generation aminoglycoside developed to counteract all clinically relevant aminoglycoside modifying enzymes (the most common resistance mechanism) that reduce the utility of the aminoglycoside class. Plazomicin is semisynthetically derived from sisomicin, and this chemical structure confers on it the ability to evade the activity of all known aminoglycoside-modifying enzyme families, except one (AAC(2')-I). Plazomicin demonstrates excellent *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms, with *in vitro* activity comparable with gentamicin, amikacin

and tobramycin against aminoglycoside-susceptible isolates and much greater activity versus comparator aminoglycosides versus aminoglycoside-resistant isolates. Pharmacokinetic properties of plazomicin are predictable and linear, with a profile similar to other members of the aminoglycoside family. Plazomicin demonstrates dose-dependent bactericidal activity in animal models and efficacy similar to or better than aminoglycoside comparators. Excellent *in vitro* synergy is observed between plazomicin and daptomycin, as well as plazomicin and piperacillin-tazobactam; synergy with plazomicin also occurs with cefepime and with doripenem. Participants in Phase I studies reported only transient, mild-to-moderate adverse effects from plazomicin. Although animal model data assessing the nephrotoxicity and ototoxicity of plazomicin showed promising results, more research is needed in this area.

Expert commentary & five-year view

Clinical use of the legacy aminoglycosides is on the rise recently in response to increasingly limited options for the treatment of multidrug-resistant bacteria; however, this increase in use has been limited by bacterial resistance and the potential, even with the advent of extended-interval dosing, for severe adverse effects. Plazomicin retains activity against important clinical isolates including *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *A. baumannii* and *S. aureus* in the presence of all clinically relevant AMEs, the most common mechanism of resistance against the aminoglycosides. In the future, plazomicin may be able to fill the role in antibacterial therapy currently occupied by other aminoglycosides (e.g., in urinary tract infections, pneumonia, bacteremia and intraabdominal infections, primarily in combination with other agents) where resistance to other aminoglycosides is known or suspected, or where severe infection dictates empirical treatment with maximum chance for success. If initial results showing lack of nephrotoxicity and ototoxicity from plazomicin are verified, or if toxicity due to plazomicin is simply found to be significantly lower than that of the other

aminoglycosides, plazomicin may become the aminoglycoside of choice. Widespread use of an aminoglycoside not susceptible to aminoglycoside-modifying enzymes (i.e., plazomicin) may increase selective pressure for the acquisition and retention of ribosome methyl transferase enzymes (currently of limited clinical significance), but if the pattern of AME dissemination is predictive of that of the methylating enzymes, this would only become a major concern over a long period of time. The pharmacokinetics of plazomicin in healthy subjects are sufficiently similar to the other aminoglycosides to allow clinicians to adapt current aminoglycoside dosing and monitoring practices for use with plazomicin. The pharmacokinetics of plazomicin remain to be determined for various types of patients including those with various illnesses, elderly patients, obese individuals, children and neonates. Further studies are also required in the areas of drug interaction and *in vivo* synergy. Plazomicin is still in the early stages of FDA testing, and the activity profile and details of the toxicity profile of plazomicin still need to be verified in large-enrollment clinical trials. Results from a Phase II trial comparing plazomicin to levofloxacin for the treatment of complicated urinary tract infections including pyelonephritis (expected completion date: early 2012) are eagerly anticipated. Pending positive results from needed clinical studies and large-scale clinical trials, plazomicin has promise to be a welcome addition to the antibacterial armamentarium in light of increasing bacterial resistance and the lack of new agents with novel mechanisms.

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Key issues

- Plazomicin is a next-generation aminoglycoside synthetically derived from sisomicin by appending a hydroxy-aminobutyric acid substituent at position 1 and a hydroxyethyl substituent at position 6'.
- Plazomicin inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity.
- Plazomicin demonstrates activity against both Gram-negative and Gram-positive organisms, including isolates harboring any of the clinically relevant aminoglycoside-modifying enzymes.
- Plazomicin demonstrates *in vitro* synergy when combined with daptomycin or ceftobiprole versus methicillin-resistant *Staphylococcus aureus*, heteroresistant vancomycin-intermediate *S. aureus*, vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus* and against *Pseudomonas aeruginosa* when combined with cefepime, doripenem, imipenem or piperacillin-tazobactam.
- After intravenous administration of plazomicin to humans at a dose of 15 mg/kg, the maximum concentration was 113 µg/ml, the area under the curve₀₋₂₄ was 239 h·µg/ml, the half-life was 4.0 h and the steady-state volume of distribution was 0.24 l/kg.
- Results from a Phase II randomized, double-blind study in patients with complicated urinary tract infection and acute pyelonephritis including cases with concurrent bacteremia comparing plazomicin 15 mg/kg intravenously once daily for 5 days to levofloxacin 750 mg intravenously for 5 days are anticipated in 2012.
- Human studies to date have not reported nephrotoxicity or ototoxicity, and lack of ototoxicity has been reported in the guinea pig model.
- Plazomicin may become a welcomed addition to the antibacterial armamentarium pending positive results from large-scale clinical trials and other required clinical studies.

References

Reference annotations

• Of interest

•• Of considerable interest

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