Plazomicin Shows Promise as New Aminoglycoside Antibiotic

CHICAGO – Plazomicin, an investigational aminoglycoside previously know as ACHN-490, is a promising new agent for treating gram-negative infections, according to George G. Zhanel, Ph.D.

"There's something exciting about working with an agent that's a modification of something you know a lot about, because you think you'll be able to predict some of the problems," Dr. Zhanel said at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC).

"But let's be clear: We have no human efficacy and safety data. We need the data to see that this agent works for aminoglycoside-resistant infections, and we need to see that data on nephrotoxicity and ototoxicity. We need to be monitoring the spread of rRNA methylases."

Dr. George G. Zhanel

Aminoglycosides have well-described pharmacokinetics and proven efficacy alone and in combination with other agents, "but you are not using them very much because there is worldwide resistance, primarily due to aminoglycoside-modifying enzymes but also well-described nephrotoxicity and ototoxicity," said Dr. Zhanel of the department of medical microbiology and infectious diseases at the University of Manitoba, Winnipeg. "However, clearly there is a need for these agents and other new antimicrobials."

In the past decade, many researchers have been working to further develop aminoglycosides, including arbekacin analogues, gentamicin analogues, isepamicin analogues, streptomycin analogues, and plazomicin, which is an analogue of sisomicin and is manufactured by San Francisco–based Achaogen. A recent study from the United Kingdom found that plazomicin MIC_{90} (minimum inhibitory concentration required to inhibit the growth of 90% of organisms) was less than or equal to 2 mg/L against carbapenem-resistant Enterobacteriaceae (J. Antimicrob. Chemother. 2011;66:48-53). The researchers also found that plazomicin was 16 times more active than amikacin and 8 times more active than gentamicin. "Importantly, none of the aminoglycosides, including plazomicin, were active against NDM-carrying strains with both metallo-beta-lactamase and methyltransferase," said Dr. Zhanel, who is director of the Canadian

Antimicrobial Resistance Alliance.

Plazomicin demonstrates synergy with other agents, he continued. In vitro time-kill studies of methicillin-resistant *Staphylococcus aureus* demonstrated 91.5% efficacy for plazomicin plus daptomycin, compared with 36.2% for plazomicin plus ceftobiprole and 12.8% for plazomicin plus linezolid (Antimicrob. Agents Chemother. 2010;54:2258-61).

In vitro time-kill studies of *Pseudomonas aeruginosa* demonstrated 92% synergy for plazomicin plus piperacillin/tazobactam, compared with 80% for plazomicin plus cefepime and 80% for plazomicin plus doripenem (Antimicrob. Agents Chemother. 2011;55:2463-5).

In a poster presented at the 2010 ICAAC meeting, researchers presented findings from a phase I pharmacokinetics and safety study of plazomicin administered to eight subjects at a dose of 15 mg/kg IV once daily for 5 days. The study, sponsored by Achaogen, found that the mean C_{max} was 113 mcg/mL, the mean AUC (0-24 hr) was 239 mcg/mL per hour, the mean C_{min} was 0.4 mcg/mL, and the mean half-life was 3 hours. There was no evidence of nephrotoxicity or ototoxicity, and all adverse events were reported as mild to moderate.

Dr. Zhanel said that a multicenter, randomized phase II trial of plazomicin for complicated urinary tract infections and acute pyelonephritis is underway. The comparator drug will be levofloxacin.

"Clearly, plazomicin is a promising new agent," Dr. Zhanel said at the meeting, which was sponsored by the American Society for Microbiology. "If future studies show that it is effective against aminoglycoside-susceptible and -resistant infections, and/or if the agent shows nephrotoxicity and/or ototoxicity less than the current aminoglycosides, you may want to use this compound in select cases as your aminoglycoside of choice."

Dr. Zhanel disclosed that he has received research funding from the National Institutes of Health and numerous other sources, including Achaogen and other pharmaceutical companies.