Plazomicin for complicated urinary tract infection

NIHR HSRIC ID: 9787

Lay summary

Serious infections caused by Gram-negative bacteria are becoming increasingly resistant to commonly prescribed antibiotics and are a serious global concern. If licensed, plazomicin will offer a treatment option for those patients who have a complicated urinary tract infection or acute pyelonephritis caused by multi-drug resistant Gram-negative bacteria, a group who currently have few effective and well tolerated therapies available.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Complicated urinary tract infection (cUTI), including acute pyelonephritis (AP); infection caused by resistant Gram-negative bacterial pathogens, including 3rd generation cephalosporin and carbapenem-resistant enterobacteriaceae (CRE) – first line, followed by appropriate, optional oral step down therapy.

TECHNOLOGY

DESCRIPTION

Plazomicin (ACHN-490) is a next-generation broad-spectrum aminoglycoside antibiotic. Aminoglycosides kill bacteria by inhibiting protein synthesis through binding to the bacterial 16S rRNA, and by disrupting the integrity of bacterial cell membranes. These compounds have been shown to be effective against difficult to treat Gram-negative infections due to their rapid bactericidal activity, predictable pharmacokinetics, excellent solubility, and safety. Plazomicin is intended for the treatment of cUTI or AP caused by resistant Gram-negative bacterial pathogens, including 3rd generation cephalosporin and carbapenem-resistant Enterobacteriaceae (CRE). In a recent phase III clinical trial, plazomicin is administered by intravenous (IV) infusion at 15mg/kg once daily for 5 consecutive days followed by optional oral step-down therapy.

Plazomicin does not currently have Marketing Authorisation in the EU for any indication.

Plazomicin is also currently in phase III clinical trials for bloodstream infections, hospital-acquired pneumonia, and ventilator associated pneumonia (VAP) due to CRE.

INNOVATION and/or ADVANTAGES

If licensed, plazomicin will offer an additional treatment option for patients with cUTI or AP caused by resistant Gram-negative bacterial pathogens, including 3rd generation cephalosporin and carbapenem-resistant Enterobacteriaceae (CRE), a group who currently have few well-tolerated effective therapies available.

DEVELOPER

Achaogen Inc.

AVAILABILITY, LAUNCH OR MARKETING

Currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Urinary tract infections (UTI) are caused by the presence and multiplication of microorganisms in the urinary tract. Microorganisms can reach the urinary tract by haematogenous or lymphatic spread, but there is abundant clinical and experimental evidence showing that the ascent of microorganisms from the urethra is the most common
pathway for infection, especially organisms of enteric origin (e.g. *Escherichia coli* and other enterobacteriaceae). This explains the greater frequency of UTI in women than in men and the increased risk of infection following bladder catheterisation or instrumentation.

UTI can result in several clinical syndromes, including acute and chronic pyelonephritis, cystitis, urethritis, epididymitis and prostatitis. Complicated urinary tract infections (cUTI) are defined as a clinical syndrome characterised by pyuria and a documented microbial pathogen on culture of urine or blood, accompanied by local and systemic signs and symptoms, including fever, chills, malaise, flank pain, back pain, and/or costo-vertebral angle pain or tenderness, that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterisation. Usually, one or more of the following conditions that increase the risk of developing a cUTI are present: indwelling urinary catheter, 100ml or more of residual urine after voiding (neurogenic bladder), obstructive uropathy (nephrolithiasis, fibrosis), azotemia caused by intrinsic renal disease, and urinary retention (including retention caused by benign prostatic hypertrophy). Patients with pyelonephritis, regardless of underlying abnormalities of the urinary tract, are considered a subset of patients with cUTI.

Enterobacteriaceae are the most frequently encountered pathogen in UTI and are also common causes of intra-abdominal and bloodstream infections. These are a large family of bacteria that usually live harmlessly in the gut and include species such as *Escherichia coli*, Klebsiella spp. and Enterobacter spp. In addition to Enterobacteriaceae, a broad range of bacteria can cause cUTI. The spectrum is much larger than found in uncomplicated UTIs, and the causative organisms are more likely to be resistant to antimicrobials, especially in cases of treatment-resistant infection.

Carbapenems are a valuable family of antibiotics normally reserved for serious infections caused by drug-resistant Gram-negative bacteria (including Enterobacteriaceae). They include meropenem, ertapenem, imipenem and doripenem. Resistance to carbapenem antibiotics is conferred by the production of carbapenemases, a situation which is found in a small but growing number of Enterobacteriaceae strains isolated from clinical samples.

**CLINICAL NEED and BURDEN OF DISEASE**

UTIs are among the most prevalent bacterial infections, with a substantial financial burden on society. The incidence of UTI is highest in young women, and around 10-20% of women will experience a symptomatic UTI at some time. Most infections in adult men are complicated and related to abnormalities of the urinary tract, although they can occur spontaneously in otherwise healthy young men. The incidence of cUTI increases with age for both sexes.

Although the frequency of cUTI due to resistant Gram-negative bacteria is increasing and most commonly acquired nosocomially, carbapenem-resistant bacteria are still very uncommon and less than 0.5% of UK population carry them (almost all asymptomatic carriage). UTI is the most common hospital-acquired infection and the majority of cases are catheter associated. UTI develops in 25% of patients who require a catheter for over 7 days, with a 5-7% daily risk. Nosocomial UTI adds to the duration and cost of hospitalisation and nosocomial uropathogens form a reservoir of antibiotic resistant bacteria. However, expert opinion notes that carbapenem-resistant bacteria pose a bigger problem and have a largest impact on outcomes for ventilator associated pneumonia in intensive care environments.

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*Expert personal communication.*
The population likely to be eligible to receive plazomicin could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

### NICE Guidance
- NICE advice. Three-day courses of antibiotics for uncomplicated urinary tract infection (KTT10) January 2015.

### NHS England Policies and Guidance

### Other Guidance
CURRENT TREATMENT OPTIONS

Antibiotic treatment for UTI is usually effective and reduces the duration of symptoms. For women with uncomplicated cystitis, empirical treatment with three days of antibiotics will achieve a cure in 85-90%. In the UK, trimethoprim or nitrofurantoin are recommended. Delaying antibiotics for up to 48 hours to allow resolution of symptoms can reduce antibiotic use without significantly prolonging symptoms. For men, because of the increased likelihood of complicated infection and/or prostatitis, at least seven days of treatment is recommended. A quinolone antibiotic is preferred because of better tissue penetration into the prostate. Mild forms of pyelonephritis can be treated with oral antibiotics, started empirically, but reviewed in light of culture results.

In cases of complicated infection, 7 days of ciprofloxacin or 14 days of co-amoxiclav are recommended for men and non-pregnant women, with 10-14 days of cepalexin recommended for pregnant women. Treatment of more severe infections may require hospital admission for IV fluids and antibiotics, which can be given orally after clinical improvement and should be continued for up to 14 days.

cUTI (including AP) are frequently caused by Gram-negative bacteria such as E coli. According to the European Association of Urology Guidelines on urological infections, second or third generation cephalosporins, beta-lactam antibiotics (such as penicillins) in combination with beta-lactamase inhibitors, and quinolones are usually recommended for treating cUTI. However, increasing resistance to commonly prescribed antimicrobial agents is a recognised serious global problem.

Commonly used antibiotics for use in serious infections caused by multidrug resistant Gram-negative bacterial pathogens of the Enterobacteriaceae family, including 3rd generation cephalosporin and carbapenem-resistant Enterobacteriaceae (CRE) include:

- Combination carbapenem therapy: including meropenem, ertapenem, imipenem and doripenem.
- Levofloxacin.
- Polymyxins, including polymyxin E and polymyxin B (Colistin).
- Tigecycline.
- Fosfomycin.
- Aminoglycosides, e.g. gentamicin.

The following drugs with activity against CRE have recently been approved for the treatment of cUTI:

- Ceftolozane in combination with tazobactam.
- Ceftazidime in combination with avibactam.

In addition, eravacycline, which has activity against CRE, is also in phase III clinical development.

EFFECTICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02486627; plazomicin vs meropenem; phase III.</th>
<th>NCT01970371; Plazomicin vs colistin; phase III.</th>
<th>NCT01096849; plazomicin vs levofoxacin; phase II.</th>
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<tr>
<td>Sponsor</td>
<td>Achaogen Inc.</td>
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<td>Source of information</td>
<td>Company, trial registry&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Company, trial registry&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Abstract&lt;sup&gt;14&lt;/sup&gt;, company, trial registry&lt;sup&gt;15&lt;/sup&gt;</td>
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<td>Location</td>
<td>EU (not UK), USA, Russia, Serbia, Georgia, and Ukraine.</td>
<td>EU (not UK), USA and Brazil.</td>
<td>USA, Chile, Colombia, and India.</td>
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<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
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<td>Participants</td>
<td>n=609; aged ≥18 years; acute UTI or pyelonephritis; pyuria; normal renal function or mild to moderate renal impairment; infection not of fungal origin; infection not Gram-positive; current cUTI or AP not known to be caused by a pathogen resistant to meropenem.</td>
<td>n=69; aged 18-85 years; Cohort 1: patients with bloodstream infection (BSI), hospital acquired bacterial pneumonia (HABP), or ventilator-associated bacterial pneumonia (VABP) due to CRE with APACHE II score between 15 and 30, inclusive; Cohort 2: BSI, HABP, VABP with an APACHE II score ≤30, or cUTI or AP; positive culture collected ≤96 hours prior to randomisation indicating CRE, or a high likelihood of a CRE infection; cUTI or AP defined by clinical signs and symptoms within 24 hours of enrolment; Cohort 2: no potentially effective antibacterial therapy within 48 hours; cUTI or AP patients do not have renal abscess, chronic bacterial prostatitis, orchitis, epididymitis, polycystic kidney disease, one functional kidney, vesicoureteral reflux, renal transplant, cystectomy, ileal loop surgery, or complete, permanent obstruction of the urinary tract.</td>
<td>n=145; aged 18-85; cUTI or AP defined by clinical signs and symptoms; normal kidney function or mild renal impairment; no signs of severe sepsis; no treatment with another antibiotic within 48 hours; no myasthenia gravis, or other neuromuscular disorder; no urinary tract surgery during the study period.</td>
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<td>Schedule</td>
<td>Patients receive plazomicin IV in combination with adjunctive antibiotic.</td>
<td>Randomised to plazomicin 10mg/kg or 15mg/kg IV once daily for 5 consecutive days; or levofloxacin 750mg IV once daily for 5 consecutive days.</td>
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<td>Cohort 1: plazomicin 15mg/kg IV once daily; or colistin 5mg/kg IV loading dose, followed by 5 mg/kg/day colistin base activity (CBA) divided as follows: once every 8 hrs or once every 12 hrs in combination with meropenem IV or tigecycline IV adjunctive therapy. Initial doses adjusted for renal impairment; subsequent plazomicin doses adjusted by therapeutic drug management (TDM).</td>
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<td>Cohort 2: plazomicin monotherapy 15mg/kg IV once daily. Combination therapy per Investigator choice for BSI, HABP and VABP. Initial doses adjusted for renal impairment; subsequent plazomicin doses adjusted by therapeutic drug management (TDM).</td>
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<td>Follow-up</td>
<td>BSI, HABP and VABP: IV study drug and adjunctive therapy for 7 to 14 days. cUTI/AP: minimum of 4 and maximum of 7 days of blinded IV study drug followed by oral levofloxacin to complete a total of 7 to 14 days of therapy (IV plus oral). Follow-up to day 28.</td>
<td>Active treatment for 5 days, and a follow-up period up to day 40.</td>
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<td>Primary outcome/s</td>
<td>Composite outcome requiring both microbiological eradication and clinical cure rate in the microbiological modified intent-to-treat population at day 5 and test of cure (day 17 +/- 2 days).</td>
<td>Microbiological eradication rates in modified intent-to-treat population and microbiologically evaluable population at test of cure visit on day 12.</td>
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<td>Secondary outcome/s</td>
<td>Composite outcome requiring both microbiological eradication and clinical cure rate in the microbiologically evaluable population at day 5 and test of cure (day 17 +/- 2 days), adverse effects (AEs). No quality of life measurement included in trial outcomes.</td>
<td>AEs; pharmacokinetics; frequency of dose adjustments. No quality of life measurement included in trial outcomes.</td>
<td>Clinical cure throughout study up to day 12. No quality of life measurement included in trial outcomes.</td>
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<td>Key results</td>
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<td>Percentage of patients with a favourable response when evaluated for clinical cure (modified intent to treat patients) for the plazomicin 10mg/kg, 15mg/kg and levofloxacin groups, respectively, were 67%, 71% and 66%. Percentage of patients with a favourable response when evaluated for microbiological eradication (microbiologically evaluable patients) for the plazomicin 10mg/kg, 15mg/kg and levofloxacin groups respectively, were 86% and 89% vs 81%.</td>
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<td>Expected reporting date</td>
<td>Primary completion date reported as Q1 2017.</td>
<td>Primary completion date reported as Q1 2017.</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of plazomicin is not yet known. The list price for meropenem 1g is £153.50-£206.28 per 10 injection vials.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other:
- No impact identified
**Impact on Health and Social Care Services**

- Increased use of existing services
  - Re-organisation of existing services: expert opinion notes that there would not be much impact at all on training, facilities and resources\(^b\).
- Decreased use of existing services
- Need for new services
- Other:
  - None identified

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other:
  - None identified

**Other Issues**

- Clinical uncertainty or other research question identified: expert opinion suggests that carbapenem-resistant bacteria are still very uncommon and carried by <0.5% of the population (almost all asymptomatic carriage)\(^c\).

  **Expert opinion also suggests uptake of plazomicin for this indication would be fairly slow initially, since clinicians are much more familiar with the other options – and currently these are usually effective. Ultimately this drug might be more useful for ventilator associated pneumonia in ICUs where carbapenem resistant bacteria can be a bigger problem and have a bigger impact on outcomes – including length of stay and mortality\(^c\).**

  **Finally, expert opinion notes, “there is always a degree of clinical uncertainty with any new drug, especially antibiotics. Companies often get a licence based on relatively small numbers of patients…in the trials – in this case only about 400. So once the drug gets the licence it is really only then that we see whether it actually works outside of the controlled trial circumstances. It may also get used ‘off licence’ for other cases of infection. This leads to uncertainty: is the dose for a cUTI the same as for a lung infection? How well does the drug penetrate the lungs? How should the dose be altered in kidney failure and liver dysfunction?”**

\(^b\) Expert personal communication.

\(^c\) Expert personal communication.
REFERENCES


14 Connolly LE, Serio AW, Riddle VD et al. Baseline pathogens and patient outcomes in a phase 2 study comparing plazomicin (ACHN-490) to levofloxacin in complicated urinary tract infection (cUTI) including acute pyelonephritis (AP). European Society of Clinical Microbiology and Infectious Diseases. 25th ECCMID. April, 2015.
