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Peramivir: A Novel Intravenous Neuraminidase Inhibitor for the Treatment of Influenza

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Influenza, also known as the flu, is an infectious viral illness associated with symptoms such as fever, muscle pain, sore throat, nonproductive cough, and headache. Clinical presentations of influenza infection can run the gamut from mild-to-moderate cases, often causing missed worked days, to more severe cases causing hospitalization or death. Greater than 200,000 people are hospitalized per year, on average, due to influenza, and 57% of these people are younger than 65 years; and, ~23,600 deaths occur as a result of influenza infections or complications from influenza infections (e.g., exacerbations of cardiopulmonary disease).[1] Hospitalization rates vary among children up to 4 years of age from 100 per 100,000 healthy children to as high as 500 per 100,000 for children with medical conditions.[1] In this past season alone, 14,162 laboratory-confirmed influenza-associated hospitalizations were reported.[2] The overall hospitalization rate was 51.7 per 100,000 population with the highest rates of hospitalization among adults aged ≥65 years.[2] And, a total of 92 influenza-associated pediatric deaths have been reported during this influenza season.[2] Research suggests that direct annual medical costs plus lost earnings due to illness or loss of life resulting from influenza infection totals $26.8 billion per year.[3] Moreover, the total economic burden of influenza in 2003 was estimated at $87.1 billion.[3]

The Advisory Committee on Immunization Practices (ACIP) recommends routine annual influenza vaccinations for all person aged ≥6 months without any contraindications. However, even in seasons with good vaccine coverage of circulating influenza strains, a substantial number of influenza cases occur which may require treatment with antiviral medications. Two classes of drugs have been used historically to treat influenza infection: adamantanes and neuraminidase inhibitors. Adamantanes (i.e., amantadine, rimantadine) are no longer recommended due to high (>99%) resistance rates among influenza A types (the predominant strains among clinical cases of influenza) and complete lack of coverage against influenza B.[4] Thus, the neuraminidase inhibitors, zanamivir and oseltamivir, have been the primary antiviral medications used for prophylaxis and treatment of influenza. These agents are effective at reducing duration of illness when used early in treatment, but do not appear to reduce hospitalizations or severe complications of influenza infection among previously healthy individuals.[5] Additionally, oseltamivir and zanamivir require 5- to 10-day courses of therapy and effectiveness may be reduced in patients who are nonadherent to these regimens. In December 2014, the Federal Drug Administration (FDA) granted a new intravenous neuraminidase inhibitor, peramivir (Rapivab®, BioCryst Pharmaceuticals, Durham, NC) an indication for treatment of influenza in patients aged ≥18 years. The purpose of this article is to review the pharmacology, safety and efficacy, dosing, administration and cost of peramivir for the treatment of influenza in adults.

Pharmacology & Pharmacokinetics

Influenza strains are categorized as type A, B, or C. Type A is the most common type of influenza seen in humans. Influenza A can be further categorized into subtypes according to the phenotypic presentation of two surface proteins, hemagglutinin (H) and neuraminidase (N). Hemagglutinin aids in binding to the host cell, while neuraminidase cleaves new virus from the host cell allowing for further infection. Hemagglutinin has 18 different known subtypes and neuraminidase has 11 different known subtypes.[1] However, only 3 types of hemagglutinin (H1-H3) and 2 types of neuraminidase (N1-N2) are responsible for influenza strains that have caused pandemics in humans. Type B influenza viruses are not divided into subtypes due to slow mutation rate and infrequent infection. Peramivir inhibits viral neuraminidase, preventing the virus from being released from the host cell, and thus averting the spread of the virus to surrounding cells.[2]

Resistance due to substitutions of amino acids in hemagglutinin and neuraminidase have been observed in laboratory cell cultures, clinical trials, and surveillance studies.[6] During the most recent influenza season in the U.S., antiviral resistance to neuraminidase inhibitors among current influenza viruses has remained low and present only among specific subtypes of influenza A H1N1 (Table 1). And, only one virus sample has demonstrated resistance to peramivir among samples collected since October 1, 2014.[2]

The maximum serum concentration (C_{max}) of peramivir is 46,900 ng/mL following intravenous administration of a 600-mg dose over 30 minutes.[6] The major route of elimination for peramivir is via the kidney, with an estimated elimination half-life of 20 hours.[6] Renal clearance accounts for about 90% of total clearance. Patients with decreased renal function have increased exposure to peramivir: subjects with creatinine clearances of 50-79 mL/min, 30-49 mL/min, and 10-29 mL/min have mean increases in expo-

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sure, as measured by AUC, of 28%, 302%, and 412%, respectively.[6] Peramivir is not metabolized by CYP enzymes, has no effect on glucuronidation, and is not a substrate for P-glycoprotein mediated transport.[6]

Clinical Trials

A randomized, double-blind, placebo-controlled trial was conducted in 75 centers in Japan to determine the efficacy and safety of IV peramivir.[7] This study recruited 300 previously healthy outpatient subjects, aged 20 to 64 years, reporting influenza-like illness with an onset in the previous 48 hours. Onset was defined as an increase in body temperature rising ≥1°C above normal, or when the subject experienced two of the seven following symptoms: headache, aches or pains in muscles or joints, feverishness, fatigue, cough, sore throat, or nasal congestion.[5] Diagnosis for influenza was confirmed with a rapid antigen test for the influenza virus, a fever of ≥38°C, and the presence of at least two of the seven symptoms listed previously at moderate to high severity, based on self-reporting.[6] Subjects were randomly assigned to receive one dose of peramivir 300 mg, peramivir 600 mg, or matching placebo. Subjects were allowed to use acetaminophen for symptom relief.

Using a digital thermometer, subjects recorded their axillary temperature twice daily for 14 days.[7] Subjects also self-assessed the seven influenza symptoms on a 4-point influenza symptom severity scale: 0, absent; 1, mild; 2, moderate; and, 3, severe.[7] The symptom assessment was recorded twice daily for the initial 9 days, then once daily for the final 5 days. Subjects also self-assessed their ability to perform usual activities using an 11-point visual analogue scale ranging from 0, indicating that the patient was unable to perform usual activity, to 10, indicating that the patient was able to perform fully.[6]

The primary efficacy endpoint was time to alleviation of symptoms.[7] The endpoint was determined from the start of treatment until all seven influenza symptom scores had been at 0 or 1 for at least 21.5 hours.[6] A total of 296 patients completed the study. The average age of participants was 34 years old and 33.7% were current smokers. Influenza A virus was the most common infection (99%), with A/H1 being the most common viral strain (72.6%).[7] The median time to alleviation of symptoms was 59.1 hours in the peramivir 300 mg group, 59.9 hours in the peramivir 600 mg group, and 81.8 hours in the placebo group. The hazard ratio for the time to alleviation of symptoms, comparing treatment to placebo, was 0.68 (95% CI, 0.51 to 0.91) in the 300-mg group and 0.67 (95% CI, 0.50 to 0.89) in the 600-mg group. Subjects in the peramivir arms, as compared to those in the placebo arm, reported shorter times to resumption of their usual activities, with resumption 43.6 hours earlier in the 300 mg arm and 41.7 hours earlier in the 600 mg arm.[6] A nasal swab and throat swab were taken from each patient at baseline to determine influenza viral titers. At subsequent visits, patients' titers were rechecked. By day 3, the peramivir arms had lower proportions of virus-positive subjects compared to placebo (36.8% for 300-mg group, 25.8% for 600-mg group vs. 51.5% for placebo).

A second phase 3, double-blind, randomized controlled trial compared treatment with a 5-day course of IV peramivir 600 mg plus standard care over standard care alone in patients with influenza that required hospitalization and had been symptomatic for <72 hours.[8] Males and females aged ≥6 years with positive influenza rapid antigen tests were eligible for the study. Subjects must have had a fever or reduced oxygen saturation (oral temperature ≥38.0°C, tympanic or rectal ≥38.6°C; oxygen saturation <92%), or ≥2 of 3 abnormal vital signs (respiration rate >30/min in children, >24/min in adolescents and adults; heart rate >110/min in children, >100/min in adolescents and adults; systolic blood pressure <80 mm Hg in children, <90 mm Hg in adolescents and adults) at screening. Other key inclusion criteria included ≥1 respiratory symptom for <72 hours (cough, sore throat, or nasal congestion), ≥1 constitutional symptom for <72 hours (headache, myalgia, feverishness, or fatigue), and onset of illness no more than 72 hours before presentation. Time to onset of illness was defined as either the time when the temperature was first measured as elevated or the time when the subject experienced one respirator symptom and one constitutional symptom. Key exclusion criteria included hospitalization for >24 hours, prior treatment with any adamantane or neuraminidase inhibitor, or confirmed bacterial infection.

Subjects were randomly assigned in a 2:1 fashion to receive IV peramivir or placebo once daily for 5 days in addition to standard treatment.[8] Randomization was stratified by duration of illness (≤48 h vs >48-72 h), influenza subtype, standard care (NAI vs. non-NAI vs. no antiviral therapy), and ICU admission status. Standard care was dependent on institution. The statistical analysis plan specified the intent-to-treat non-NAI population (i.e., all those not receiving an NAI as standard care) as the primary efficacy analysis population. The study enrolled 338 subjects from 323 hospitals in 21 countries, with 121 subjects in the non-NAI population. The other 217 subjects were part of the NAI population and had received oseltamivir or zanamivir as per the institution's standard care treatment. The primary end point was time to clinical resolution, defined as time from initiation of study treatment to resolution of ≥4 of 5 vital sign abnormalities (temperature, oxygen saturation, respiratory rate, heart rate, systolic blood pressure) for 24 hours. The study was subsequently terminated during interim analyses due to futility and the sample size required to maintain power was impractical. In the primary efficacy analysis population (i.e., non-NAI standard care intent-to-treat population), peramivir-treated subjects demonstrated a time to clinical resolution time of 42.5 (95% CI 34.0 to 57.9) hours compared to 49.5 (95% CI 40.0 to 61.9) hours for placebo (p=0.97). Similar results were seen in the population treated with standard care of an NAI (peramivir, 41.8 hours [95% CI, 30.9 to 56.8] vs. placebo, 48.9 hours [95% CI, 31.0 to 65.8]; p=0.74).[8]

Table 1 | Neuraminidase inhibitor resistance among influenza samples collected between October 1, 2014 and February 21, 2015.[2]

Influenza Strain	Peramivir	Oseltamivir	Zanamivir
Influenza A (H1N1)pdm09	1/32 (3.1%)	1/32 (3.1%)	0/28 (0%)
Influenza A (H3N2)	0/1128 (0%)	0/1762	0/1762 (0%)
Influenza B	0/217 (0%)	0/217	0/217 (0%)

$t_{1/2}$ = half-life; T_{max} = time to maximum concentration; V_d = volume of distribution.

TABLE 2 | Laboratory abnormalities in subjects treated with peramivir 600 mg.[6]

Lab Parameter	Peramivir 600 mg	Placebo
Alanine Aminotransferase (>2.5 x ULN)	3%	2%
Serum Glucose (>160 mg/dL)	5%	3%
Creatinine Phosphokinase (≥6.0 x ULN)	4%	2%
Neutrophils (<1.0 x 10^9/L)	8%	6%

ADVERSE EFFECTS AND PRECAUTIONS

In 5 randomized, double-blind, controlled trials, in which 664 subjects received peramivir 600 mg either IV or intramuscularly, the most common observed adverse reaction was diarrhea, occurring in 8% of these patients, compared to 7% receiving placebo.[6] A subset of subjects with serious influenza requiring hospitalization treated with peramivir 600-mg exhibited the following side effects more frequently compared to placebo: constipation (4% vs. 2%), insomnia (3% vs. 0%), and hypertension (2% vs. 0%).[6] Laboratory abnormalities were also observed with the same dose and route: the most common abnormality involved decreased neutrophils to <1 x 10^9/L in 8% of the subjects treated with peramivir, compared to 6% of those treated with placebo. Other laboratory abnormalities are summarized in Table 2.[6]

Cases of erythema multiforme and Stevens-Johnson syndrome have been reported following peramivir administration in post marketing experience.[2] Neuropsychiatric events such as hallucinations, delirium, and abnormal behavior have been reported in patients receiving neuraminidase inhibitors.[6] The reports, coming mostly from Japan, occurred primarily among pediatric patients and often had abrupt onset and rapid resolution upon discontinuation.[6] Neuropsychiatric adverse events were reported in a phase 2 trial of hospitalized patients with serious influenza.[9] The subjects received IV peramivir 200-mg (n=41) or 400-mg (n=40) or oral oseltamivir 75-mg twice a day (n=41) for 5 days.[9] More psychiatric events were reported in patients receiving IV peramivir 200 or 400-mg (11%) compared to those receiving oseltamivir (4%).[9] Other adverse events reported by patients treated with peramivir were insomnia (n=4), depression (n=2), anxiety (n=2), confusion (n=1), restlessness (n=1), and alteration of mood (n=1).[11] A causal link between these adverse events and neuraminidase inhibitors has not been established and influenza infection, *per se*, has been associated with similar events in patients not taking neuraminidase inhibitors.

DOSING AND ADMINISTRATION

The recommended dose of peramivir in patients 18 years of age or older with acute uncomplicated influenza is a single 600-mg dose administered via IV infusion over 15 to 30 minutes.[2] Peramivir should be administered within 2 days of onset of influenza symptoms; after this time frame, the virus has typically replicated sufficiently that neuraminidase inhibition is ineffective in reducing symptoms associated with influenza infection. In patients with a CrCl of 30-49 mL/min, the recommended dose is 200 mg, whereas for patients with a CrCl of 10-29 mL/min, the recommended dose is 100 mg.[6] For patients with renal impairment on hemodialysis, peramivir should be administered following dialysis.

Although the concurrent use of peramivir and the live attenuated influenza vaccine (LAIV) has not been studied, neuraminidase inhibitors inhibit replication of live virus and, consequently, may reduce the efficacy of the live vaccine. The peramivir package insert recommends avoiding the use of the LAIV within 2 weeks before or 48 hours after administration of peramivir.[6] The trivalent inactivated vaccine can be administered at any time relative to peramivir administration.[6]

COST

The costs for a single course of influenza prophylaxis or treatment with the currently-available neuraminidase inhibitors are summarized in Table 3. The wholesaler acquisition cost (WAC) for three 200 mg/20 mL vials of peramivir is $950.00, considerably greater than the average costs for oseltamivir and zanamivir. The retail cost of peramivir is estimated to be $978 for 3 vials of peramivir 200 mg/20 mL.[10]

SUMMARY

Peramivir (Rapivab®) is an IV neuraminidase inhibitor recently granted an FDA-approved indication for treatment of uncomplicated influenza in adults within ≤48 hours of symptom onset. Peramivir has a limited side effect profile consisting mainly of gastrointestinal effects like diarrhea. Neuropsychiatric side effects may be a concern in pediatric patients but the evidence for causality is not conclusive. Peramivir reduces time to alleviation of flu symptoms in patients with uncomplicated influenza infection,

TABLE 3 | Dosing and average cost of antiviral drugs for prevention and treatment of seasonal influenza.[12,13]

Drug	Formulation	Adult Dosing	Cost[a]
Peramivir	200 mg/20 mL single-use vials	**Prophylaxis:** not approved **Treatment:** 600 mg IV once	$950.00
Oseltamivir	30 mg, 45 mg, and 75 mg caps; 6 mg/mL oral suspension	**Prophylaxis:** 75 mg orally once daily for 7-10 days **Treatment:** 75 mg orally twice daily for five days	$120.60
Zanamivir	5 mg/blister for inhalation	**Prophylaxis:** 2 inhalations once daily for 7 days (household exposure) or ≥2 weeks (institutional exposure) **Treatment:** 2 inhalations twice daily for 5 days	$59.00

[a]Per 5-day course of treatment.[13]

but a phase 3 trial failed to show benefit over standard care in hospitalized patients, an area where an IV infusion may be most effective. The cost of treatment, at $950 per course, is another limitation compared to other neuraminidase inhibitors. Additional research is needed to identify the appropriate place in therapy for peramivir.

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Ceftolozane/tazobactam (Zerbaxa®) for Treatment of Complicated Urinary Tract Infections and Intra-abdominal Infections

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Urinary tract infections (UTIs) are among the most common conditions encountered in office practice and hospitals.[1] Urinary tract infections account for approximately 7 million office visits and more than 1 million hospitalizations per year.[2] Additionally, the economic burden associated with UTI is estimated to be in excess of $1 billion each year.[2] Complicated UTIs (cUTIs) represent those associated with structural or functional urinary tract abnormalities.[3] Factors that make a UTI complicated may include foreign bodies, kidney stones, indwelling catheters, obstruction, neurogenic bladder, renal failure, renal transplantation, immunosuppression, and pregnancy.[3] These factors predispose patients to persistent or recurrent infection, or treatment failure.[2] Clinically, the spectrum of cUTIs may range from cystitis to urosepsis with septic shock.[2] Patients with cUTIs are more likely to develop severe renal damage, bacteremia, and sepsis and to have an increased mortality.[1]

Complicated intra-abdominal infections (cIAIs) result from perforation of the gastrointestinal tract that extends into the peritoneal space and are associated with either abscess formation or peritonitis.[4] Complicated IAI is a common problem, with appendicitis alone affecting approximately 300,000 patients per year and accounting for 11 million hospital days.[5] Also, IAIs are the second most common cause of infectious mortality in the intensive care unit.[5] Patients who have these serious infections are at risk of sepsis and mortality.[6] Initial empiric therapy that is not effective against infecting pathogens increases costs, treatment failure, and death.[6]

The Study for Monitoring Antimicrobial Resistance Trends (SMART) showed that the five most commonly isolated Gram-negative pathogens in IAIs and UTIs were *Escherichia coli* (47.8%), *Klebsiella pneumoniae* (14.5%), *Pseudomonas aeruginosa* (9.4%), *Enterobacter cloacae* (6%), and *Proteus mirabilis* (3.6%).[6] Gram-negative bacteria are highly adaptive pathogens that can acquire resistance to antibacterials through multiple mechanisms, including β-lactamase production (resistance to β-lactams), *K. pneumoniae* carbapenemases (resistance to carbapenems), altered penicillin-binding proteins (PBPs; resistance to β-lactams), AmpC overexpression (resistance to β-lactams), decreases in outer membrane protein expression (resistance to imipenem and aminoglycosides), and efflux pump upregulation (resistance to fluoroquinolones, aminoglycosides, and β-lactams).[4,7] Recent data suggest that an increasing percentage of Enterobacteriaceae isolates from intra-abdominal sources produce extended-spectrum β-lactamases (ESBLs) and are resistant to mainstay antibiotics.[4] The increased use of carbapenems may lead to an increase in carbapenem resistant strains.[4] Similarly, the number of cUTIs due to resistant Gram-negative bacteria has been rising over the past few years, mainly due to the spread of ESBL-producing bacteria.[3] Fluoroquinolone resistance is an increasing problem in Gram-negative pathogens that cause UTIs and the resistance of *P. aeruginosa* to fluoroquinolones has significantly increased from 22% in 2005 to 33% in 2010.[4,8]

As a consequence, in 2010, the Infectious Disease Society of America called for the development of 10 new systemic antibacterial drugs by 2020 to help combat increasing antimicrobial resistance rates.[9] The 10 by '20 Initiative and the passage of the Generating Antibiotics Initiative Now (GAIN) Act has helped to stimulate the development of new antibiotics and give new antibiotics that treat serious and life threatening infections fast track status.[9] One of the new antibiotics that recently gained FDA approval for complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) is ceftolozane/tazobactam (Zerbaxa®; Cubist Pharmaceuticals; Lexington, MA), a combination of a cephalosporin and a β-lactamase inhibitor.[10] The objective of this article is to review the pharmacology, clinical trial data, adverse effects, and dosing considerations of ceftolozane/tazobactam for the treatment of complicated UTIs and intra-abdominal infections.

Pharmacology

Mechanism of Action

Ceftolozane is a novel cephalosporin that inhibits essential PBPs which results in the inhibition of cell wall synthesis and subsequent cell death.[11] Ceftolozane also inhibits select PBPs of

P. aeruginosa (PBP1b, PBP1c, and PBP3) and *E. coli* (PBP3).[12,13] In addition, ceftolozane has a greater affinity for PBPs when compared with ceftazidime and imipenem.[14] Ceftolozane was developed by adding amino groups to the 4-position of a 3-amino-2-methylpyrazole cephalosporin. This addition reduces the minimum inhibitory concentration (MIC) values against AmpC β-lactamases.[14]

Tazobactam is a β-lactamase inhibitor that binds to the active sites of class A and some class C β-lactamases to protect β-lactam antibiotics, including ceftolozane, from hydrolysis. Tazobactam broadens coverage against Enterobacteriaceae to include most ESBL-producing strains.[14]

Spectrum of Activity

Ceftolozane/tazobactam is indicated for the treatment of cUTIs caused by the following Gram-negative microorganisms: *E. coli, K. pneumoniae, P. mirabilis*, and *P. aeruginosa*. Ceftolozane/tazobactam used in combination with metronidazole is indicated for the treatment of cIAIs caused by the following Gram-negative and Gram-positive microorganisms: *E. cloacae, E. coli, K. oxytoca, K. pneumoniae, P. mirabilis, P. aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus*, and *Streptococcus salivarius*.[13]

Resistance

Ceftolozane/tazobactam is stable against common cephalosporin resistance mechanisms, including penicillinases, cephalosporinases, and class A β-lactamases. The combination of ceftolozane and tazobactam also has *in vitro* activity against *P. aeruginosa*, including drug-resistant strains, and other common Gram-negative pathogens, including most ESBL producing Enterobacteriaceae.[8] Furthermore, ceftolozane/tazobactam has the most potent antipseudomonal activity among the currently available cephalosporins.[15] Ceftolozane/tazobactam demonstrates *in vitro* activity against *P. aeruginosa* isolates with certain mechanisms of resistance including chromosomal AmpC, loss of outer membrane porin, and upregulation of efflux pumps.[13] Among *P. aeruginosa* strains susceptible to ceftazidime and imipenem, ceftolozane/tazobactam was shown to have greater *in vitro* activity against *P. aeruginosa* than piperacillin/tazobactam and imipenem.[11] Ceftolozane/tazobactam also demonstrated superior *in vitro* activity against ceftazidime-resistant *E. coli* and *K. pneumoniae* when compared with ceftriaxone, cefepime, and piperacillin/tazobactam.[11]

Pharmacokinetics

Ceftolozane demonstrates linear pharmacokinetics for single doses of 500 mg up to 2,000 mg.[11] The pharmacokinetic profile of ceftolozane coadministered with tazobactam is very similar to that of ceftolozane administered alone after single- and multiple-dose administration. Current data suggest ceftolozane is not metabolized to any appreciable extent and clearance occurs exclusively via renal elimination.[11,13] Tazobactam is metabolized to an inactive metabolite, M1, that is renally eliminated.[13] Pharmacokinetic parameters of ceftolozane/tazobactam are summarized in **Table 1**.

Table 1 | Pharmacokinetics of ceftolozane/tazobactam 1 g/0.5 g administered every 8 hours.[22]

Parameter	Day 1	Day 10
C_{max} (mcg/mL)	69.1	74.4
T_{max} (h), median	1.02	1.07
AUC (mcg*h/mL)	172	197
$T_{1/2}$ (h)	2.77	3.12
V_{SS}	14.6	14.2

Data represent mean values except where noted.
C_{max} = Maximum plasma concentration; **T_{max} =** Time of maximum plasma concentration; **AUC =** Area under the plasma concentration-time curve; **$T_{1/2}$=** half-life; **V_{SS} =** Volume of distribution at steady state.

Clinical Trials

Complicated Urinary Tract Infections

The Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in patients with complicated urinary tract infections (ASPECT-cUTI) trial was a phase 3 multicenter, double-blind, randomized noninferiority clinical trial that compared IV ceftolozane/tazobactam 1 g/0.5 g every 8 hours for 7 days versus IV levofloxacin 750 mg once every 24 hours for 7 days in 1,068 patients with cUTIs.[11,16] Patients were included if they were aged ≥18 years, presented with pyuria, had clinical signs/symptoms of a cUTI (pyelonephritis or complicated lower UTI) requiring antimicrobial therapy, and had a pretreatment baseline urine culture specimen obtained within 24 hours before the start of administration of the first dose of study drug.[11,16] Patients were excluded if they had a history of moderate or severe hypersensitivity to any β-lactam or quinolone, had a concomitant infection that required non-study antibiotics that covered gram-negative pathogens, had received a potentially therapeutic antimicrobial agent for the treatment of the current cUTI within 48 hours before the pretreatment baseline urine culture, had a UTI that the investigator anticipated would require >7 days of therapy, had complete and permanent obstruction of the urinary tract, confirmed fungal urinary tract infection, permanent indwelling catheter or urinary stent including nephrostomy, prostatitis, renal abscess, ileal loop, CrCl <30 mL/min, oliguria, immunocompromising conditions, or presented with one or more of the following: liver enzyme more than 3 times the upper limit of normal, absolute neutrophil count less than 500/μL, platelet count less than 40,000/μL, or hematocrit <20%.[11,16] The primary endpoint was the percentage of subjects in the modified microbiological intention-to-treat (mMITT) population with both microbiological eradication and clinical cure at the test of cure (TOC) visit 7 ± 2 days after the last dose. The secondary endpoint was the same measure in the microbiologically-evaluable population. Fifteen percent of the *E. coli* and *K. pneumoniae* isolates from both treatment arms that met pre-specified criteria for β -lactam susceptibility were ESBL-producing.[12] The primary endpoint of microbiological eradication and clinical cure at TOC was achieved in 76.9% of patients in the ceftolozane/tazobactam arm and 68.4% of patients in the levofloxacin arm (mean difference, 8.5%; 95% CI 2.3% to 14.6%); the lower bound of the 95% CI was above the predetermined lower bound of -10% for determining noninferiority.[16] In the per-protocol population, 83.3% and 75.4% of patients met the primary endpoint in the ceftolozane/tazobactam and levofloxacin arms, respectively (mean difference, 8.0%; 95% CI 2.0% to 13.9%).[12,16] The microbiological and clinical cure rates in ASPECT-cUTI are shown in **Tables 2** and **3**.

Complicated Intra-abdominal Infectiouns

The Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in patients with complicated intra-abdominal infections (ASPECT-cIAI) trial was a phase 3, multicenter, randomized, double-blind trial comparing ceftolozane/tazobactam to meropenem for treatment of cIAI.[17] A total of 993

TABLE 2 | Combined microbiological and clinical cure rates of complicated urinary tract infections.[13]

Analysis Population	Ceftolozane/tazobactam[a]	Levofloxacin[b]	Difference (95% CI)
mMITT	76.9%	68.4%	8.5% (2.3% to 14.6%)
Levofloxacin-resistant pathogen(s)	60%	39.3%	NR
Non-levofloxacin-resistant pathogen(s)	82.6%	79.7%	NR
ME	83.3%	75.4%	8.0% (2.0% to 14.0%)

[a]1 g/0.5 g ceftolozane/tazobactam intravenously every 8 hours.
[b]750 mg intravenously once daily.
ME = microbiologically-evaluable; **mMITT =** modified microbiological intention-to-treat; **NR =** not reported

patients were randomly assigned to treatment with intravenous ceftolozane/tazobactam 1 g/0.5 g every eight hours plus intravenous metronidazole 500 mg every eight hours or intravenous meropenem 1 g every eight hours, for 4 to 14 days. Patients were included in the study if they required surgical intervention (e.g., laparotomy, laparoscopic surgery, or percutaneous drainage of an abscess) within 24 hours of the first dose of study drug.[17] Patients were excluded if they were diagnosed with simple appendicitis, acute suppurative cholangitis, infected necrotizing pancreatitis, pancreatic abscess, or pelvic infections, or had additional infections requiring additional gram-negative coverage, an infection managed by staged abdominal repair or any situation where infection source control is not likely to be achieved, rapidly progressing or life-threatening disease, CrCl <30 mL/min, oliguria, hepatic disease, or any moderate-to-severe hypersensitivity to the study drugs.[6,11] The primary endpoint was the clinical cure rate at day 26 to 30 after the first dose of the study drug in the mMITT population.[11,17] The key secondary endpoint was clinical response at the test of cure visit in the per-protocol population.[11]

At baseline, the most common diagnosis was appendiceal perforation or peri-appendiceal abscess, occurring in 47% of patients in the mMITT population.[13] The most common gram-negative aerobes isolated at baseline from intra-abdominal specimens in the mMITT population were *E. coli* (65.1%), *K. pneumoniae* (9.4%) and *P. aeruginosa* (8.9%).[6] In the mMITT population, the primary endpoint was met in 83% of patients in the ceftolozane/tazobactam + metronidazole arm and 87.3% of patients in the meropenem arm, demonstrating noninferiority between the two treatments (mean difference, -4.2%; 95% CI -8.9% to 0.5%).[17] Statistical noninferiority was also demonstrated for the microbiological evaluable population where clinical cure rates were 94.2% in the ceftolozane/tazobactam + metronidazole arm and 94.7% in the meropenem arm (mean difference, -1.0%; 95% CI -4.5% to 2.6%).[17]

Clinical outcomes in the subgroup analyses were generally consistent with the primary and secondary analyses, with no meaningful differences between treatment groups.[6] However, clinical cure rates with ceftolozane/tazobactam were lower in patients with baseline CrCl of 30 to ≤50 mL/min (47.8%) compared to those with CrCl >50 mL/min (85.2%). The reduction in clinical cure rates was also present in the meropenem arm, however it was less marked (69.2% versus 87.9%, respectively).[13] Also, in the microbiologically-evaluable population, cure rates in those aged 65-74 years were 85.7% in the ceftolozane/tazobactam + metronidazole arm compared with 94.7% in the meropenem arm (mean difference, -9.0%, 95% CI -24.7% to 5.4%), suggesting that ceftolozane/tazobactam may be less effective in those aged 65-74 years.[6] However, the sample size for this analysis (n=73 total) was small, and one of many subgroup analyses; thus, whether this apparent difference is spurious is not known. The prescribing information for Zerbaxa explicitly notes that this agent may be less effective in those aged ≥65 years.[13]

Cure rates were similar among patients with infections caused by ESBL-producing *E. coli* and *K. pneumonia* and the entire study population. Nine percent of the *E. coli* and *K. pneumoniae* isolates from both treatment arms that met pre-specified criteria for β-lactam susceptibility were ESBL-producing.[12] Among patients with ESBL-producing Enterobacteriaceae (n=50), clinical cure rates were 95.8% in the ceftolozane/tazobactam + metronidazole treatment arm and 88.5% in the meropenem treatment arm. In patients with CTX-M-14/15 ESBLs (the most common type of ESBL), clinical cure rates were 100% (13/13) and 72.7% (8/11) in the ceftolozane/tazobactam + metronidazole and meropenem arms, respectively.[6] The clinical cure rates in ASPECT-cIAI are shown in **Table 4**.[13]

TABLE 3 | Combined microbiological and clinical cure rates in complicated urinary tract infections, by baseline pathogen (mMITT population).[13]

Pathogen	Ceftolozane/tazobactam	Levofloxacin
E. coli	81% (247/305)	70.4% (228/324)
K. pneumoniae	66.7% (22/33)	48% (12/25)
P. mirabilis	91.7% (11/12)	50% (6/12)
P. aeruginosa	75% (6/8)	46.7% (7/15)

Data represent percent cure rate (number of cures divided by total population under study).

ADVERSE EVENTS

Two phase 2 trials which compared ceftolozane alone or in combination with tazobactam to ceftazidime or meropenem suggest that ceftolozane/tazobactam is tolerated similarly to these antibiotics.[11] The incidence of adverse effects that developed during treatment between the ceftolozane/tazobactam + metronidazole arm and the meropenem arm was 44% and 42.7%, respectively, and most events were mild-to-moderate in severity.[6] **Table 5** summarizes adverse effects in the ASPECT-cUTI and ASPECT-cIAI trials. The most common adverse reactions associated with ceftolozane/tazobactam are nausea, diarrhea, headache and pyrexia.[12,13] In ASPECT-cUTI, headache was the most common side effect, occurring in 5.8% of the ceftolozane/tazobactam arm.[16] In ASPECT-cIAI, the most common adverse effects reported were nausea (7.9%), diarrhea (6.2%), fever (5.2%), insomnia (3.5%), and vomiting (3.3%) in the ceftolozane/tazobactam arm.[11] In general, adverse effects appeared to occur more often in the phase 3 trials in both treatment arms among those aged ≥65 years.[13]

TABLE 4 | Clinical cure rates in a phase 3 trial of complicated intra-abdominal infections.[11]

Analysis Population	Ceftolozane/tazobactam + Metronidazole[a]	Meropenem[b]	Difference (95% CI)
mMITT	83%	87.3%	-4.3% (-9.2% to 0.7%)
ME	94.2%	94.7%	-0.5% (-4.5% to 3.2%)

[a]Ceftolozane/tazobactam 1 g/0.5 g intravenously every 8 hours + metronidazole 500 mg intravenously every 8 hours.
[b]1 gram intravenously every 8 hours.
ME = microbiological evaluable; **mMITT =** modified microbiological intention-to-treat.

Clostridium difficile-associated diarrhea has also been reported with ceftolozane/tazobactam, as with other systemic antibiotics, and may range in severity from mild diarrhea to fatal colitis.[13] *Clostridium difficile* infection occurred in one patient in each treatment groups in ASPECT-cIAI.[6] In ASPECT-cIAI, death occurred in 2.3% of patients receiving ceftolozane/tazobactam and in 1.6% of patients receiving meropenem.[6] The causes of death varied and included worsening or complications of infection, surgery and underlying conditions, but no death was considered by the investigators to be related to study treatment.[6,13]

DOSING AND ADMINISTRATION

Ceftolozane/tazobactam is available as a white to yellow sterile powder for reconstitution in single-dose vials containing 1 g ceftolozane (equivalent to 1.147 g ceftolozane sulfate) and 0.5 g tazobactam (equivalent to 0.537 g tazobactam sodium). For both cUTIs and cIAIs, FDA-approved labeling recommends administration of ceftolozane/tazobactam 1.5 g (i.e., 1 g/0.5 g) every 8 hours by intravenous infusion administered over 1 hour for patients aged ≥18 years with CrCl >50 mL/min. Ceftolozane/tazobactam is used in conjunction with metronidazole 500 mg intravenously every eight hours for cIAI. The duration of therapy for cUTIs, including pyelonephritis, is 7 days, whereas the duration of therapy for cIAIs is 4-14 days. In ASPECT-cIAI, decreased efficacy was seen in patients with renal impairment. Thus, dosage adjustments are required in patients with moderate (CrCl 30 to 50 mL/min) or severe renal impairment (CrCl 15 to 29 mL/min) and in patients with end-stage renal disease on hemodialysis (Table 6). Ceftolozane/tazobactam is contraindicated in patients with known serious hypersensitivity to ceftolozane/tazobactam, piperacillin/tazobactam, or other members of the β-lactam class.[13]

COST

The wholesale acquisition cost (WAC) per vial is $83. A support program called AccessZerbaxa is available for healthcare professionals and patients who are prescribed ceftolozane/tazobactam which may provide reimbursement support and patient assistance.[18]

SUMMARY

The growing concern over antimicrobial resistance has led to an increased need for research for novel, safe, and effective antibiotics.[11] Ceftolozane/tazobactam is one of four new antibiotics that have been approved by the FDA in 2014, but it is the only one of the four that addresses serious and resistant Gram-negative bacteria, including ESBL–producing Enterobacteriaceae and multidrug-resistant *P. aeruginosa*.[19] On the basis of phase 3 clinical

TABLE 5 | Adverse reactions occurring in ≥1% of patients on ceftolozane/tazobactam in phase 3 trials.[12,13]

	Complicated IAIs		Complicated UTIs[a]	
Adverse Event	**Ceftolozane/tazobactam**	**Meropenem**	**Ceftolozane/tazobactam**	**Levofloxacin**
Nausea	7.9%	5.8%	2.8%	1.7%
Headache	2.5%	1.8%	5.8%	4.9%
Diarrhea	6.2%	5	1.9%	4.3%
Pyrexia	5.6%	4%	1.7%	0.9%
Constipation	1.9%	1.2%	3.9%	3.2%
Insomnia	3.5%	2.2%	1.3%	2.6%
Vomiting	3.3%	4%	1.1%	1.1%
Hypokalemia	3.3%	2%	0.8%	0.4%
ALT increased	1.5%	1%	1.7%	0.9%
AST increased	1%	0.6%	1.7%	0.9%
Anemia	1.5%	1%	0.4%	0.9%
Thrombocytosis	1.9%	1%	0.4%	0.4%
Abdominal pain	1.2%	0.4%	0.8%	0.4%
Anxiety	1.9%	1.4%	0.2%	0.7%
Dizziness	0.8%	1%	1.1%	0.2%
Hypotension	1.7%	0.8%	0.4%	0.2%
Atrial fibrillation	1.2%	0.6%	0.2%	0%
Rash	1.7%	1.4%	0.9%	0.4%

[a]Including pyelonephritis.
IAIs = intra-abdominal infections; **UTIs =** urinary tract infections.

Table 6 | Dosage of ceftolozane/tazobactam based on estimated creatinine clearance.[13]

CrCL (mL/min)	Recommended Dosage Regimen
>50	1.5 g (1 g/0.5g) every 8 hours
30-50	750 mg (500/250mg) IV every 8 hours
15-29	375 mg (250/125mg) IV every 8 hours
ESRD on hemodialysis	Single 750-mg (500 mg/250 mg) loading dose followed by 150-mg (100 mg/50 mg) maintenance dose every 8 hours for the remainder of the treatment period. On hemodialysis days, administer the dose at the earliest possible time following completion of dialysis.

trials, ceftolozane/tazobactam appears to be generally well-tolerated and effective for treating complicated urinary tract infections and intra-abdominal infections. The most common adverse effects associated with ceftolozane/tazobactam include nausea, diarrhea, headache, and pyrexia.[13] Usual dosing for complicated urinary tract infections is ceftolozane/tazobactam 1 g/0.5 g every 8 hours for 7 days; for complicated intra-abdominal infections, the usual dose is 1 g/0.5 g every 8 hours used in conjunction with metronidazole 500 mg intravenously every 8 hours for 4 to 14 days. An ongoing phase 3 study is assessing the use of ceftolozane/tazobactam for the treatment of ventilated nosocomial pneumonia.[11] Ongoing phase 1 studies are assessing the pharmacokinetics of ceftolozane/tazobactam in pediatric patients and critically ill patients.[20,21]

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