REVIEW ARTICLE

A NOVEL COMBINATION TO DEFEAT LIFE THREATENING ORGANISM PSEUDOMONAS AERUGINOSA

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ABSTRACT

There is global increase in resistance among bacterial species that lead to critical infections. Most of the Gram-negative bacteria are labelled as multi drug resistant. Among all different species, the Pseudomonas aeruginosa (P.aeruginosa) is one of the leading causes of life-threatening infections. It has become difficult to treat P.aeruginosa infections in current scenario as antimicrobial resistance has increased against antimicrobial drugs. So it has become a challenge to select optimal antibacterial drug or regimen for the patient treatment to prevent further resistance.

Ceftolozane/tazobactam (C/T) is a novel combination of broad spectrum antibacterial agents that is 5th generation cephalosporin antibiotic and β-lactamase inhibitor. It is considered a best choice for the treatment of complicated infections including ventilator-associated bacterial pneumonia, nosocomial pneumonia, urinary tract infections and intra-abdominal infections.

Ceftolozane/tazobactam possess sensitivity of about >90% against β-lactam resistant strains of P.aeruginosa. This combination is superior to various other antibiotics and antibacterial regimen so it has initiated a new chapter in an era of complicated infections.

This review appraises the comparison of different broad spectrum antibiotics like levofloxacin, meropenem and tobramycin and antibacterial combinations including tazobactam/cefepime, ceftazidime/avibactam, tazobactam/piperacillin, with the Ceftolozane/tazobactam combination. This article also evaluates the effect of C/T if given in combination with other drugs like daptomycin, metronidazole and amikacin.

KEYWORDS: Critical infections, Multi drug resistant, P.aeruginosa, Ceftolozane/tazobactam.

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INTRODUCTION

Antibiotic resistance is increasing day by day drastically, either due to poor diagnosis, irrational use of antibiotics or the failure of infection control.[1,2] Hence there is a global increase in resistance among bacterial species leading to critical infections. Most of the Gram-negative bacteria like Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P.aeruginosa and Enterobacter species are labelled as multi drug resistant (MDR) species because of their resistant effect against many antibiotics either in term of increasing β-lactamases, numerous efflux pump, lessen porins expression, modification(s) of antimicrobial targets or AmpC over expression.[3-6] Among all different species, the MDR P.aeruginosa, worldwide is one of the leading cause of life-threatening infections and in Pakistan its prevalence is about 22.7%.[7,8] C/T is a broad-spectrum 5th generation cephalosporin antibiotic[9], having highly effective antipseudomonal activity

including against those strains which are resistant to other antibiotics.[10-12]

Data was collected through a web based search and online data bases from PUBMED and MEDLINE for P.aeruginosa. The key words used for the search were critical infections, multi drug resistant, P.aeruginosa, ceftolozane/ tazobactam and ceftolozane/tazobactam comparison with other drugs. This article reviews the comparison of different broad spectrum antibiotics and their combinations with the C/T combination. Another objective of this review is to find out the effect of C/T if given in combination with other drugs like daptomycin, metronidazole, and amikacin.

DISCUSSION

P.aeruginosa is notorious gram-negative bacillus that is associated with many ailments diseases such as pneumonia, bacteremia, urinary tract infections, skin and soft tissues infections especially in immunocompromised patients.[13] Clinical isolates of P. aeruginosa may demonstrate resistance to multiple classes of antimicrobials, leaving clinicians with few therapeutic antibacterial drugs or their regimen options from which to choose.[14] This emergence of resistance could be due to number of mechanisms such as production of enzymes against drug or alterations in membrane structure of proteins or alterations in target sites. Efflux pumps system are extremely important cause of multidrug resistance (MDR) for P.aeruginosa.[15] MDR P. aeruginosa has been associated with adverse clinical outcomes, including increased mortality and morbidity rates.[16] MDR P.aeruginosa is defined by European center for disease prevention and control as "resistance to at least three or more than three antibiotics such as aminoglycoside, antipseudomonal penicillin, carbapenems, cephalosporins and fluoroquinolones".[17] Data presented by the Center for Disease Control and Prevention (CDC), revealed that P.aeruginosa caused diverse variety of infections and was found to be one of the most common causes of nosocomial pneumonia, urinary tract infections, bacteremia and surgical site infections.[18] One study reported that it is the major cause of morbidity and mortality in patients suffering from cystic fibrosis (CF).[19] Globally MDR P.aeruginosa has been detected in Middle East, subcontinent and other countries worldwide. India showed (29.6%) of prevalence rate, Colombia showed (16.5%), Iraq showed (27%), and South Africa showed (14.5%).[20, 21]

Currently, available drugs against MDR P.aeruginosa include Fluoroquinolones (ofloxacin, ciprofloxacin, levofloxacin) antipseudomonal penicillins (ticarcalin, piperacllin) 3rd and 4th generation cephalosporins (ceftriaxone, ceftazidime, cefepime) aminoglycosides (amikacin, gentamicin, tobramycin) and carbapenems (Imipenem, doripenem meropenum).[22]

Food and drug administration authority (FDA) approved new drug that contain 5th generation cephalosporin (Ceftolozane) and beta lactamase inhibitor (tazobactam). It has broad Gram positive and Gram negative antibacterial covering.[23] The chemical structure of ceftolozane is similar to that of ceftazidime, with the exception of a modified side-chain at 3-position of the cephem nucleus, which confers potent antipseudomonal activity.[9]

Ceftolozane/tazobactam (C/T) is considered the best choice for the treatment of complicated infections including the ventilator-associated bacterial pneumonia(VABP), nosocomial pneumonia, complicated urinary tract infections(cUTIs) and complicated intra-abdominal infections(cIAIs) that are either because of Gram-positive or Gram-negative bacteria plus some of the multidrug resistant (MDR) strains as well.[24]

P. aeruginosa showed less resistance to ceftolozane compared to ceftazidime reported by Takeda etal. Ceftolozane showed a significant stability against class AmpC beta lactamase. The synergistic effect of C/T with tazobactum makes it more stable against extended spectrum beta lactamases (ESBL) producing organisms and make it preferable drug against infections caused by these organisms.[25]

More specifically, C/T is unaffected by efflux pumps or loss of porins channels that may affect other antibiotics. However, C/T maintained its activity against imipenem-resistant clinical isolates of P. aeruginosa that showed resistance with mutational change in OprD.[25-27]

Phase I and phase II clinical drug trials have reported that ceftolozane possess a good safety and tolerability profile, which is consistent with other cephalosporins.[25] Ceftolozane/tazobactam empirical therapy is also recommended in clinical scenario where infections are suspected by resistant Gram-negative organisms (e.g., ESBL producing organisms). It is also strongly recommended as a part of combination therapy (e.g., with metronidazole) where a polymicrobial infection(s) is/are suspected.[28] In addition, ceftolozane/tazobactam may represent alternative therapy to the third-generation and fourth-generation cephalosporins after treatment failure.[29]

C/T Comparison with Cefepime/Tazobactam:
Extensive literature survey revealed that the combination of cefepime/tazobactam in a dose of 1g/125mg showed bacterial stasis within 24 hours and the 1g/250-500mg dosage regimen has the maximum effect. This maximum effect of cefepime/tazobactam formulation (1g/250-500mg) was compared with C/T (1g/500mg) combination and

the results manifested that C/T was superior to tazobactam/cefepime combination in bacterial stasis.[9, 30, 31]

C/T Comparison with Ceftazidime/Avibactam:
Multiple studies in vitro showed that ceftazidime has lesser bactericidal effect particularly against P. aeruginosa when comparing with ceftolozane.[5] One of the studies done in 2013 on neutropenic mice reported that C/T has the fastest killing capability at therapeutic dose so this is considered the most effective combination with reference to reduction in minimum inhibitory concentration (MIC) and highest efficacy.[32] The efficacy of ceftazidime was enhanced against meropenem resistant strains when it was given in combination with avibactam, as avibactam inhibits AmpC enzymes, but comparison of this regimen with C/T combination, revealed that the later was more potent combination than ceftazidime/avibactam.[33]

C/T Comparison with Piperacillin/Tazobactam:
In the treatment of ventilator associated pneumonia Mai-chi hong et al, reported that C/T with MIC50/90,1/4µg/ml is more potent than pieracillin/tazobactam with MIC 50/90, 8/>64 µg/ml25. Another study that was done by Gurudatt Chandorkar, et al, in 2012 showed good penetration rate of C/T into the epithelial lining fluid when compared with piperacillin/ tazobactam, for the treatment of nosocomial pneumonia in 50 healthy adults.[31, 34-36.]

C/T Comparison with Levofloxacin:
In complicated UTIs, the seven-day treatment with levofloxacin or the presence of high level of urinary levofloxacin was not a reliable indicator for the eradication of infection, most probably due to either irrational therapeutic prescription or very frequent usage of the same drug[37] but treating the same complicated UTIs with C/T combination has shown effective results. On the basis of aforementioned evidence, C/T was recommended as one alternative treatment options for the complicated UTIs. This finding is opening a new chapter in the field of high fluoroquinolone resistance.[38]

C/T Comparison with Meropenem:
One of the survey reported a high prevalence of meropenem non-susceptible P.aeruginosa.[39] A study done by kuti jl et al, manifested that C/T monotherapy showed 86% susceptibility while meropenem showed 46% susceptibly against 50 MDR P. aeruginosa isolates collected from children with cystic fibrosis.[40] Another study documented that meropenem had 39-45% efficacy against some β-lactam resistant strains of P. aeruginosa while C/T showed about 86-90% susceptibility in most of the β-lactam resistant species.[41]

Evidences also reported that C/T exhibited its efficacy in those infectious cases as well where many extended spectrum antibiotics including meropenem showed treatment failure. One of the cases of chronic pulmonary infection with bronchiectasis reported by Reham et.al, showed pan-resistant P.aeruginosa. After failure of Meropenem/colistin combination therapy, only the C/T in a dose of 2/1g eight hourly for 14 days was an important regimen towards good prognosis.[36]

C/T Comparison with tobramycin:
On reviewing literature, it was revealed that susceptibility rate of tobramycin monotherapy was 94-95% while that of C/T was 92-98%. Although the efficacy of both mentioned drugs was comparable in terms of susceptibility but more adverse effects were exhibited with the use of tobramycin in general and specially when used as a part of treatment in renally compromised patients.[42] Hence C/T is considered superior antibacterial regimen to tobramycin on the basis of its safety profile.[41,43]

C/T antimicrobial activity comparison with other antimicrobial agents against P.aeruginosa isolates
Literature search came up with the fact that C/T combination was one of the widely tested antibiotics against MDR P.aeruginosa and it was inferred that C/T was most active antibiotic amongst other tested drugs. Table1 showed that on the basis of MIC50, C/T was 4 times more potent than cefepime. Table also showed that C/T was 2 times and 16 times more potent than meropenem and piperacllin/tazobactum respectively. The table supports the facts that ceftolozane/tazobactam is the novel combination in vitro activity against P. aeruginosa among various antibiotics. [6, 33]

Figure 1: Comparison of C/T with various drugs (26-37).

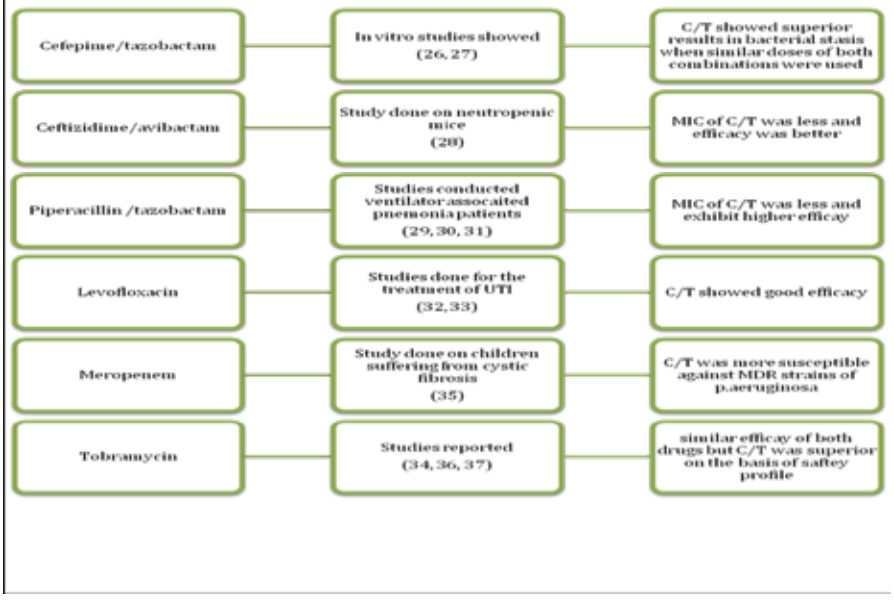

Table 1.: Activity of ceftolozane/tazobactam and comparative antimicrobial agents when tested against P. aeruginosa (2011–2012).

Antimicrobial agents	MIC50/MIC90 mcg/L All isolates of P.aeruginosa n= 2197	MIC50 /MIC90 mcg/L MDR isolates n=698
Ceftolozane/tazobactam	1/>32	4/>32
Piperacllin/tazobactam	8/>64	>64/>64
Meropenem	1/>8	8/>8
Cefepime	4/>16	16/>16
Levofloxacin	1/>4	>4/>32

C/T interactions with other drugs

Different studies have been conducted which showed enhancing effect of C/T when used in combination with other antibiotics.[44,45] Synergistic effect of C/T with daptomycin represents an important therapeutic option against resistant bacteria that are very frequently observed in all health care units globally. Data from the same study suggested that the mentioned therapeutic regimen was very effective for the methicillin resistant S.aureus (MRSA) as well that makes this combination more valid for serious life threatening infections.[46]

Other studies reported that the metronidazole along with C/T showed the cure rate of about 83.6-90.6% in complicated intra-abdominal infections, so interestingly C/T enhanced the effect of metronidazole.[47,48] When comparing C/T with amikacin, the C/T manifested higher efficacy and lower MIC than amikacin but in combination regimen the amikacin showed synergistic effect with C/T specially in the patients of cystic fibrosis.[43,49]

CONCLUSION

Keeping in view the literature facts and figures it is concluded that increasing resistance pattern and its impact on clinical utility of conventional antibiotics is the most concerning and challenging problem globally to optimal care of infected patients especially in tertiary care units. To date, C/T has demonstrated an excellent safety profile and therapeutic efficacy comparable to contemporary antibacterial drugs. Further to it, C/T exhibited an inherently low tendency to inducing resistance in general and especially against Gram-negative organisms so it is an initiative of a new phase in the world of complicated infections.

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