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Efficacy of Antibiotics in Complex Treatment of Pneumonia or Effectiveness of Modern Antibiotics

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Abstract: Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae are examples of multidrug-resistant (MDR) Gram-negative bacteria. Methicillin-resistant Staphylococcus aureus is primarily an example of Gram-positive bacteria. These bacteria have been reported to exist globally in recent years, which has limited the options for effective antibiotic therapy. For these reasons, delayed prescription filling and incorrect antibiotic medication might have a negative effect, particularly in patients who have pneumonia. Approved new antibiotics fall within antimicrobial groups such as aminoglycosides, oxazolidinones, quinolones, tetracyclines, beta-lactams with or without beta-lactamase inhibitors, or are based on novel mechanisms of action. A wide range of efficacy against MDR microorganisms, good lung penetration, safety and tolerability, and the potential for intravenous and/or oral formulations are just a few of the many benefits these novel compounds exhibit. Nonetheless, the novel antibiotics in development offer a significant potential defense against illnesses that are challenging to treat.

Keywords: Pneumonia, multidrug resistant bacteria, new antimicrobial options, clinical efficacy, drugs under development.

Introduction

New antibiotics for the treatment of pneumonia, particularly severe types, have been developed and licensed recently, taking into account the ongoing rise in antimicrobial resistance.

An empirical antibiotic lacking in vitro action was the basis for treating pneumonia brought on by multidrug-resistant (MDR) Gram-negative organisms such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae.1-3 In the context of carbapenem resistance, numerous medicines and antibiotic combinations were widely used due to the absence of fresh therapeutic choices; yet, the mortality rates remained very high.4 Importantly, methicillin-resistant Staphylococcus aureus (MRSA) is the cause of more than 30% of hospital-acquired pneumonia (HAP) infections.5,6; vancomycin is currently the main choice for treating MRSA pneumonia, although opinions on how to balance the risk of nephrotoxicity and the limited lung penetration. For these reasons, therapeutic drug monitoring (TDM) is necessary to achieve an adequate plasma concentration.7,8 In the setting of severe MRSA pneumonia, the role of linezolid was widely assessed9 although some limits in its use are represented by side effects like hematological alterations and drug interactions with selective serotonin reuptake inhibitors and other drugs with serotonergic activity.

Then, the high reported rates of treatment failure caused by administration of inadequate antibiotic treatment lead to increased morbidity and mortality, prolonged length of hospital stay, and, not less importantly, an increase in healthcare costs.

The aim of this review is to analyze the characteristics of new approved antibiotics for the treatment of pneumonia due also to MDR pathogens. This review is focused on the spectrum of activities and the possible role in daily clinical practice. Finally, the characteristics of the drugs under development are briefly reported.

Ceftobiprole is a cephalosporin of a new generation with broad-spectrum action, showing in vitro activity against Gram-positive and Gram-negative strains; it was approved in Europe for the treatment of adults with HAP, but it did not receive approval for the treatment of ventilator-associated pneumonia (VAP). Moreover, ceftobiprole was approved for the treatment of community-acquired pneumonia. The in vitro activity includes MRSA, *H. influenzae* (comprising b-lactamase-producing strains), *M. catarrhalis, K.* pneumoniae, and *E. coli*. It is also reported good activity against *P. aeruginosa*. Of note, the in vitro activity against *S. aureus* strains resistant to vancomycin and linezolid has been reported. Finally, ceftobiprole shows no activity against *Acinetobacter* spp. and extended-spectrum beta-lactamases (ESBLs)-producing Enterobacterales. Ceftobiprole exerts its antibacterial activity through the inhibition of transpeptidase activity and binding to penicillin binding proteins (PBPs), an essential component for synthesis of the peptidoglycan layer of bacterial cell walls.

Of interest, studies about PK/PD showed that 500 mg every 8 hours dosage is considered the optimal dosage to provide activity against Gram-positive strains. Two trials evaluated its clinical efficacy for the treatment of patients with HAP or CAP. Ceftobiprole was non-inferior to ceftazidime plus linezolid in patients with HAP and to ceftriaxone ± linezolid in patients with severe CAP in phase III trials. Compared to ceftazidime plus linezolid, ceftobiprole did not show non-inferiority in the subgroup of patients with VAP, with the exclusion of this indication. Ceftobiprole achieved a cure rate of 76.4% compared with that of 79.3% for ceftriaxone/linezolid group [95% CI: −9.3% to 3.6%].

Finally, ceftobiprole showed good safety as demonstrated by adverse events (AEs) related to treatment and occurring in patients with HAP or CAP. Most frequent AEs included diarrhea, infusion site reactions, nausea, vomiting, hepatic enzyme elevation, and hyponatremia. However, ceftobiprole showed a good profile of tolerance in all clinical experiences reported in the literature.

Of importance, dose adjustment is required for patients with moderate or severe renal impairment and for patients with end-stage renal disease: 500 mg every 12 hours for creatinine clearance from 30 to 50 ml/min, 250 mg every 12 hours for creatinine clearance <30 ml/min. Dose adjustment is required also for hemodialysis.

Ceftazidime is an old third-generation cephalosporin, administered intravenously and bound to a variety of PBPs including the PBP3 of Gram-negative bacteria, including *Pseudomonas aeruginosa*. Avibactam is a non-beta-lactam semisynthetic with beta-lactamase inhibitor action that differs from other beta-lactamase inhibitors (like sulbactam, clavulanic acid, and tazobactam) in structure, mechanism and spectrum of inhibition. The main mechanism of action is represented by its in vitro activity against ESBL and *Klebsiella pneumoniae* carbapenemase (KPC), AmpC, and OXA-48 enzymes; however, no activity is reported against MBLs strains or against OXA-type carbapenemases expressed by *Acinetobacter* spp.

Ceftazidime/avibactam (CAZ-AVI) is licensed for the treatment of HAP and VAP caused by carbapenem-resistant *Enterobacterales* (CRE), both in empiric or targeted therapy, and in critically ill patients. CAZ-AVI can therefore be considered as an important alternative to the use of colistin in the treatment of infections caused by KPC strains, comprising patients with primary and secondary bacteremia. In addition, data about PK/PD of CAZ-AVI confirmed the good lung penetration as demonstrated by the levels reported in the epithelial lung fluid (ELF), representing

about 30-35% of the plasma concentration. In clinical trials, CAZ-AVI at the dosage of 2000 mg/500 mg every 8 hours achieved the optimal PK/PD target in patients with HAP. Thus, CAZ-AVI represents an important option in critically ill patients with HAP caused by MDR Gram-negative strains.

In clinical trials, CAZ-AVI was considered overall well tolerated with the most common adverse events represented by abdominal pain, nausea, vomiting, and constipation, and infusion-site reactions.

Ceftolozane/tazobactam

Ceftolozane/tazobactam is a new beta-lactam/beta-lactamase inhibitor combination that shows its action by bactericidal activity through inhibition of bacterial cell wall synthesis, binding PBPs. Ceftolozane is an inhibitor of PBP3 with higher affinity for PBP1b if compared with other beta-lactam agents; its property gives to ceftolozane/tazobactam a peculiar action against AmpC β-lactamases in *P. aeruginosa*. In combination with tazobactam, ceftolozane showed enhanced activity against ESBL-producing Enterobacterales.

Ceftolozane/tazobactam was recently licensed for the treatment of pneumonia at a dosage of 3 g every 8 hours, expanding its previous indications. Ceftolozane/tazobactam confirmed its specific action in severe infections caused by MDR and extensively drug-resistant (XDR) *P. aeruginosa.* Studies showed also that ceftolozane/tazobactam has a high cure rate in patients with pulmonary infections and cystic fibrosis, with excellent safety and tolerability. Furthermore, ceftolozane/tazobactam showed a good ELF penetration like CAZ-AVI, confirming its role for the treatment of severe pneumonia. A Phase III trial (ASPECT-NP) assessed the efficacy of ceftolozane/tazobactam (3 g every 8 hours) compared with meropenem (1 g every 8 hours) for the treatment of HAP. In this trial were also included VAP caused by *P. aeruginosa* (Clinicaltrials.gov, Identifier NCT02070757). At 28 days, 87 (24%) patients in the ceftolozane/tazobactam group and 92 (25.3%) in the meropenem group died [95% CI −5.1 to 7.4]. At the test-of-cure visit, 197 (54%) patients in the ceftolozane/tazobactam group and 194 (53%) in the meropenem group were clinically cured [95% CI −6.2 to 8.3]. Ceftolozane/tazobactam was thus noninferior to meropenem in terms of both 28-day all-cause mortality and clinical cure at the test of cure.

Of importance, recent studies reported the clinical experience of ceftolozane/tazobactam for the treatment of MDR-*P aeruginosa* infections. Considering data from clinical trials, ceftolozane/tazobactam (like other cephalosporins) showed a good safety profile.

Of interest, in a Phase 3 trial of patients with intra-abdominal infections was reported a moderate renal impairment (CrCl 30-50 ml/minute), and was reported a lower cure rate in the ceftolozane/tazobactam plus metronidazole group compared to the meropenem group (48% vs 69.2%, respectively). This decreased cure rate, especially in the subgroup of patients ⩾65 years, compared to younger ones (69% vs 82%, respectively), was also considered directly secondary to changes in renal clearance. To date, FDA included a warning for the use of ceftolozane/tazobactam in patients with impaired renal function, monitoring creatinine's levels.

Conclusion

A high number of new drugs were recently approved for the treatment of pneumonia, including severe forms of community, hospital and ventilator-associated.

The most attractive characteristic of new drugs is represented by the broad spectrum of activity against MDR pathogens, in particular ESBL-producing Enterobacterales and CRE, which still represent a major threat in clinical practice, considering the lack of therapeutic options. Moreover, these new antibiotics in most cases are characterized by favorable toxicity profiles compared with old drugs that are currently used in clinical practice. Some of the new antimicrobials will be also available as oral formulations, with the potential for oral shift even in infections due to resistant pathogens.

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