Review

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β-Lactam/β-Lactamase Inhibitor Combination Antibiotics Under Development

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Review

β-Lactam/β-Lactamase Inhibitor Combination Antibiotics Under Development

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Abstract: Antimicrobial resistance remains a public health problem of global concern with a great health and financial burden. Its recognition as a threat by political leadership has boosted the research and development of new antibiotics and particularly novel combinations of β-lactams/β-lactamase inhibitors against multidrug-resistant (MDR) Gram-negative pathogens which remain the major concern in clinical practice. The incorporation of ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, and imipenem/cilastatin/relebactam has provided new therapeutic options in the treatment of patients with infections due to MDR pathogens. Cefiderocol along with cefepime/enmetazobactam, avibactam/aztreonam, and sulbactam/durlobactam have been recently added to these agents as therapeutic choices, particularly for metallo-β-lactamase producing Gram-negative bacteria. Currently, many combinations are being studied for their *in vitro* activity against both serine- and metallo-β-lactamases. However, only a few have advanced through phase 1, 2, and 3 clinical trials. Among them, in this article, we focus on the most promising combinations of cefepime/zidebactam, cefepime/taniborbactam, and imipenem/cilastatin/funobactam, which are currently under investigation in phase 3 trials.

Keywords: antimicrobial resistance; metallo-β-lactamases; β-lactams/β-lactamase inhibitors; cefepime/zidebactam; cefepime/taniborbactam; imipenem/cilastatin/funobactam; meropenem/nacubactam; xeruborbactam/β-lactams

1. Introduction

Antimicrobial resistance (AMR) has been recognized as a global public health problem by the World Health Organization (WHO) [1]. A recent meta-analysis showed that AMR was associated with almost 5 million deaths in 2019; among these, 1.27 million were directly attributed to bacterial resistance [2]. Particularly, multidrug resistance (MDR) in Gram-negative bacteria, which is mostly mediated by β-lactamases, is a major problem in clinical practice. The difficulty in combating MDR Gram-negative bacteria is largely attributed to their distinct cell wall structure compared to Gram-positive bacteria, which impedes antibiotic penetration. Gram-positive pathogens lack the outer membrane found in Gram-negative bacteria, which contains lipopolysaccharides and functions as a barrier to antibiotic penetration [3].

The impact of AMR is not limited to human health [4]. Along with mortality and morbidity, AMR brings a great economic burden according to data from a recent meta-analysis in middle and high-income countries, the healthcare cost associated with drug-resistant infections can vary from $2,371 to $29,289 [4]. In a study of the United States of America's national estimates of healthcare costs associated with AMR in hospitalized patients with bacterial infections, considerably high costs were especially attributable to methicillin-resistant *Staphylococcus aureus* [$30 998 (95% confidence intervals $25 272-$36 724)] and carbapenem-resistant *Acinetobacter baumannii* [$74 306 (95% confidence intervals $20 377-$128 235)] infections [5]. In 2017, the World Bank estimated that by 2050, AMR could reduce global gross domestic product by 3.8% each year and push 28 million people into poverty. Losses resulting from the impact of drug resistance on livestock could cost global gross domestic product (GDP) up to $950 billion, while the spread of resistant pathogens from livestock to humans could cost up to $5.2 trillion [1]. The recognition of the problem led the American presidency a decade ago to characterize AMR in general as a "threat to public health and economy", and the fight against it as "a national security priority" [6]; so, new antibiotic development became one of the US government goals for AMR management [7].

The progress in research has brought to the fore of clinical practice new antibiotics, including β-lactam/β-lactamase inhibitor (BL/BLI) combinations, specifically ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam [6].. Cefepime/enmetazobactam [8], sulbactam/durlobactam [9], and aztreonam/avibactam are among the recently-approved BL/BLI combinations for use in clinical practice. Drug development has not remained in the realm of BL/BLI combinations, and novel cephalosporins have been incorporated in the pharmaceutical arsenal following U.S. Food and Drug Administration (FDA) approval of cefiderocol in 2019 [6] and of ceftobiprole medocaril sodium earlier this year [10]. Despite the progress and innovation, MDR Gram-negative pathogens remain a significant public health concern and are listed on the WHO Bacterial Priority Pathogens List for 2024 [11].

β-lactam antibiotics are the largest class of antibiotics that is further subdivided into the penicillins, caphalosporins, carbapenems, and monobactams. They bind to and inactivate the transpeptidase domain of penicillin-binding proteins (PBPs) and thus inhibit bacterial cell wall synthesis [12]. The most common mechanism of resistance of Gram-negative bacteria to β-lactams (BL) is through the expression of β-lactamases, which hydrolyze the amide bond within the β-lactam ring leading to antibiotic inactivation. β-lactamases are structurally subdivided into four Ambler classes (Class A, B, C, and D) [12]. Functionally, classes A, C, and D hydrolyze BLs via nucleophilic attack through a conserved serine residue and are thus termed serine-β-lactamases. Class B, on the other hand, requires Zn^{2+} for BL hydrolysis and are termed metallo-β-lactamases (MBLs) [12]. The most difficult-to-treat Gram-negative pathogens e.g. *Pseudomonas aeruginosa* [13] and *Acinetobacter spp.*[14] express extended-spectrum β-lactamases (ESBL) e.g. AmpC-producing Enterobacteriaceae, and/or KPC- or OXA-like carbapenemases e.g. carbapenem-resistant Enterobacteriaceae (CRE).

In this article, we aimed to focus on BL/BLI combination antibiotics under investigation in clinical trials of phases 1, 2, and 3. However, at the time of the writing of this article (11/2024), there were no BL/BLI combination antibiotics at the stage of development of phase 2 clinical trials (with published results) thus, we included relevant agents in the phase 1 and 3 clinical trials.

To provide a comprehensive overview, we compiled the information into three tables. Table 1 presents BL/BLI combination antibiotics currently under investigation in phase 1 trials, while Table 2 includes those in phase 3 trials. Table 3 presents a detailed insight into the antibiotic class, mechanism of action and antimicrobial spectrum of these agents.

2. β-Lactam/β-Lactamase Inhibitor Combination Antibiotics in Phase 3 Trials

2.1. Cefepime/Zidebactam

Cefepime/zidebactam is one of the combinations of BL/BLI under development. Cefepime, a fourth-generation cephalosporin [15], has a broad-spectrum activity against Gram-positive and Gram-negative bacteria; it is used for complicated urinary tract infections (cUTI), intra-abdominal infections, respiratory tract infections, and neutropenic fever [16]. Cefepime alone retains activity against AmpC-producing Gram-negative pathogens [17]. Zidebactam belongs to a new β-lactamase inhibitor category (along with avibactam and relebactam) known as diazabicyclooctanes (DBO) [18].

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In particular, zidebactam is an 'enhancer' that binds with high affinity to penicillin-binding protein 2 (PBP2) and inhibits β-lactamases, thereby preventing hydrolysis of cefepime and enhancing its antimicrobial activity [10, 14]. The combination of these two agents has proven *in vitro* activity against Enterobacteriaceaeand *Pseudomonas aeruginosa* that produce β-lactamases, including extended-spectrum β-lactamases (ESBL), *Klebsiella pneumoniae* carbapenemase (KPC), and metallo-β-lactamase (MBL) [20]. However, the *in vitro* antimicrobial activity of cefepime-zidebactam against *Acinetobacter baumannii* [21], *Stenotrophomonas maltophilia*, *Proteus* species, and *Serratia* seems limited [18]. Interestingly, zidebactam improved cefepime pharmacodynamics [22] *in vivo* and the combination effectively reduced carbapenem-resistant *Acinetobacter baumannii* burden in neutropenic murine lung [23] and thigh [24]infection models.

Cefepime/zidebactam has been reported to be effective in treating patients with extensively drug-resistant *Pseudomonas aeruginosa* infections under compassionate use as salvage treatment [25,26]. More specifically, its use concerned the case of a young adult suffering from acute T-cell leukemia and disseminated infection from extensively drug-resistant (XDR) *Pseudomonas aeruginosa* producing New Delhi Metallo-β-Lactamase (NDM) [25]. The isolate was resistant to the combinations of ceftolozane/tazobactam, ceftazidime/avibactam, and carbapenems, yet susceptible to colistin (polymyxin E). The patient was treated with a combination of polymyxin B and meropenem [25]. However, the clinical deterioration with necrotizing ecthyma gangrenosum and lung involvement, along with the polymyxin B-induced neurotoxicity led to the cefepime/zidebactam use as a last-resort treatment; the prolonged antibiotic administration along with surgical source control resulted in gradual clinical improvement [25]. Another female patient with a history of bariatric surgery suffering from multi-organ dysfunction after intra-abdominal infection with XDR *Pseudomonas aeruginosa* expressing NDM was successfully treated with the new combination after polymyxin failure [26].

Currently, the combination is being investigated in a phase 3, randomized, double-blind clinical trial (NCT04979806) expected to be completed by the end of 2024. It is a multicenter, non-inferiority trial comparing cefepime/zidebactam against meropenem in patients hospitalized for cUTI or acute pyelonephritis. However, pharmacokinetic data in healthy adults showed that plasma and lung concentrations of this drug combination could also support its use for nosocomial pneumonia by susceptible pathogens [27]. Additionally, its use has a reported safety in patients with renal impairment as long as there is a dose adjustment [15].

2.2. Cefepime/Taniborbactam

Taniborbactam is a boronic-acid-containing β-lactamase inhibitor of β-lactamases of class A, C, and D, as well as some of class B (including VIM, NDM, SPM-1, GIM-1, but not IMP) [28]. The combination of the fourth-generation cephalosporin with the inhibitor provides an extended *in vitro* activity against carbapenem-resistant Enterobacteriaceae(CRE) and *Pseudomonas aeruginosa* (CRPA), either isolates producing carbapenemase or non-producing, as well as against isolates with resistance to the novel combinations (ceftolozane/tazobactam, meropenem/varorbactam, ceftazidime/avibactam) [29]. It also exhibited activity against *Pseudomonas aeruginosa* resistant to meropenem, ceftazidime-avibactam, ceftolozane/tazobactam, and meropenem/varobactam, as well as MDR and difficult-to-treat resistant (DTR) isolates. DTR refers to isolates resistant to fluoroquinolones and β-lactams, excluding the newer BL/BLI ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/varobactam [30].

The combination has exhibited *in vivo* activity against Enterobacteriaceae, *Pseudomonas aeruginosa,* and *S. maltophilia* in murine models of cUTI [31]. A relevant study also demonstrated the *in vivo* activity against Enterobacteriaceae and *Pseudomonas aeruginosa* that were not susceptible to the cephalosporin alone in the pneumonia murine model [32]. Among the novel BL/BLI combinations under investigation, cefepime/taniborbactam is the most studied. The positive results from a phase 3 trial led the pharmaceutical company to apply for drug approval. However, the FDA rejected the company's application in February 2024 [33]. The results from this randomized, non-inferiority trial comparing the combination *vs.* meropenem for the treatment of cUTI were recently published [34]. Cefepime/taniborbactam was proven to be superior to meropenem in terms of microbiologic and clinical success in patients with Gram-negative pathogens susceptible to both agents of the study (70.6% in the cefepime/taniborbactam group *vs.* 58% of meropenem-treated, 95% CI, 3.1-22.2; p=0.009) [34]. Adverse events were reported at a similar frequency in the combination-treated patients (35.5% *vs.* 29%) [34].

2.3. Imipenem/Cilastatin/Funobactam

Funobactam is a serine-β-lactamase inhibitor (in the past known as XNW4107) with a spectrum against β-lactamases of class A, C, and D [35]. Its co-administration with imipenem broadens the activity against *Acinetobacter baumannii* and *Klebsiella pneumoniae* resistant to carbapenems; funobactam enhances the activity of imipenem against the above bacteria (previously resistant to imipenem) *in vitro* and *in vivo* in mouse models [36]. Currently, two randomized, phase 3 trials are in progress. The first one investigates the role of the intravenous combination of imipenem-cilastatin/funobactam *vs.* meropenem for cUTI in hospitalized adults (NCT05204368) [37]. The second one evaluates the efficacy of imipenem/cilastatin/funobactam against imipenem/cilastatin/relebactam for the treatment of hospital-acquired pneumonia including ventilator-associated (NCT05204563) [38].

3. B-Lactams/B-Lactamase Inhibitors in Phase 1 Trials

3.1. Meropenem/Nacubactam

Nacubactam is the fourth agent of the bridged DBO β-lactamase inhibitors [39]. When used alone, it has proven effectiveness against Gram-negative bacteria; its activity may be broadened against Enterobacteriaceae producing ESBL, KPC, MBL, AmpC, and OXA-48 when the inhibitor is combined with β-lactams [39]. Consequently, this antimicrobial activity is attributed both to the direct impact on pathogens by targeting PBP2 and concurrently, by enhancing the action of the second β-lactam agent on PBP3 [40]. Additional activity of the combination against *Pseudomonas* yet not *Acinetobacter* is supported according to a multi-center study trying to determine the *in vitro* activity against GNB [28].

When the combination was tested in neutropenic mice, its concentration in the human-simulated epithelial lining fluid was effective against Enterobacteriaceae producing class A serine carbapenemases; the combination was superior to either agent alone in terms of bacterial density decline [41]. Similarly, the meropenem/nacubactam combination was more efficacious than either agent alone in reducing MDR Enterobacteriaceae isolates in neutropenic mice with cUTI [42] supporting potential clinical use in cUTI

The pharmacokinetics of the co-administration of the two drugs for up to 2 weeks has also been studied in a non-randomized trial (NCT03174795) in patients with cUTI [43]; yet the results have not been publicly announced. In 2020, the results from a phase 1 clinical trial showed that nacubactam alone or in combination with meropenem was well tolerated in healthy participants; the adverse reactions were mostly apparent after the intravenous administration of nacubactam [44].

3.2. Xeruborbactam/β-Lactams

Xeruborbactam (previously known as QPX7728) is a cyclic boronate inhibiting both serine-β-lactamases and metallo-β-lactamases [45]. This BLI alone has a broader activity spectrum compared to the second dual inhibitor - taniborbactam - since it is effective against MBL including IMP [46]. *In vitro*, xeruborbactam has been proven to be effective against MBL-producing Enterobacteriaceae[45]; when combined with meropenem was more potent than cefepime/taniborbactam against MBL-negative CRE (MIC_{90}=1 μg/ml vs MIC_{90}=16 μg/ml) [45]. The drug safety in combination with meropenem has been tested in a phase 1 trial of which the results were announced in late 2022 [47].

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The trial showed the drug safety and tolerance in healthy adults when administered either alone or in combination with meropenem; the authors pointed out that its favorable pharmacokinetics may provide the potential for co-administration with other β-lactams [47].

To date, no other clinical trials have been published regarding this combination. Currently, two phase 1 trials are testing the pharmacokinetics of xeruborbactam in combination with other β-lactams as shown in **Table 1**. The first one is a double-blind randomized controlled trial concerning its administration with cefiderocol (NCT06547554) [48]. The second one is about the administration of xeruborbactam oral prodrug combined with ceftibuten (NCT06079775) [49]. Finally, another pharmacokinetics trial concerning xeruborbactam oral prodrug with ceftibuten in patients with varying degrees of kidney impairment is expected to start in the coming months (NCT06157242) [50].

3.3. Meropenem/Pralurbactam

Pralurbactam (also known as FL058) is another novel DBO active against β-lactamases of class A, C, and D [51]. The first trial testing the safety of the combination of meropenem/pralurbactam in healthy subjects was recently published, showing the combination safety and tolerability. The most common adverse events concern the gastrointestinal ones, such as nausea and vomiting [51]. A phase 3, randomized, double-blind, multicenter, positive control trial aimed at comparing the efficacy, safety, and pharmacokinetics of meropenem/pralurbactam to that of ceftazidime/avibactam/metronidazole in the treatment of adult complicated intra-abdominal infections is reported to start this year (NCT06633718).

Other BL/BLI being investigated in phase 1 trials, either completed with the results pending to be publicly announced or in progress, are depicted in **Table 1**.

4. Discussion

Antimicrobial resistance remains a global public health problem as WHO has pointed out (1) with a great impact in terms of health and financial burden. In clinical practice, the combinations of ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, and imipenem/cilastatin/relebactam have provided and expanded the therapeutic choices against most of the classes of β-lactamases. However, the choices are limited when it comes to class B β-lactamases (MBL), making the development of effective antibiotics still an unmet need. The only options in our pharmaceutical armamentarium for MBL-producing Enterobacteriaceaeare the combination of ceftazidime/avibactam with aztreonam and the newer cefiderocol [52]. Meanwhile, the novel combination of avibactam/aztreonam has been recently approved by the European Medicines Agency for hospital-acquired pneumonia, complicated urinary tract infections, and intra-abdominal infections by Gram-negative pathogens [53] covering additionally MBL-producing bacteria [54]. Combinations such as cefepime/zidebactam, meropenem/nacubactam, and cefepime/taniborbactam may exhibit potential activity against Gram-negative bacteria producing β-lactamases, including MBL [28]. Among these, cefepime/taniborbactam has reached closer to approval after the positive results of a phase 3 trial were published for the treatment of complicated urinary tract infections [31,32].

β-lactamases are enzymes hydrolyzing the β-lactam ring resulting in resistance to β-lactams [55]. The enzymes are further classified into classes A, B, and D which are serine lactamases, and class B which are metallo-β-lactamases (MBL) [55]. The zinc ion is a prerequisite for MBL activity since it opens the β-lactam ring by activating a water molecule [56], inducing particularly a carbapenemase function [57]. The rapid appearance of new variants, the gene transferability of encoding genes, and the different structure from serine-β-lactamases (49] contribute to the difficulty in managing infections by MBLs. Consequently, the development of agents with potential activity against MBL remains of particular interest. The drug evolution has led us to the promising incorporation of the third generation of β-lactamase inhibitors, known as boronates compounds, such as taniborbactam [57]. Interestingly, considering the crucial role of zinc ion in MBL activity, chelating agents such as Aspergillomarasmine A may play a role in MBL management [58].

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BL/BLI are still the leading antibiotic class targeting the pathogens that have been prioritized by WHO [11]. However, the research should be intensified to enlighten the exact underlying mechanism of action of the enzymes responsible for antibiotic resistance. In addition, among the questions to be answered are the variable effectiveness of BL/BLI (such as boronates) against the different MBLs, to provide crucial information for further innovation. The in-depth knowledge along with antibiotic stewardship targeting the rational use of antibiotics can be the leading edge to the battle against multidrug-resistant pathogens.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Conflicts of Interest: None for all authors.

Abbreviations List

AMR: Antimicrobial resistance
BL/BLI: β-lactam/ β-lactamase inhibitors
cUTI: Complicated urinary tract infections
ESBL: Extended-spectrum β-lactamases
GIM-1: German imipenemase-1
IMP: Imipenemase metallo-β-lactamase
KPC: Klebsiella pneumoniae carbapenemase
MBL: Metallo-β-lactamase
MDR: multidrug resistance
NDM: New Delhi Metallo-β-Lactamase
SPM-1: São Paulo metallo-beta-lactamase-1
VIM: Verona integron-encoded metallo-β-lactamase
WHO: World Health Organization
XDR: extensively drug-resistant

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