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Future alternatives for the treatment of infections caused by carbapenemase-producing Enterobacteriaceae: What is in the pipeline?

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ABSTRACT

The emergence and spread of carbapenemase-producing Enterobacteriaceae is an important and very concerning problem. There is an urgent need of new antibimicrobials for treating these infections. Currently there are some options in the pipeline. Several new beta-lactamase and carbapenemase inhibitors as avibactam and MK-7655, combined with old or new betalactams are a very interesting option. Some combinations as ceftazidime-avibactam are in the late stages of clinical development and could reach the market in the next years. New aminoglycosides as plazomicin, tetracycline derivates as eravacycline, and several other new molecules as monosulfactams are currently in different stages of development.

Alternativas futuras para el tratamiento de las infecciones causadas por enterobacterias productoras de carbapenemasas: ¿qué hay en proyecto?

Palabras clave:
Inhibidores de betalactamasas
Avibactam
Biapenem/RPX7009
Plazomicina
Eravacilina
BAL-30072

RESUMEN

La aparición y diseminación de enterobacterias productoras de carbapenemasas es un problema importante y muy preocupante. Existe una necesidad urgente de nuevos antimicrobianos para tratar estas infecciones. Actualmente hay varias opciones en desarrollo. Varios inhibidores nuevos de betalactamasas y de carbapenemasas, como el avibactam y el MK-7665, combinados con betalactámicos antiguos y nuevos son una opción interesante. Algunas combinaciones como ceftazidima-avibactam están en las últimas fases del desarrollo clínico y podrían llegar al mercado en los próximos años. Otros compuestos que están en diferentes fases de desarrollo son aminoglucósidos nuevos, como la plazomicina, derivados de las tetraciclinas como la eravacilina, y otras moléculas nuevas como los monosulfactams.

Introduction

The emergence and spread of carbapenemase-producing Gram-negative bacilli is an important and very concerning problem. Bacteria producing these enzymes are susceptible to a few antibiotics (colistin, tigecycline, and one or more aminoglycosides), but some are resistant even to these drugs. Therefore, besides infection control measures and antimicrobial stewardship programs aimed to reduce their incidence and transmission, there is an urgent need of new antimicrobials for treating these infections. Currently there are several options in the pipeline. One alternative is the combination of beta-lactam antibiotics with new beta-lactamase and carbapenemase inhibitors. Some of these combinations are now in the late stages of clinical development and could reach the market in the next several years. Avibactam and MK-7655 are good examples. New aminoglycosides and tetracyclines, and several other new molecules are also a new hope for treating these infections.

In this article we review the new drugs that are in the pipeline, in different stages of development, but that could be in the market in a near future.

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New beta-lactamase inhibitors

– Avibactam (NXL104) is a non-beta-lactam semi-synthetic beta–lactamase inhibitor, member of a new class of inhibitors called the diazabicyclooctanes. It is active *in vitro* against class A and C beta-lactamases and versus some class D enzymes.[1] Avibactam has activity similar to clavulanic acid against SHV-4 beta-lactamases and similar to clavulanic acid and tazobactam against CTX-M-15, but shows greater activity in all other beta-lactamases, particularly against KPC carbapenemases and class C beta-lactamases. Avibactam binds covalently to beta-lactamases through a carbamate bond with the active-site serine that participates in bonding with beta-lactam substrates. Given its mechanism of action, avibactam is not active against metallo-beta-lactamases (MBLs) such as New Delhi MBL (NDM), Verona imipenem MBL (VIM) and IMP carbapenemases.[2] Although avibactam is active against OXA-48 enzymes, it lacks of activity against other carbapenem-hydrolyzing OXA enzymes most frequently found in *Acinetobacter baumannii* (i.e., OXA-23, -24/40, -51, and -58).[3]

Avibactam enhances the activity of ceftazidime against *Escherichia coli* and *Klebsiella pneumoniae*-producing extended-spectrum beta-lactamase (ESBL) from Ambler clases A (4-1024-fold MIC reduction) and D (2-512-fold MIC reduction), KPC carbapenemases (32-8192-fold MIC reduction) and both chromosomal and mobile class C beta-lactamases (2-512-fold MIC reduction).[4] Although avibactam does not enhance the activity of ceftazidime versus *Acinetobacter* species, it potentiates the activity of ceftazidime and imipenem against ceftazidime-resistant or imipenem-resistant *Pseudomonas aeruginosa.*[5]

Ceftaroline is a fifth generation cephalosporin active against methicillin-resistant Staphylococcae, as well as against third generation cephalosporin susceptible Gram-negative bacilli.[6] This molecule combined with avibactam becomes a very broad spectrum antimicrobial, including methicillin-resistant *Staphylococcus aureus,* ESBL, amp-C and class A, C and some D carbapenemase-producing Enterobacteriaceae.[7-10]

Avibactam is dosed in humans at a ratio of 1:4 in combination with ceftazidime.[11] The best pharmacokinetic (PK) parameter for this combination is time over the MIC. The PKs of avibactam and ceftazidime appear to be very complementary, with similar Vd, t1/2 and clearance. Therefore, no additional considerations need to be taken when dosing ceftazidime-avibactam compared with ceftazidime alone.[4]

Ceftaroline–avibactam efficacy depends on concentration above the MIC over some fraction of the dosing interval. One model using high bacterial inoculum showed that trough concentrations of avibactam of 1–3.4 μg/mL were required to protect ceftaroline. They predicted that 600 mg of ceftaroline plus 600 mg of avibactam every 8 h would be required to maintain efficacy under those stringent circumstances.[7]

Ceftazidime-avibactam and ceftaroline-avibactam have been shown to be effective in several animal infection models infected with a variety of beta-lactamase-producing organisms including ESBL, KPC and AmpC, using humanized exposures in some cases.[4,10,12-15]

The first clinical study with ceftazidime-avibactam was a phase 2 randomized (1:1) study comparing the safety and efficacy of ceftazidime-avibactam (500/125 mg 3 times daily) to imipenem/cilastatin (500 mg 4 times daily) for the treatment of complicated urinary tract infections (UTI) (NCT00690378). Favourable clinical response rates and adverse events were 85.7% and 67.7% for the ceftazidime-avibactam arm, and 80.6 % and 76.1% for the imipenem/cilastatin arm.[16] Next phase 2 study was a randomized (1:1) trial comparing safety and efficacy of ceftazidime-avibactam (2000/500 mg) plus metronidazole (500 mg) with meropenem (1000 mg), each administered intravenously 3 times daily for the treatment of complicated intraabdominal infection in hospitalized adults (NCT00752219). This trial demonstrated comparable clinical responses (91.2% and 93.4%, respectively) and similar rates of adverse events (64.4% and 57.8%, respectively).[17] Currently, several ceftazidime-avibactam phase 3 trials are ongoing for complicated UTI and intraabdominal infections, as well as for nosocomial pneumonia (FDA, http://clinicaltrials.gov/).

Ceftaroline–avibactam clinical development is ongoing, with phase II trials in complicated UTI that began in 2011. One of them, that has ben recently completed, compared this combination to doripenem for complicated UTIs (NCT01281462).

– MK-7655 is a novel beta-lactamase inhibitor that, similar to avibactam, has a diazabicyclooctane structure. *In vitro* studies have demonstrated its inhibition of class A and class C beta-lactamase.[18] A recent study investigated the combined killing activity of imipenem and MK-7655 against four imipenem resistant strains.[19] Other study that also examines the potential of MK-7655 to protect imipenem showed a reduction in MICs for Enterobacteriaceae with KPC carbapenemases, with weaker synergy for isolates with the OXA-48 enzyme. On the other hand, imipenem/MK-7655 failed to demonstrates *in vitro* activity against Enterobacteriaceae with MBL.[20]

MK-7655 has completed phase 1 trials.[21,22] Reduction of MK-7655 doses and dosing frequency recommended are similar with those for imipenem in subjects with impaired renal function.[21] In addition, two separate phase 2 studies of 2 doses (125 and 250 mg) of MK-7655 plus imipenem-cilastatin versus imipenem-cislatatin alone for treatment of Gram-negative bacterias are currently recruiting (Table 1).

– RPX7009 is a boron-containing beta-lactamase inhibitor with potent activity against serine carbapenemases.[23] In pre-clinical evaluation[24] of 167 serine-carbapenemase-producing Enterobacteriaceae, RPX7009 restored the activity of biapenem from 15% (biapenem alone) to 95.8-98.8% of isolates inhibited at ≤2 μg/mL. Other study evaluated biapenem/RPX7009 activity against Enterobacteriaceae carrying acquired beta-lactamases and isolates of *Enterobacter* spp. hyperproducing chromosomal AmpC; 98% of isolates were inhibited with this combination.[25] A recent study[26] in 300 Enterobacteriaceae strains representing major carbapenemase types, RPX7009 strongly potentiated biapenem against Enterobacteriaceae with class A carbapenemases and showed a weak potentiation against strains with combinations of AmpC or ESBL activity and impermeability. Class B and D carbapenemases were not inhibited.

In vivo studies of pulmonary and thigh infection models due to carbapenem-resistant KPC-producing *K. pneumoniae* showed that the addition of RPX7009 leads to a marked increase in antimicrobial activity of the biapenem against these strains.[27,28]

The combination of biapenem/RPX7009 (Carbavance™) is being developed and is in late phase 1 study (Table 1). Study designs are pending.

– FPI-1465 is a non-beta-lactam beta-lactamase inhibitor that strongly potentiates beta-lactam antibiotics activity against beta-lactamase containing organisms, including strains that harbor all four Ambler classes of beta-lactamase.[29] *In vitro* studies with isolates of Enterobacteriaceae producing ESBL and Enterobacteriaceae producing class A, B, and D carbapenemases showed great synergistic effects when combined with aztreonam and ceftazidime.[30] In the thigh model caused by KPC-2 producing *K. pneumoniae* and VIM-1 and KPC-3 producing *Enterobacter cloacae* resulted in therapeutic efficacy.[31]

LN-1-255. OXA-type beta-lactamase inhibitor

OXA beta-lactamases are largely responsible for beta-lactam resistance in *Acinetobacter* spp. and *P. aeruginosa*. The JDB/LN-1-255 molecule is a new inhibitor of broad-spectrum beta-lactamases

Table 1
Clinical trials with novel antibiotics with activity against carbapenemase-producing Gram-negative pathogens registered in FDA, http://clinicaltrials.gov/ (February 2014)

Antibiotic	Study	Status	Study results	NCT
MK-7655	A single dose study to investigate the pharmacokinetics of MK-7655 in participants with impaired renal function	Completed	Reference 5	01275170
	Study of the safety, tolerability, and efficacy of MK-7655 + imipenem/cilastatin versus imipenem/ cilastatin alone for the treatment of complicated urinary tract infection	Recruiting	No results available	01505634
	Study of the safety, tolerability, and efficacy of MK-7655 + imipenem/cilastatin versus imipenem/ cilastatin alone to treat complicated intra-abdominal infection	Recruiting	No results available	01506271
RPX7009	Safety, tolerability, pharmacokinetics of intravenous RPX 2014 and RPX7009 in health adult subjects	Completed	No results available	01897779
	Safety study of intravenous biapenem (RPX2003) and RPX7009 given alone and in combination	Completed	No results available	01772836
	Safety, tolerability, pharmacokinetic of intravenous RPX 7009 in health adult subjects	Completed	No results available	01751269
	The safety and pharmacokinetic of Carbavance™ (RPX 2014/RPX7009) in subjects with renal insufficiency	Recruiting	No results available	02020434
FPI-1465	None			

active against class A SHV-1, SHV-2 and class D oxacillinase-, ESBL-, and also carbapenemase-type OXA enzymes.[32-36]

Penam sulfones. SA2-13

The penam sulfone compound SA2-13 is a good inhibitor of SHV-1 beta-lactamases.[37-40] The compound is covalently bound to the active site of SHV-1 similar to tazobactam, yet forms an additional salt-bridge with K234 and hydrogen bonds with S130 and T235 to stabilize the trans-enamine intermediate. Kinetic measurements show that SA2-13, once reacted with SHV-1 beta-lactamase, is about 10 fold slower at being released from the enzyme compared to tazobactam.[39]

Metallo-beta-lactamases inhibitors

– Substituted maleic acid derivatives were patented as MBL inhibitors in 2007.[41] They can have varying inhibitory activity, showing better inhibitory potency against the MBLs IMP-1 and VIM-2 in biochemical assays.[41] ME1071 has been evaluated combined at 32 μg/mL, with piperacillin, ceftazidime, aztreonam, imipenem, meropenem, biapenem or doripenem against IMP-1 or VIM-2 producing strains of *P. aeruginosa*.[41] Synergy was observed with ceftazidime and with the carbapenems.

– Isatin-derived thiosemicarbazones have recently been patented as NDM-1 inhibitors. Substituted dihydrothiazole carboxylic acids have been patented as MBL inhibitors, with the best compound having an IC50 of 5.5 μM against IMP-1.[42]

– 3'-thiobenzoyl cephalosporin derivatives have been patented as dual MBL/serine beta-lactamase inhibitors. Interestingly, these compounds exhibit not only inhibition of the MBLs IMP-1 (3.1 μM), VIM-2 (1.8 μM) and NDM-1 (33 μM) but also low level inhibition of KPC-2 (71 μM) and the class D OXA-10 (8.1 μM) and OXA-45 (24 μM).[43]

The thiol derivatives including the clinically available antihypertensive agent L-captopril, have shown effective inhibition of NDM-1 and subclass B1, B2, and B3 enzymes.[44-47]

New aminoglycoside: plazomicin

Plazomizin (ACHN-490, Achaogen) is a next-generation aminoglycoside.[48,49] It has enhanced activity against many multidrug-resistant Gram-negative bacteria and methicillin-resistant *S. aureus* isolates.[49-55] It has potent activity versus carbapenem-resistant isolates, including those with multidrug resistant phenotype (ESBL, KPC and VIM-MBL resistance mechanism). Plazomicin has shown *in vivo* efficacy in two murine models: the septicemia and the neutropenic thigh models.[56] In first studies no evidence of nephrotoxicity or ototoxicity was observed.[57,58]

The clinical development include infections due to carbapenem-resistant Enterobacteriaceae (compared with colistin) and complicated UTI and acute pyelonephritis (compared with levofloxacin) (FDA, http://clinicaltrials.gov/) (Table 2).

Table 2
Clinical trials with novel antibiotics with activity against carbapenemase-producing Gram-negative pathogens registered in FDA, http://clinicaltrials.gov/ (February 2014)

Antibiotic	Study	Recruitment	Study results	NCT
Plazomicin	A study of plazomicin compared with colistin in patients with infection due to carbapenem-resistant Enterobacteriaceae (CPE)	No yet recruiting	No results available	1970371
	Study of plazomicin (ACHN-490) compared to levofloxacin for the treatment of complicated urinary tract infection and acute pyelonephritis	Completed	No results available	1096849
	Phase 1 study to determine safety blood PK, and lung penetration	Completed	No results available	1034774
	A study to evaluate the effect of IV ACHN-490 injection on the QT/QTC interval in healthy volunteers	Completed	No results available	1514929
	Phase 1 study for safety of ACHN-490	Completed	No results available	822978
	PK study of ACHN-490 injection in renally impaired subjects	Completed	No results available	1462136
BAL 30072	None			

Siderophore monosulfactam BAL30072

BAL 30072 (Basilea Pharmaceutica International Ltd) is a monosulfactam antibiotic conjugated with an iron-chelating dihydroxypyridone moiety.[59] It inhibits most Gram-negative bacteria at low concentrations.[60-64] Unlike aztreonam, BAL30072 retains activity against most Enterobacteriaceae with CTX-M and ESBLs, although its MICs are raised for many with TEM and SHV ESBLs or copious AmpC activity.[62] As a monocyclic beta-lactam, BAL 30072 is stable to MBLs.[62] It is active against KPC-producing *K. pneumoniae* unless an SHV-ESBL or AmpC activity is also present.[62] Adding clavulanate, BAL30072 has extended activity against carbapenem-resitant Enterobacteriaceae.[60] The addition of meropenem resulted in variable increases in activity against individual isolates, depending of the study.[60,65,66] Additive and synergistic effects were observed in Enterobacteriaceae and *P. aeruginosa.*[65,66] Resistance remained common in the *K. pneumoniae* ST258 KPC clone, even with both inhibitors or menopenem added.[60,63,64] This antibiotic is now entering in Phase I.

Fluorocycline eravacycline (TP-434)

Eravacycline (TP-343), a novel fluorocycline antibiotic, was made by total synthesis using a novel methodology and further developed by Tetraphase Pharmaceuticals.[67] It has improved activity against major tetracycline resistance mechanism and is 4-fold more potent than tigecycline in *E. coli* expressing a widespread tetracycline efflux pump, Tn*1721*-associated *tet*(A).[67] These properties give to eravacycline a broad spectrum of activity against multidrug-resistant Gram-positive and Gram-negative pathogens, including tetracycline-resistant Enterobacteriaceae producing ESBLs or carbapenemases.[67,68] The activity against *P. aeruginosa* and *Burkholderia cenocepacia* is lower (MIC90 32 µg/mL).[68,69] Its excellent *in vitro* activity extended to promising *in vivo* efficacy in different animal infection models (septicemia and neutropenia models).[69] Oral bioavailability is poor indicating that the future development of the drug must be driven to severe infections.[69,70] Pulmonary disposition of eravacycline support further study for patients with respiratory infections.[71] The efficacy and safety of two dose regimens (1.5 mg/kg q24 h and 1.0 mg/kg q24 h) of eravacycline in adult community-acquired complicated intra-abdominal infections has been studied.[72] The efficacy and safety of both dose regimens were comparable to ertapenem (1 g q24 h). The efficacy and safety of eravacycline in complicated UTI are also being studied in a prospective, randomized trial (FDA, http://clinicaltrials.gov/, NCT01978938) (Table 2). It is necessary to study its efficacy in the setting of carbapenem-resistant pathogens.

Conflicts of interest

The authors have no conflicts of interest to declare.

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