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REVIEW

Investigational and Experimental Drugs for Community-Acquired Pneumonia: the Current Evidence

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Abstract: Community-acquired pneumonia (CAP) is a common infection with a constantly evolving etiological spectrum. This changing etiology conditions the adequate selection of optimal therapeutic regimens, both in empirical and definitive treatments. In recent years, new antimicrobials have been approved by regulatory authorities for use in CAP, although it is necessary to continue incorporating new antimicrobial agents that improve the activity profile in relation to the appearance of bacterial resistance in certain pathogens, such as pneumococcus, *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Delafloxacin, omadacycline and lefamulin are the most recently approved antibiotics for CAP. These three antibiotics have shown non-inferiority to their comparators for the treatment of CAP with an excellent safety profile. However, in the 2019 ATS/IDSA guidelines, it has been considered that more information is needed to incorporate these new drugs into community-based treatment. New antimicrobials, such as solithromycin and nemonoxacin, are currently being studied in Phase III clinical trials. Both drugs have shown non-inferiority against the comparators and an acceptable safety profile; however, they have not yet been approved by the regulatory authorities. Several drugs are being tested in Phase I and II clinical trials. These include zabofloxacin, aravofloxacin, nafithromycin, TP-271, gepotidacin, radezolid, delpazolid, and CAL02. The preliminary results of these clinical trials allow us to assure that most of these drugs may play a role in the future treatment of CAP.

Keywords: community-acquired pneumonia, new antimicrobial drugs, fluoroquinolones, macrolides, tetracyclines, oxazolidinones

Introduction

Community-acquired pneumonia (CAP) continues to be an important challenge in the field of infectious diseases because is one of the most common infections that require hospitalization, especially in the elderly population and persons with comorbid conditions.[1–5]

In the case of a patient with CAP, doctors have to decide which tests should be performed in order to determine the cause of pneumonia, which is the appropriate location to treat the patient and which is the best antibiotic therapy for this patient. Understanding the burden and the etiology of CAP is critical to making these decisions. Initial treatment of patients with CAP is empirical so the antibiotics chosen should cover the most common pathogens causing CAP but also those uncommon pathogens that may cause CAP in certain patients. This is one of the most important challenges in patients with CAP because the microbial etiology of CAP is constantly changing. The

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main features that have contributed to these changes in the last years are the widespread introduction of the pneumococcal conjugate vaccine, the emergence of resistant pathogens such as *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* (MRSA) and the increased recognition of the role of viral pathogens.

Numerous antibiotics have been approved for the treatment of CAP by the Food and Drug Administration (FDA); however, it is necessary to continue the research of new drugs that are able to cover the entire etiological spectrum of CAP and with novel mechanisms of action that can overcome the increase of resistances and the emergence of resistant pathogens. In this article, we will perform a narrative review about the existing treatments for CAP and we will focus on the new drugs that are currently being investigated.

Etiology of CAP

Knowledge of the pathogens causing CAP is essential to select correct empirical treatments. The etiology of CAP is conditioned by several factors. The presence of underlying conditions, such as chronic lung disease or immunosuppression, local epidemiology or previous exposure to antibiotics is the most important.

In any textbook, the pathogen referred as the main cause of CAP is *Streptococcus pneumoniae*, accounting for up to two-thirds of bacteremic cases and for 30% of all CAP. Other pathogens include *Haemophilus influenzae*, which represents 12% and atypical microorganisms such as *Mycoplasma pneumoniae, Chlamydiophila pneumoniae* and *Legionella* spp. that account for 20% of CAP.[1,6,7] Despite *S. pneumoniae* is the main bacterial microorganism isolated in CAP, in the latest studies its proportion is decreasing. This may partially be due to the introduction of the conjugated anti-pneumococcal vaccine in the United States and other countries.[2]

Moreover, recent studies point out that respiratory virus should also be taken into account. In these studies, viral isolates represent 20–30%, with influenza and rhinovirus in the head of viral pathogens.[8] In fact, 2019 Infectious Diseases Society of America (IDSA) guidelines suggest that when influenza viruses are circulating, their presence should be investigated in patients with CAP.[9] Such information has an impact, since a meta-analysis showed a higher risk of death in patients with viral-bacterial co-infection compared to patients with non-dual infection.[10]

On the other hand, with usual microbiological methods, pathogen detection is achieved in less than 50%.[11] New diagnostic tools such as molecular techniques could contribute to the diagnosis of CAP, raising the level of microbiological diagnosis up to 85%. Therefore, these new methods have pointed out that mixed infections can represent 10–25% of all CAP.[8,11] In the latest studies, etiologies of CAP include Gram-negative bacilli, such as *Escherichia coli* (11.5%), *Klebsiella pneumoniae* (4%) or *P. aeruginosa* (2.8%), and *S. aureus* (10.2%).[12]

Finally, multidrug-resistant organisms (MDRO), including MRSA and extended-spectrum beta-lactamase (ESBL) *Enterobacteriaceae* and *P. aeruginosa*, represent 6% of pathogens isolated in CAP, mostly in older patients with previous exposure to antibiotics, and they are associated with higher mortality.[13] In North America, community-acquired MRSA, specially the USA300 clone, can cause a severe CAP presenting with rapid progression and hemoptysis.[14]

Current Treatment of CAP

Several guidelines for the diagnosis and treatment of CAP have been published, each one taking into account local epidemiology, health system particularities, drug side effects and cost-effectiveness. In this part, we assess general and most updated recommendations for the treatment of CAP in adults.

Most recommendations take into consideration the level of care (inpatient or outpatient) and severity of the disease. Severity can be assessed by scores, such as IDSA criteria, for severe pneumonia or by clinical judgment supported by CURB65, as recommended in British guidelines.[9,15]

The recommended treatment for healthy outpatients with CAP is amoxicillin, doxycycline or, in areas with low prevalence of macrolide-resistant *S. pneumoniae*, a macrolide. On the other hand, outpatients with co-morbidities, such as chronic lung disease, diabetes mellitus or alcoholism should be treated with amoxicillin-clavulanate acid plus a macrolide or with a respiratory fluoroquinolone.[9]

Treatment of hospitalized patients depends on severity. Patients with severe CAP should be treated with combined therapy with β-lactam plus macrolide or β-lactam plus fluoroquinolone. Several studies and meta-analysis support combined therapy for critically ill patients with CAP.[16,17] In hospitalized patients with non-severe CAP, combination of a β-lactam plus a macrolide or a respiratory fluoroquinolone is recommended. Evidence of superiority of combined treatment with β-lactam plus macrolide over β-lactam monotherapy in non-critically ill patients with CAP is less robust and studies have drawn contradictory conclusions on this issue.[18,19]

Finally, previous guidelines defined "healthcare-associated pneumonia" (HCAP) as a pneumonia occurring in patients with higher risk of MDRO. Risk factors considered are residence in nursing homes, recent hospitalization, or chronic conditions, among others.[20] The latest guidelines recommend avoiding the term as it leads to an increase in the use of broad-spectrum antibiotics without better results.[21] Therefore, the current recommendation is to individually assess clinical probability of resistant-pathogens and to adjust treatment to local epidemiology.[9]

Do We Need New Antibiotics for CAP?

The constant epidemiological changes have raised some issues that justify the research of new antibiotics for CAP. Although penicillin resistance has been a matter of concern for many years, currently we have learned that levels of β-lactam resistance in most settings generally do not result in treatment failure for patients with pneumococcal pneumonia when appropriate agents and doses are used.[22–24] On the contrary, resistance of *S. pneumoniae* to macrolides is significant, with a prevalence of 20 to 40% in some settings.[25,26] In the same way, resistance of *M. pneumoniae* to macrolides is also emerging worldwide.[27] For these reasons, macrolide monotherapy, that was recommended for outpatients in the 2007 American Thoracic Society (ATS)/IDSA guidelines, has evolved to a conditional recommendation because of concerns on resistance levels to macrolides in the 2019 ATS/IDSA guidelines.[9,28]

On the other hand, the emergence of MDRO, including MRSA and *P. aeruginosa*, requires consideration in the empirical treatment coverage in some patients with risk factors for these etiologic agents.[29] Although infection by *S. aureus* is still uncommon in most patients with CAP, its incidence is increasing in pediatric population and during the influenza season. *Enterobacteriaceae* and *P. aeruginosa* accounts in <2% of cases of CAP, but they are increasing in elderly patients with co-morbidities. So, appropriate therapy for these pathogens may be necessary for selected patients, since the impact of failing in initial treatment may be high, especially in critically ill patients.[2]

Finally, the description of adverse events related to the use of fluoroquinolones has raised concerns regarding its generalized use in all patients with CAP. While some of these adverse events, such as tendinopathy and tendon rupture were already known since years ago, others have become relevant more recently for their severity (severe hypoglycemia, adverse psychiatric events, QT prolongation or aortic rupture and dissection). For these reasons FDA has suggested that fluoroquinolones should be reserved for those patients who have no other treatment options.[30]

New Antimicrobials Recently Approved for CAP

Delafloxacin

Delafloxacin is a novel fluoroquinolone with a broad spectrum that includes Gram-positive and Gram-negative organisms, including MRSA and *P. aeruginosa*.[31] It is also active against atypical microorganisms causing CAP. Delafloxacin differs from other fluoroquinolones in that delafloxacin exerts a minimal effect on cytochrome P450 enzymes and on the corrected QT interval so there does not seem to be a risk of QT prolongation. The efficacy of delafloxacin for CAP was demonstrated in a Phase 3, randomized double-blind trial.[32] In this study iv delafloxacin, with potential to switch to oral delafloxacin, was compared to iv moxifloxacin, with potential to switch to oral moxifloxacin and potential to switch moxifloxacin to iv linezolid for confirmed MRSA. A total of 860 patients with CAP in PORT risk class of II to V were planned to be enrolled and finally 859 were included in the intention-to-treat (ITT) population. Overall, 88.9% of patients who received delafloxacin and 89.0% of patients who received moxifloxacin met the primary end-point of statistical non-inferiority for early clinical response at 96 hours. Delafloxacin was well-tolerated. The most common adverse events (≥2%) were diarrhea and increases in transaminase levels, which were generally mild and did not lead routinely to treatment discontinuation. As a consequence of these results, the FDA approved delafloxacin for the treatment of adults with CAP the past 10/24/2019.[33]

Omadacycline

Omadacycline is a new aminomethylcycline, a derivate of tetracycline, with a mechanism of action based on its binding to the primary tetracycline site on bacterial 30S ribosomal subunit with high specificity. An advantage over older tetracyclines is that it is able to overcome the efflux and ribosomal protection mechanisms of tetracycline resistance. Omadacycline is active against pathogens that cause CAP, including *S. pneumoniae, H. influenzae, S. aureus*, and atypical pathogens.[34] The efficacy of omadacycline was evaluated in the OPTIC trial, a double-blind trial in which once-daily omadacycline was compared to moxifloxacin for the treatment of adults with CAP in PORT risk class II to IV.[35] The ITT population included 386 patients in the omadacycline group and 388 patients in the moxifloxacin group. Omadacycline showed non-inferiority to moxifloxacin for early clinical response (81.1% and 82.7%, respectively), and for the rates of investigator-assessed clinical response at the post-treatment evaluation (87.6% and 85.1%, respectively). The most frequent events were gastrointestinal side effects (10.2% and 18.0%, respectively). Although FDA approved omadacycline for CAP the 10/02/2018,[36] recent ATS/IDSA guidelines state that omadacycline needs further validation in the outpatient setting.[9]

Lefamulin

Lefamulin is a semi-synthetic agent that belongs to the pleuromutilin class of antibiotics. The precise mechanism of action is based on the binding to the peptidyl-transferase center of the 50S ribosomal subunit of the bacteria. Lefamulin has a potent antimicrobial activity against Gram-positive microorganisms, including *S. pneumoniae*, and some Gram-negative pathogens *(H. influenzae, Moraxella catarrhalis* and *Neisseria* spp.), as well as against mycoplasmas and intracellular organisms, such as *Chlamydia* spp. and *Legionella pneumophila*.[37] It has a good oral bioavailability and an excellent penetration into epithelial lining fluid of the lung. The clinical efficacy of lefamulin in patients with CAP was evaluated in two multicentre, randomized, double-blind, double-dummy, phase 3 trials, the Lefamulin Evaluation Against Pneumonia (LEAP 1 and 2) trials. The LEAP 1 study demonstrated the clinical efficacy and safety of iv-to-oral lefamulin compared to moxifloxacin ± linezolid in adult patients with moderate to severe CAP.[38] The LEAP 2 study compared the safety and efficacy of oral lefamulin twice daily for 5 days versus oral moxifloxacin once daily for 7 days in 738 adult patients with moderate CAP, and also demonstrated non-inferiority between the two therapeutic options.[39] On August of 2019, based on the results of these trials, the FDA announced the approval of lefamulin for the treatment of CAP.[40] Despite this approval the ATS and the IDSA demand further validation in the outpatient setting.[9]

Investigational Drugs Currently in Phase III Clinical Trials

The phase III clinical trials including these drugs for patients with CAP are listed in Table 1.

Solithromycin

Solithromycin is a fourth-generation macrolide and the first fluroketolide in development. Solithromycin acts binding to three different sites of 50S ribosomal unit, resulting in a potent antibacterial activity and a low tendency to select for resistant mutants.[41] This drug has activity against the most common typical and atypical CAP pathogens, including fluoroquinolone-, macrolide-, and penicillin-resistant isolates.[41] Two phase III trials, SOLITAIRE-ORAL and SOLITAIRE-IV, have evaluated the safety and efficacy of oral and iv solithromycin, respectively, for the treatment of CAP.[42,43] Both trials have shown non-inferiority compared with moxifloxacin for the early clinical response meeting the FDA's primary end-point (SOLITAIRE-ORAL, difference = −0.19, 95% CI, −5.8 to 5.5, and SOLITAIRE-IV, difference = −0.46,

Table 1 Antimicrobials in Phase III Clinical Trials

Drug Name	Drug Class	Development Phase	Study Results *	Data Approval by FDA
Omadacycline	Aminomethylcycline (derivate of tetracyclines)	Phase III	Clinical response: 81.1% (313/386) vs 82.7% (321/388) comparator.	10/02/2018
Delafloxacin	Fluoroquinolone	Phase III	Clinical response: 90.5% (390/431) vs 89.7% (384/428) comparator	10/24/2019
Lefamulin	Pleuromutilin	Phase III	Clinical response: 89.3% (577/646) vs 90.2% (582/645) comparator	8/19/2019
Solithromycin	Macrolide	Phase III	Clinical response: 78.7% (677/860) vs 78.8% (680/863) comparator	Not yet approved
Nemonoxacin	Non-fluorinated quinolone	Phase III	Clinical cure: 89.1% (542/608) vs 88.5% (261/295)	Not yet approved

Note: * Expressed in percentage and number.

95% CI, −6.1 to 5.2). In SOLITAIRE-ORAL, side effects were comparable between both groups. However, in SOLITAIRE-IV more than 50% of patients in the solithromycin arm had drug-related adverse events, compared with 35% in the moxifloxacin arm. This difference was driven mainly by infusion reactions, more common in the solithromycin group (31.3%) compared to the moxifloxacin group (5.4%).[43] Nevertheless, hepatic safety remains a concern, with 5–10% of patients experiencing mild asymptomatic transaminase elevations. Given the relatively small sample sizes (<1000 patients) in which solithromycin was studied, the FDA recommended that the company initiates a new clinical study with a greater number of patients to better evaluate its safety profile before formally granting approval.[44]

Nemonoxacin

Nemonoxacin is a recently developed non-fluorinated quinolone antibiotic. Nemonoxacin has a broad spectrum of activity against Gram-positive, Gram-negative, and atypical pathogens, and a reduced resistance profile compared with other fluoroquinolones. It displays good in vitro activity against MRSA, penicillin-resistant *S. pneumoniae*, and ertapenem-non-susceptible *Enterobacteriaceae*.[45–47] This is achieved by its targeting to both topoisomerase II and IV.

Different Phase II and III clinical trials have investigated the clinical efficacy and safety of nemonoxacin in the treatment of CAP in comparison with levofloxacin.[48–51] A recent meta-analysis of most recent phase III trial found that nemonoxacin and levofloxacin had similar clinical cure rates in the treatment of CAP (OR = 1.05, 95% CI, 0.67–1.64). Nemonoxacin also had a similar microbiologic response rate than levofloxacin (OR = 0.89, 95% CI, 0.44 to 1.81). The safety/tolerability of nemonoxacin was also comparable with levofloxacin, so no significant differences were found in adverse events between the two drugs (OR = 1.08, 95% CI, 0.81 to 1.43). In subgroup analysis of dose of nemonoxacin (500 or 750 mg) and individual pathogens, results remained unchanged.[47] It has received priority review status by the FDA as a "qualified infectious disease product" once further phase III studies are available documenting its safety and efficacy.

Investigational Drugs in Phase I and II Clinical Trials

Several drugs for the treatment of CAP are currently being investigated in phase I and phase II clinical trials. Quinolone are the leading antibiotic class, with 6 compounds under clinical testing. Of this, ACH-702, WCK-771, WCK-2389 and KPI-10 are new quinolones with activity against common respiratory pathogens, including resistant isolates, and with potential to treat respiratory tract infections. Nevertheless, these drugs have not yet been studied in phase I clinical trials. The next groups of antibiotic are tetracyclines and ketolides, with three drugs in study. Oxazolidinones are also an important class, with two compounds currently in clinical trials. Finally, a non-antibiotic drug with antitoxin activity completes the compounds under investigation. The targets of most of these drugs are not only patients with CAP but also patients with other types of infections. The phase I and II clinical trials including these drugs for patients with CAP are listed in Table 2.

Zabofloxacin

Zabofloxacin is a novel fluoroquinolone with identical mechanism of action than other quinolones and with a broad-spectrum against respiratory pathogens. It has proven bactericidal efficacy both in vitro and in vivo against Gram-positive and Gram-negative pathogens, including *S. pneumoniae, S. aureus, H. influenzae, and M. catarrhalis*. By contrast, zabofloxacin has no activity against major pathogens associated with hospital-acquired pneumonia, such as *P. aeruginosa* and *Acinetobacter baumannii*.[52,53] Scarce clinical data exist regarding the efficacy of this drug in pneumonia. Only, a phase II clinical trial to evaluate the safety and efficacy of oral zabofloxacin compared with oral levofloxacin in CAP has been performed, and although it was finished in 2012, results have not been yet published.[54]

Aravofloxacin (JNJ-Q2)

Aravofloxacin (JNJ-Q2) is a novel fifth-generation fluoroquinolone that has excellent in vitro and in vivo activity against a variety of Gram-positive and Gram-negative organisms. In vitro studies that included 3757 isolates indicate that aravofloxacin has potent activity against pathogens responsible for CAP, such as *S. aureus* (MIC_{50}, 0.12 μg/mL) and *S. pneumoniae* ($MIC_{50/90}$, 0.008/0.015 μg/mL), being >16-fold more potent than moxifloxacin and levofloxacin. The activity of avarofloxacin was equivalent to that of moxifloxacin against Gram-negative microorganisms.[55,56] Aravofloxacin has also been shown to have a higher barrier to resistance compared to other agents in the class and it remains highly active against drug-resistant organisms, including MRSA, ciprofloxacin-resistant *S. aureus*, and drug-resistant *S. pneumonia*.[55,56] A Phase II, randomized,

Table 2 Compounds in Phase I and II Clinical Trials

Drug name	Drug Class	Development Phase	Study Results *	NCT	Reference
Zabofloxacin	Fluoroquinolone	Phase II	No results available	NCT00640926	
Aravofloxacin	Fluoroquinolone	Phase II	Clinical cure: 87.5% (14/16) vs 81.3% (13/16) comparator	NCT01198626	57
Nafithromycin	Ketolide	Phase II	Clinical response: 91.9% (68/74) vs 87% (67/77) comparator	NCT02903836	61
TP-271	Tetracycline	Phase I	No results available	NCT02724085	
Gepotidacin	Tetracycline	Phase I	No results of efficacy available	NCT02853435	64
Radezolid	Oxazolidinone	Phase II	Clinical cure: 78% (103/132)	NCT00640926	66
Delpazolid	Oxazolidinone	Phase I	No results of efficacy available	NCT01842516	68
CAL02	Antitoxin agent	Phase II	Clinical cure: 100% (12/12) vs 100% (5/5) comparator	NCT02583373	70

Note: * Expressed in percentage and number.

double-blind, multicenter study evaluating the efficacy of aravofloxacin (150 mg iv every 12 hours, followed by 250 mg orally every 12 hours) versus that of moxifloxacin (400 mg iv or orally every 24 hours) for the treatment of CAP has been published.[57] The study was designed to enroll 120 subjects to ensure ability to detect non-inferiority of aravofloxacin to moxifloxacin; however, this was not feasible due to the strict inclusion criteria. Clinical cure was achieved in 87.5% (14/16) and 81.3% (13/16) of patients treated with aravofloxacin and moxifloxacin, respectively (OR = 1.66, 95% CI, 0.23 to 11.75). However, the small sample sizes preclude to have sufficient power to detect non-inferiority for clinical test of cure. Adverse events were comparable between aravofloxacin and moxifloxacin, with the exception of nausea and vomiting.[57] Considering its early stage of development, the definitive role of aravofloxacin against these infections and its safety profile will have to be determined in future phase III studies.

Nafithromycin

Nafithromycin (WCK 4873) is a novel antimicrobial agent of the ketolide class that interacts at multiple positions on the ribosome, thus allowing for activity against macrolide-resistant organisms.[58] In a collection of 4739 clinical isolates, compiled worldwide, the antibiotic showed in vitro potency against *S. pneumoniae* ($MIC_{50/90}$, 0.015/0.06 µg/mL), *S. aureus* ($MIC_{50/90}$, 0.06/>2 µg/mL), and comparable in vitro activities against *H. influenzae* and *M. catarrhalis* isolates (MIC_{90} 0.25 µg/mL).[59] This drug has also an attractive pharmacokinetic profile, a good absorption, high levels in lung tissue, a good penetration in alveolar macrophages, and it seems to have an acceptable hepatic safety.[60] A phase II, randomized, placebo-controlled study evaluated the safety, tolerability, pharmacokinetics, and efficacy of oral nafithromycin (800 mg 3 days and 5 days) versus oral moxifloxacin in the treatment of CAP in adults. The primary endpoint (clinical response at day 4, tested in the ITT population) was achieved in 91.9% (68/74), 89% (65/73) and 87% (67/77) of patients in the nafithromycin 3 days, nafithromycin 9 days and moxifloxacin groups, respectively. Rates of serious adverse events were similar between groups (around 1–2%), nevertheless, nafithromycin had more non-serious adverse events, mainly gastrointestinal disorders (14.9% versus 12.5% versus 7.9%, respectively).[61]

TP-271

TP-271 is a promising new tetracycline with in vitro activity against the major pathogens associated with CAP.[62] TP-271 is currently under assessment in phase I trial, single ascending-dose, in order to evaluate its safety, tolerability, and pharmacokinetics in patients with pneumonia.[63]

Gepotidacin

Gepotidacin is a broad-spectrum antibacterial agent with a novel mechanism of action. It inhibits the B subunit of DNA gyrase. Initial phase I studies with escalating oral dosing have demonstrated a safety profile similar to those of other marketed antibiotics.[64] Its antibacterial activity and its properties make it have a potential role in the treatment of CAP.

Radezolid

Radezolid (RX-1741) is a novel oxazolidinone antibiotic agent and is the first biaryloxazolidinone in clinical development. It is being developed for the treatment of serious MDRO infections, including infections caused by linezolid-resistant strains. Radezolid has shown excellent activity against a number of key CAP pathogens, including *S. pneumoniae, S. aureus, H. influenzae*, and atypical respiratory pathogens.[65] It is 11 times more active in comparison to linezolid against a series of bacterial species capable of surviving intracellularly, such as *Staphylococcus, Chlamydia*, and *Legionella* species. A phase II clinical trial has been completed evaluating radezolid in mild-to-moderate CAP at three different doses: 300 mg once daily, 450 mg once daily, and 450 mg twice daily for 7–10 days. The study showed comparable efficacy across all three doses, with clinical cure rates ranging from 78 to 92%.[66] However, its safety profile has not been established and its advantages over linezolid and tedizolid are not clear at present. Redezolid is ready for entering a phase III trial.

Delpazolid

Delpazolid (LCB01-0371) is a new oxazolidinone with good in vitro and in vivo activities against Gram-positive bacteria, similar to linezolid.[67] The drug has also interesting properties such as high aqueous solubility and good absorption, distribution, metabolism, excretion, and toxicity and PK profiles.[68] There are no phase II studies ongoing; however, its characteristics make it have a potential role in the treatment of CAP.

CAL02

CAL02 is a non-antibiotic drug, a novel antitoxin agent with a singular mechanism of action. CAL02 consists of a mixture of liposomes that capture bacterial toxins known to dysregulate inflammation, cause organ damage, and impede immune defense. Preclinical data show that when combined with antibiotics, CAL02 substantially improves survival outcomes in mice with severe pneumonia and bacteremia.[69] A randomized, phase II, double-blind, multicentre, placebo-controlled trial was done in patients with severe pneumococcal CAP who required ICU admission. Nineteen patients were randomly assigned, resulting in 14 patients in the CAL02 groups (3 assigned to low-dose CAL02 and 11 assigned to high-dose CAL02) and 5 in the placebo group. Despite the limited number of patients, better patient outcomes were observed in the high-dose CAL02 group compared with placebo, with similar rates of side effects.[70] The results of this study support further clinical development of CAL02 and provide a solid basis for a larger clinical study.

Conclusion

The treatment of CAP is a continuous challenge due to the constant changes in its etiological spectrum and the appearance of bacterial resistances. In recent years, new antimicrobials have been approved for use in CAP therapy, both at the hospital and community levels. Currently, several antimicrobials are being evaluated in phase III clinical trials and their results allow their possible incorporation into the treatment of CAP. Several drugs are being evaluated in preclinical phases with the aim of demonstrating efficacy against the majority of pathogens causing CAP. Quinolone are the leading antibiotic class, with more compounds under clinical testing. However, increasing concerns exist about its safety due to the reporting of some rare adverse events as tendinopathies or aortic dissection. On this basis, tetracyclines and ketolides could be interesting drugs to explore.

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