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NOVEL ANTIMICROBIAL AGENTS: A REVIEW

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Abstract

Microbiological evolution and bacterial resistance have accelerated dramatically over the last decade. Today, bacterial infections have become an important cause of morbidity and mortality, as well as a major challenge to antimicrobial therapy. The need for novel antimicrobials has been greater than ever in the face of increasing resistance to the older ones, and increasingly tough management of bacterial infections due to the augmented prevalence of multidrug-resistant (MDR) pathogens. Appropriate stewardship infection control is being optimized, whilst pharmaceutical industrial research appears to be a step behind. Currently, there is stagnation in the development of novel antibacterial classes and significant limitations in the advancement of already existing ones. A review of the available literature regarding newer antimicrobial agent was conducted. A number of novel antibacterial agents are being clinically evaluated to target MDR bacteria; however, most of these current clinical progressions involve existing antimicrobial drug classes rather than discovering new ones. This paper reviews antibacterial compounds, in clinical development, derived from known and new classes of antibiotics which show promising activity against MDR bacteria. A major emphasis will be on antibacterial coverage, promising indications, current development stage, and pharmacological action.

Key Words: Novel antimicrobial agents, MDR, MRSA, VRSA, VRE, *Pseudomonas*.

1. Introduction

Antimicrobials are distinguished pharmacotherapeutic agents among other medicinal classes. They are the only class which acts primarily on bacteria rather than human tissues or endogenous products [1]. Apparently, these anti-infective substances have decreased mortality rates of serious infections, and performed a cardinal function in medicinal and surgical advancements [2].

In the past years, health-care associated infections have become an important cause of morbidity and mortality, whilst the incidence of antibiotic-resistant bacteria has increased dramatically and become a serious threat. In fact, the management of bacterial infections is getting increasingly tough due to augmented prevalence of MDR pathogens, which represent a major challenge to antimicrobial therapy [3–6].

There are several reasons which led to this alarming situation, major concerns include the rising menace of methicillin-resistant *Staphylococcus aureus* (MRSA) strains, as well as other drug-resistant Gram positive pathogens, particularly vancomycin-resistant enterococci (VRE) and penicillin-resistant *Streptococcus pneumonia* [7]. Similarly, a striking increase of infections due to fluoroquinolone-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Klebsiella* species, as well as *Acinetobacter* species has been obviously noted [8].

Microbial resistance is now frequently confronted to common antibiotics being used in clinical settings, and there is an imperative demand for newer anti-infective agents to overcome emerging multi-drug resistance. Today, the need for novel antimicrobials has been greater than ever in the face of increasing resistance to the older ones and increasingly tough management of bacterial infections. In spite of urge for such agents, the scientific progression in terms of antimicrobial research and discovery of new antibacterial molecules has declined dramatically in the past few years. Currently, there is stagnation in the development of novel antibacterial classes and significant limitations in the advancement of already existing ones.

This review focuses on antibacterial compounds, in clinical development, derived from known and new classes of antibiotics which show promising activity against MDR bacteria. A major emphasis will be on antibacterial coverage, promising indications, current development stage, and pharmacological action.

2. Methods

A systemic review of relevant studies was conducted using the PubMed database from 2000 to 2013. The keywords used were ‘novel antimicrobial agents’, ‘newer antimicrobial agents’, ‘new antibiotics’, ‘multi drug resistant’, ‘MRSA’, ‘VRSA’, ‘VRE’, and ‘*Pseudomonas*’. Studies written in English were only considered eligible for inclusion.

3. Results

Table 1 presents novel antimicrobial agents in clinical development with focus on the pharmacological class, clinical development stage, main indications, and route of administration, as well as the developing pharmaceutical company.

The table illustrates that most newantibacterialsbelong to already existing antimicrobial classes, and are promising for

CAP, cSSSIs, and other common bacterial infections. A detailed description about novel antimicrobial findings is as follows:

3.1. New Generation Aminoglycosides: Neoglycosides

Aminoglycosides are well known antibacterials for more than 50 years. They are broad-spectrum agents that can be used solely as a monotherapy or synergistically with other antibiotics such as β -lactams.

Plazomicin is a new generation aminoglycoside known as neoglycoside. It is a novel agent with resistance to enzymatic inhibition [9]. Therefore, bacterial enzymes that inactivate gentamicin do not affect plazomicin [10]. With respect to its mechanism of action, plazomicin inhibits bacterial protein synthesis and exhibits a dose-dependent bactericidal activity; as well, it retains the broad spectrum of activity against Gram negative and Gram positive bacteria. Furthermore, it displays synergy against MRSA when combined with daptomycin and ceftobiprole, and against *Pseudomonas* when combined with cefepime, doripenem, and piperacillin-tazobactam [11]. Comparing it to current licensed aminoglycosides, plazomicin was found to have a lower minimum inhibitory concentration (MIC) for *Acinetobacter* species; and there was no evidence of ototoxicity or nephrotoxicity on healthy volunteers [12,13].

3.2. Quinolones

A number of newer fluoroquinolones are under development to cover *Pseudomonas* and have additional anti-MRSA activity [14]. For instance, NXL-101, primarily a topoisomerase IV inhibitor, covers Gram negative bacteria and MRSA. It possesses activity against strains with mutation in the gyrase enzyme, which is the main target for the fluoroquinolones. However, NXL-101 was associated with significant QT prolongation, and thus it was terminated after phase I clinical trials [10,15,16].

Two more compounds are in phase II studies. Delafloxacin is active against a number of quinolone-resistant strains. It is notably more active than other quinolones against Gram positive organisms including MRSA, as well as Gram negative organisms and anaerobes. It is currently in phase II clinical trials for oral treatment of community-acquired pneumonia (CAP) and for intravenous treatment of complicated skin and skin structure infections (cSSSIs). Unlike other agents within this group, delafloxacin maintains activity in acidic mediums, thus being suitable for treatment of infections in low pH environments such as the skin, as well as vaginal and urinary tracts [17].

Nemonoxacin, on the other hand, is a non-fluorinated quinolone with a wide spectrum covering MDR Gram positive and Gram negative pathogens, including MRSA and VRE [18,19]. It has completed phase II clinical studies for the

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treatment of CAP and diabetic foot infections[19]. For CAP, it has been found to be comparable to levofloxacin in terms of safety and efficacy [18].

Finaxofloxacin, a third newer quinolone, demonstrates activity against MRSA, VRE, anaerobes, and other drug-resistant strains. Oral and intravenous formulations of this novel agent appear to be safe without QT prolongation and other serious adverse events associated with fluoroquinolones[20].Interestingly, finaxofloxacinactivity is enhanced under acidic pH,making its oral formulation a promising option in acidic conditions,such as *Helicobacter pylori*related diseases andurinary tract infections (UTIs)[21].

Another related agent, prulifloxacinmay have a role in acute exacerbation of chronic bronchitis [22].Similarly, ACH-702 is another agent that is highly active against a spectrum of Gram positive and Gram negative bacteria including MRSA and *Mycobacterium tuberculosis*.Yet, because of extensive metabolism following systemic administration, this molecule is being followed up for topical use only[23-25].

3.3.Oxazolidinone

Oxazolidinones are new antibiotics with proven efficacy against MDRGram positive bacteria including MRSA, VRE, and *Streptococcus pneumoniae*. They also have an appreciable efficacy against *Mycobacterium tuberculosis* and *Nocardia*[26].

Tedizolid and radezolid are two noveloxazolidinoneswith a fewbetterments over linezolid. Tedizolid, formerly known as torezolid,is a second-generation oral oxazolidinone. It has proven a good potency against Gram positive bacteria, including linezolid-resistant strains [27,28]. It can be administered both intravenously and orally [29]. Oral tedizolid is active against MRSA [30,31]. In fact, MICs are lower compared with linezolid for staphylococci, streptococci, and enterococci;thus it may retain sufficient activity against a number of linezolid-resistant strains [32].Moreover, tedizolidhas a mean half-life of 8 – 11.1 hours, which is about two-fold longer than that of linezolid;hence,it may be dosed once-daily [33].

Radezolid also displays a good activity against linezolid-resistant strains. Available data have demonstrated an interesting property of this molecule in the treatment of persistent infections with intracellular organisms, due to the fact that it was shown to achieve 11 times higher levels inside macrophages and neutrophils [34,35].Radezolid has completed phase II clinical trials in complicated skin and soft tissue infections, and CAP with positive results [15].

Among other oxazolidinones being developed, sutezolid was shown to be superior to linezolid in terms of antimycobacterial activity [36].

3.4. β -lactams and β -lactamase Inhibitors

Ceftaroline is a new fifth generation cephalosporin that has been recently approved by the US Food and Drug Administration (FDA) for clinical use. It is distinguished with proven activity against MDR Gram positive organisms including MRSA and vancomycin-resistant *S. aureus* (VRSA). Ceftaroline was found to be non-inferior to standard regimens for the treatment of CAP and cSSSIs in phase III clinical studies [37]. Another agent, ceftobiprole, possesses similar features, yet it has failed to gain FDA approval [38,39].

With respect to newer carbapenems undergoing clinical evaluation, a new β -methyl carbapenem, razupenem, has completed phase II clinical studies in complicated skin and soft-tissue infections. The spectrum of razupenem activity includes MRSA and vancomycin-resistant *Enterococcus faecalis* but not *Enterococcus faecium*, as well as, Enterobacteriaceae [14,40].

Likewise, sulopenem is being evaluated in phase II clinical trials for skin and soft-tissue infections, and CAP. It is active against Gram positive and Gram negative organisms, as well as anaerobes, yet it lacks antipseudomonal coverage [15].

New β -lactamase inhibitors development is also in progress. Among these, avibactam has a broad spectrum of activity including the *Klebsiella pneumoniae* carbapenemase (KPC) enzyme family. A couple of investigations have evaluated the spectrum of activity in combination with ceftazidime and ceftaroline. The spectrum of such combinations relies obviously on the spectrum of the β -lactam compound. For instance, ceftazidime-avibactam is active against *Pseudomonas* but not MRSA, whereas, the opposite is true for ceftaroline-avibactam [41,42].

3.5. Macrolides/Ketolides

Ketolides are derivatives of macrolides with replacement of L-cladinose on the macrolide ring with a 3-keto group [15]. Fidaxomicin is one of the recently approved antimicrobials for clinical use. It is mainly indicated for *Clostridium difficile*-associated diarrhea. Clinical trials comparing it to vancomycin have demonstrated lower rates of recurrence for some strains of *Clostridium difficile*, hence it may be favored in recurrences [43].

Cethromycin and solithromycin are two new ketolides that are highly active against Gram positive organisms, yet their spectrum of coverage is modest with respect to Gram negative ones. Cethromycin, a novel once daily oral ketolide, was

FDA approved as an orphan drug for the treatment of bioterrorist threats such as anthrax and plague[39,44,45]. Similarly, it has been submitted as a New Drug Application (NDA) for the treatment of mild-to-moderate pneumonia; and phase III studies have revealed positive outcomes. Cethromycin has proven good activity against *S. pneumoniae*, including drug-resistant strains, with some additional activity against *Moraxella catarhalis*, *Haemophilus influenza*, and atypicals[46].

On the other hand, solithromycin is another promising agent being developed for the treatment of CAP and other infections[47]. Based on the evaluation of in vitro studies comparing its MIC for various pathogens, solithromycin may have a future place in the pharmacotherapy of skin and soft tissue infections, as well as CAP[48].

3.6. Tetracyclines

Tigecycline is relatively a new broad-spectrum glycylicycline among approved tetracyclines. It is useful in polymicrobial infections, yet it has no anti-pseudomonal coverage. The advantage of tigecycline over its congeners is that it is not a substrate for drug efflux or the ribosomal protection proteins, mechanisms by which tetracyclines' resistance usually develops.

Amongst novel anti-infective molecules within this class, omadacycline is a broad-spectrum aminomethylcycline with similar attributes of tigecycline including anti-MRSA coverage. Unlike tigecycline, omadacycline is absorbed orally with the possibility to be administered once daily. Evidently, oral and intravenous forms are being under development for the treatment of cSSSI and CAP[39,49].

Similarly, TP-434 is another new compound that displays several similar properties of omadacycline[39].

3.7. Glycopeptides

Telavancin, a once daily derivative of vancomycin, is a newly approved lipoglycopeptide for the treatment of cSSSI. It covers all Gram positive pathogens including vancomycin-resistant isolates. Telavancin acts by targeting cell wall synthesis and affecting membrane integrity[50,51]. A detailed description about its mechanism of action reveals that this agent exhibits a dual one. First, it inhibits peptidoglycan chain formation by blocking transpeptidation and transglycosylation during cell wall formation. Second, it increases bacterial cell membrane permeability[52].

Likewise, oritavancin is a bactericidal lipoglycopeptide that exhibits a concentration dependent post antibiotic effect [52]. It acts by binding to the terminal D-alanyl-D-alanine, and to the pentaglycyl bridge in the peptidoglycan moiety; therefore, it inhibits transglycosylation. Oritavancin has a broad-spectrum of activity against Gram positive pathogens

Fouad R. Sakr*et al. /International Journal Of Pharmacy&Technology including MRSA, VRSA, and VRE. Pharmacokinetically speaking, it has long half-life and thus it is suitable for once daily dosing. Moreover, unlike other lipoglycopeptides, oritavancin may not require significant dosage adjustment in renal failure, since it undergoes mainly hepatic elimination [51,53].

A third agent in this class that covers some strains of VRE is dalbavancin. It is a very long acting glycopeptide with a half-life exceeding 10 days in humans, hence, it may be candidate for once weekly dosing [51].

3.8. Glycolipodepeptide

Ramoplanin is a glycolipodepeptide that acts by inhibiting peptidoglycan formation, and thus inhibits cell wall synthesis, without complexing with the D-Ala-D-Ala sequence of cell wall precursors like other glycopeptides. When administered orally, it is not absorbed systemically, so it may play an important role in local gastrointestinal infections. With respect to its current clinical development, ramoplanin is undergoing phase III clinical trials for use in *Clostridium difficile*-associated diarrhea [54].

3.9. Trimethoprim-Related Drug

Iclaprim is a dihydrofolate reductase inhibitor being developed as a sole agent, in spite of the synergy that it has demonstrated in combination with sulfonamides. It has been accepted as a NDA by the US FDA for the treatment of complicated skin and soft-tissue infections. Phase III clinical studies have demonstrated that oral and intravenous iclaprim displays good activity against *S. aureus* and *S. pneumoniae*, including several resistant strains, as well as *H. influenzae*, *Moraxella catarrhalis*, and *Legionella pneumophila*. Therefore, this agent appears promising for respiratory tract infections [55].

3.10. Pleuromutilins: Pleuromutilins are antimicrobial agents that exert their antibacterial activity by protein synthesis inhibition. Retapamulin is the first pleuromutilin licensed for clinical use. It is approved topically for the treatment of uncomplicated superficial skin infections [56].

BC-3781 is a novel agent within this category being developed for systemic use. It has completed phase II clinical studies, with intentions to have a place in treating serious skin infections. Compared to vancomycin, BC-3781 appears to have similar efficacy, along with its good safety and tolerability profile [57].

3.11. Efflux Pump Inhibitors

Efflux pumps are amongst the well known mechanisms by which antibacterial resistance commonly develops. Efflux pumps are able to extrude structurally diverse compounds, including antibiotics used in a clinical setting. In the

continuous search for resistance-modifying agents, efflux pump inhibitors are novel compounds that target the bacterial efflux pumps. Clinical investigations are in progress, and the outcomes appear to be promising[58,59].

4. Conclusion

The continuous research and development of new antibacterial agents is an active progressive advancement in the pharmacotherapeutics of infectious diseases. However, the rate of antimicrobial resistance is increasing while efforts in discovering new agents are turning down and getting lessened.

Recently, the most dangerous MDR bacteria were described as the “ESKAPE” pathogens: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species underline that these pathogens are significantly breaking free the antibacterial action of most antibiotics [60].

Adding to these concerns, the current status has been aggravated by the stagnation in the development of novel antimicrobial agents to treat these threats. Similarly, according to the Infectious Diseases Society of America (IDSA), the number of approved antibacterial drugs has steadily declined in the past decade [16,61,62].

Despite the fact that there is no existing antibiotic to which resistance does not develop, available clinical efforts, in the mean time, are directed against emerging invasive MDR pathogens including MRSA, VRSA, VRE, *Pseudomonas* species, and others. Furthermore, it is obvious that the majority of these advances are in terms of upgrading previously existing antibiotic classes, and upgrades for novel classes are still poor. In short, these novel agents require further clinical evaluation to ensure a very appropriate, and maybe restricted, future clinical applications in an attempt to combat the active evolution of bacterial resistance, as well as the persistent need of new antibacterials.

Table 1: Novel antimicrobial agents: a focus on the pharmacological class, development stage, main indications, and route of administration.

Compound name	Pharmacological class	Development stage	Main indications	Route of administration	Developing company
Plazomicin	Neoglycoside (aminoglycoside)	Phase 2	Serious Gram negative infections	iv	Achaogen
Delafloxacin	Quinolone	Phase 2	CAP cSSSIs	Oral iv	Rib-X
Nemonoxacin	Quinolone	Phase 2	DFI CAP	Oral iv	TaiGen
Finafloxacin	Quinolone	Phase 3	<i>H. pylori</i> UTI AOM	Oral iv Topical	MerLion

Prulifloxacin	Quinolone	Phase 3 Approved in Japan, Italy	AECB UTI Infectious diarrhea	Oral	Optimer
ACH-702	Quinolone	Preclinical	-	Topical	Achillion
Tedizolid	Oxazolidinone	Phase 3	ABSSSI	Oral iv	Trius
Radezolid	Oxazolidinone	Phase 2	CAP cSSSIs	Oral iv	Rib-X
Sutezolid	Oxazolidinone	Phase 2	TB	Oral	Pfizer
Ceftaroline	Cephalosporin (5 th generation)	FDA approved	CAP cSSSIs	iv	Forest
Razupenem	Carbapenem	Phase 2	cSSSIs	iv	Novartis
Sulopenem	Carbapenem	Phase 2	CAP cSSSIs	Oral iv	Pfizer
Fidaxomicin	Ketolide	FDA approved	CDAD	Oral	Optimer
Cethromycin	Ketolide	FDA approved (orphan drug)	Bioterrorist threats	Oral	Advanced Life Sciences
Solithromycin	Ketolide	Phase 2	CAP	Oral iv	Cempra
Omadacycline	Tetracycline	Phase 3	CAP cSSSIs	Oral iv	Paratek
TP-434	Tetracycline	Phase 2	cIAI	Oral iv	Tetraphase
Telavancin	Glycopeptide	FDA approved	cSSSIs	iv	Theravance
Oritavancin	Glycopeptide	Phase 3	ABSSSI	iv	The Medicine Co
Dalbavancin	Glycopeptide	Phase 3	ABSSSI	iv	Durata
Ramoplanin	Glycolipodepeptide	Phase 3	CDAD	Oral	Nanotherapeutics
Iclaprim	Dihydrofolatereductase inhibitor	Phase 3	cSSSIs	Oral iv	Arpida
BC-3781	Pleuromutilin	Phase 2	cSSSIs	Oral iv	Nabriva

Abbreviations:

iv: intravenously; CAP: community acquired pneumonia; cSSSIs: complicated skin and skin structure infections; DFI: diabetic foot infection; *H. pylori*: *Helicobacter pylori*; UTI: urinary tract infection; AOM: acute otitis media; AECB: acute exacerbation of chronic bronchitis; ABSSSI: acute bacterial skin and skin structure infections; TB: tuberculosis; FDA: Food and Drug Administration (USA); CDAD: *Clostridium difficile*-associated diarrhea; cIAI: complicated intra-abdominal infection.

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