Clinical Microbiology and Infection 23 (2017) 697–703

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Review

New and improved? A review of novel antibiotics for Gram-positive bacteria

M. Abbas [1, 2, *], M. Paul [3, 4], A. Huttner [1, 2]

[1] Infection Control Programme, Geneva University Hospitals, Geneva, Switzerland
[2] Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland
[3] Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel
[4] The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

ARTICLE INFO

Article history:
Received 7 April 2017
Received in revised form
30 May 2017
Accepted 1 June 2017
Available online 19 June 2017

Editor: Prof. L. Leibovici

Keywords:
Antibiotics
Community-acquired pneumonia
Gram-positive bacteria
Healthcare-associated pneumonia
Methicillin-resistant *Staphylococcus aureus*
Novel antimicrobials
Skin and soft-tissue infections
Vancomycin-resistant *Enterococcus faecium*

ABSTRACT

Background: The number of antibiotics in the pipeline targeting Gram-positive pathogens has increased in recent years.
Aims: This narrative review aims to provide a summary of existing evidence on efficacy, microbiological spectrum and safety of novel systemic antibiotics that have either recently been licensed or completed phase III trials, and possess activity predominantly against Gram-positive organisms.
Sources: A review of the published literature via the MEDLINE database was performed. In addition, ongoing trials were identified through a search of the clinical trial registration platform clinicaltrials.gov, and when necessary, pharmaceutical companies responsible for the development of the drug were contacted for further information.
Content: Data on development, microbiological spectrum, pharmacokinetic/pharmacodynamic properties, clinical efficacy, safety and cost are presented for the new cephalosporins ceftaroline and ceftobiprole; the lipoglycopeptides dalbavancin, oritavancin and telavancin; the fluoroquinolones delafloxacin, nemonoxacin and zabofloxacin; the dihydrofolate-reductase inhibitor iclaprim; the pleuromutilin lefamulin; and the tetracycline omadacycline.
Implications: Although promising, these new antibiotics have so far been tested in non-severe infections whose treatment is generally uncomplicated and whose aetiologies were not predominantly multidrug-resistant pathogens. None of the new antibiotics have shown superiority to standard care, and none have been investigated for patient-relevant outcomes. Safety and pharmacokinetic data continue to be lacking. How these new drugs are to be integrated into the current armamentarium remains to be established.
M. Abbas, Clin Microbiol Infect 2017;23:697

Introduction

The emergence and spread of resistant Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* spp. (VRE) have spurred the development of new drugs, with recent legislative and regulatory changes promoting and facilitating antibiotic discovery and development [1]. These include granting 'fast-track' or 'qualified infectious disease product' (QIDP) status, which provides expedited review or five additional years of market exclusivity, respectively [2].

The purpose of this narrative review is to summarize the existing evidence on efficacy, microbiological spectrum, and safety of systemic antibiotics (a) predominantly targeting *S. aureus* or enterococci and (b) that have been recently licensed or have undergone clinical phase III trials for which at least preliminary results are available.

Expectations from evidence on antibiotics against Gram-positive bacteria

We considered the evidence in relation to the following clinical expectations. In the community, we need oral antibiotics active against penicillin-resistant *Streptococcus pneumoniae* and MRSA. The relevant infections are upper or lower respiratory infections

* Corresponding author. M. Abbas, Infection Control Programme, Geneva University Hospitals, Geneva, Switzerland.
E-mail address: Mohamed.Abbas@hcuge.ch (M. Abbas).

http://dx.doi.org/10.1016/j.cmi.2017.06.010
1198-743X/

and skin/soft-tissue infections, respectively. The patient-relevant outcomes of interest are days of illness, time to return to baseline activity and admissions to hospital. In hospitals, we need better antibiotics against MRSA and VRE. The infections of interest are mainly bacteraemia, hospital-acquired and ventilator-associated pneumonia and endocarditis caused by these pathogens. The main outcome of interest is all-cause mortality. Other outcomes of interest include duration of hospital stay, resource use, adverse events and resistance development.

Cephalosporins

Often called 'fifth-generation' cephalosporins, ceftaroline and ceftobiprole are the first β-lactams to possess anti-MRSA activity as a result of their high affinity for penicillin-binding protein-2a. Though both have some activity against select Gram-negative pathogens, these drugs achieved approval for their anti-Gram-positive activity. Their pharmacokinetic profiles are detailed in the Supplementary material (Table S1). Both are expensive (Table 1).

Ceftaroline

Ceftaroline fosamil (Teflaro® in the USA and Zinforo® in Europe) achieved European Medicines Agency (EMA) approval in 2012. An inactive prodrug, ceftaroline fosamil, is rapidly converted *in vivo* to the active metabolite ceftaroline.

Ceftaroline has a broad range of activity (Table 1). However, both low-level [3] and high-level [4] resistance to ceftaroline have been observed in MRSA strains; particularly concerning are recent reports of resistance discovered in clinical MRSA isolates from patients in geographic regions never exposed to the drug [5,6]. Little is known of ceftaroline's ecological impact, though it is expected to be minor, as the drug is not excreted in the faeces [7].

Two multicentre international phase III non-inferiority randomized controlled trials (RCT) for community-acquired pneumonia (CAP) were conducted [8,9] in which ceftaroline achieved non-inferiority to ceftriaxone (see Supplementary material, Table S2). Both studies excluded patients admitted to the intensive care unit (ICU) and those with co-morbidities; there were no more than ten multidrug *S. pneumoniae* isolates and one MRSA isolate in any of these trials. Three phase III non-inferiority RCT for complicated skin and soft-tissue infections (cSSTI) showed ceftaroline to be non-inferior to vancomycin plus aztreonam (see Supplementary material, Table S2) [10–12]. One of the studies had broader inclusion criteria and tested a higher dose of the drug [12]. In these trials, MRSA represented between 30% and 40% of positive cultures. Although retrospective data from the industry-sponsored CAPTURE registry suggest that ceftaroline may have a role in hospital-acquired pneumonia (HAP) [13] and diabetic foot infections [14], patients with these infections were excluded from the trials.

Ceftaroline appeared, in those trials, to be well tolerated (see Supplementary material, Table S3), but several post-market reports of severe myelotoxicity associated with prolonged exposure (>7 days) to ceftaroline have emerged [15,16].

Ceftobiprole

Although still unapproved by the US Food and Drug Administration (FDA) and EMA, ceftobiprole medocaril (Zevtera®, Mabelio®) is approved in 14 European countries and received FDA QIDP status in 2015.

An inactive prodrug, ceftobiprole medocaril, is rapidly converted to the active metabolite ceftobiprole and has a broad range of activity (Table 1), including variable activity against *Pseudomonas aeruginosa* and other AmpC over-expressors [17,18]. Given its undetectable concentrations in faeces, ceftobiprole is expected to have a minor effect on intestinal flora [19].

Two phase III trials showed non-inferiority of ceftobiprole (see Supplementary material, Table S2) in the treatment of complicated skin and skin-structure infections [20,21], but the drug was not approved for these indications due to FDA concerns regarding the trials' data quality control. In more recent trials, non-inferiority to ceftriaxone with or without linezolid (see Supplementary material, Table S2) was demonstrated for treatment of CAP [22] as was non-inferiority to ceftazidime with linezolid for non-ventilator-associated HAP [23]. In the latter trial, however, non-inferiority was not achieved in patients with ventilator-associated pneumonia (VAP), with cure rates in the VAP subpopulation of only 23% versus 36%. The drug's variable activity against *P. aeruginosa* and the fact that it is hydrolysed by extended-spectrum β-lactamase and AmpC β-lactamases may have played a role [18]. Also, in this trial, there were more patients with MRSA cultures (11.4%) than in the earlier trial (only one patient).

Limited experience from these trials shows that ceftobiprole appears to be well-tolerated (see Supplementary material, Table S3).

Lipoglycopeptides

Both dalbavancin and oritavancin are newly on the market but are not new drugs. Like vancomycin, they exert their bactericidal activity by binding to the D-alanyl-D-alanine residue on growing peptidoglycan chains, preventing transpeptidation and hence cell-wall formation [24]. Unlike vancomycin, these semi-synthetic molecules possess a lipid side-chain conferring new pharmacokinetic properties (see Supplementary material, Table S1), including high protein-binding and unusually long half-lives, which allow for single-dose therapy. They are active against MRSA, coagulase-negative staphylococci, vancomycin-susceptible *Enterococcus faecium*, but not VRE (Table 1). Their current price is very high (Table 1).

Dalbavancin

Dalbavancin (Xydalba®) was developed in the 1980s through chemical modifications of the teicoplanin scaffold. FDA and EMA approved dalbavancin for the treatment of adult acute bacterial skin and skin-structure infections (ABSSSI) in 2014 and 2015, respectively.

After a single dose in healthy subjects, measurable concentrations in the faeces are found up to day 14, with increased *Enterobacteriaceae* colonies observed. Dalbavancin therefore has an ecological impact on intestinal flora, although its extent is currently unknown [25].

Although the phase III trials DISCOVER 1 and 2 showed non-inferiority to vancomycin followed by oral linezolid in the treatment of ABSSSI [26], durations and serum trough levels of intravenous vancomycin were not reported. MRSA was isolated in 12.0% of all patients, and 23.6% of patients with positive cultures. These two studies evaluated the efficacy of two weekly doses of dalbavancin. To allow marketing of a single-dose regimen, an additional phase III RCT was performed that showed non-inferiority to the two-dose regimen [27].

Dalbavancin was well-tolerated in these trials (see Supplementary material, Table S3), although liver enzymes were more frequently elevated in dalbavancin-treated versus vancomycin-treated patients [28].

Oritavancin

A vancomycin derivate, oritavancin (Orbactiv®) obtained FDA and EMA approvals for ABSSSI in 2014 and 2015, respectively.