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Emerging drugs for treating methicillin-resistant Staphylococcus aureus

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Abstract

In clinical practice, methicillin-resistant Staphylococcus aureus (MRSA) represents a major threat and has been associated with high rates of inadequate antibiotic treatment and significant increases in morbidity, mortality and overall healthcare costs. The association between the prescription of an inappropriate or delayed antibiotic and impaired clinical outcomes has been widely described, with clinical implications mainly depending on the type of infection and the illness severity.

To face off the threat of MRSA, many new therapeutic options with a peculiar activity against MRSA have been recently developed and approved. New agents are characterized by peculiar issues in terms of spectrum of activity, pharmacokinetics, risk of drug-drug interactions and toxicity, with potential main advantages that should be considered in everyday clinical practice. The most attractive characteristic of new drugs is represented by the broad spectrum of activity against multi-drug resistant pathogens; moreover, new compounds in most cases are characterized by favorable toxicity profiles compared with old drugs currently used in clinical practice.

Some of the new antimicrobials will be also available as oral formulations, with the potential for oral shift even in infections due to resistant pathogens. In particular conditions/populations (e.g. liver failure, renal disease, pregnancy, diabetic, children, elderly) novel antibiotics with reduced toxicity could be an important option, also in discharged patients.

Background

During last decade alarming rates of methicillin-resistance in S. aureus have been reported worldwide, with up to 25% of S.aureus isolates displaying methicillin-resistance in the majority of countries, including USA, Latin America, Sub-Saharian Africa, Russia, India and China[1]. The large SENTRY Antimicrobial Survillance Program has been monitoring S.aureus susceptibility patterns in 45 countries from 1997 to 2016; methicillin-resistant S.aureus (MRSA) accounted for 40,3% of isolates overall, with a geographical variability ranging from 26.8% in Europe to 47.0% in North America[2]. In Europe, MRSA accounts for 17% of isolates overall, even with a wide regional variability, ranging from <1% in northern Europe and up to 25% in southern Europe, including Spain, Portugal, Italy and Greece[3].

Although the burden of MRSA still belongs to hospital setting[4-5], during the last years MRSA has progressively spread also into the community, particularly among outpatients affected by complex clinical problems and having frequent contact with the healthcare system (e.g. residence in a nursing home or long- term-care facility; recent hospitalization during the past 3 months; hemodialysis or intravenous chemotherapy receipt; intravenous therapy, wound care or enteric nutrition at home), thus expanding the at-risk population for the acquisition of infections due to MRSA[6-7-8]. Injection drug users represent an additional expanding population for MRSA colonization and infection development, as recently reported[9].

In clinical practice, MRSA represents a major threat and has been associated with high rates of inadequate antibiotic treatment and significant increases in morbidity, mortality and overall healthcare costs[10-11].

A recently published retrospective analysis using data from the National Inpatient Sample from the Agency for Healthcare Research and Quality for the years 2010-2014 found increasing MRSA-related health-care costs during last years, although costs associated with methicillin-susceptible S.aureus (MSSA)-related infections have converged with costs of similar MRSA-related hospitalizations.

However, MRSA-related hospitalizations have been associated with a higher adjusted mortality rate compared with MSSA infections[12].

A multicenter, retrospective cohort study including inpatient acute-care episodes in ten European hospitals during the period 2010-2011 tried to estimate the impact of antimicrobial resistance on hospital mortality, excess length of stay (LOS) and overall costs. Per infection, S. aureus bloodstream infections had a greater effect on mortality, LOS and costs compared with bloodstream due to Enterobacteriaceae. In this study, however, methicillin resistance did not significantly increase the hazard of death or further prolong the excess LOS compared with bloodstream infections due methicillin-susceptible S. aureus[13].

In clinical practice, S.aureus and its methicillin-resistant variant represent a major problem in a wide spectrum of both community and hospital-acquired infections.

According with data from the SENTRY Antimicrobial Surveillance Program, S.aureus represents the most frequently encountered pathogen in bacteremia worldwide, accounting for 20,7% of cases, with a significant increase in MRSA prevalence until 2008[14].

In the setting of complicated skin and skin structure infections (cSSTIs) MRSA is a major concern. A recently published study evaluated susceptibility patterns of pathogens isolated from patients with community-acquired cSSTIs and reported MRSA rates varying between 15,8% and 21,4%, with the higher rates in Asia and Pacific regions[15]. Moreover, approximately 9% of diabetic patients are colonized by MRSA, and up to 16% of diabetic foot infections are currently due to MRSA[16]. Traditionally, MRSA represents a major problem in hospital- and in Intensive Care Unit – acquired pneumonia[17]. However, recent data emphasized the emerging role of MRSA also in community acquired pneumonia, particularly among patients presenting with specific risk factors such as age > 65 years, with previous antibiotic use, underlying chronic respiratory disorder or chronic renal failure[18-19]

Medical need and existing treatment

The association between the prescription of an inappropriate or delayed antibiotic and impaired clinical outcomes has been widely described, with clinical implications mainly depending on the type of infection and the illness severity[20-21-22-23].

The prompt identification of at-risk population for the development of MRSA infections is crucial to reduce the risk of prescribing an inappropriate empiric antibiotic treatment. However, majority of the recognized risk factors for the acquisition of infections due to MRSA (e.g. older age, hospital-acquired infection, recent antibiotic treatment or hospitalization, chronic underlying diseases) is generic and algorithms with good sensitivity and specificity for the identification of these patients are lacking. MRSA colonization has been strongly associated with an increased risk for the development of infections due to the same pathogen, but nasal swabs are not always performed in routine clinical practice and no recommendations can be made in this regard so far, except for specific clinical settings[24-25].

In this setting, in areas with high MRSA prevalence, the prescription of an early broad-spectrum empiric therapy followed by a prompt de-escalation upon availability of microbiological data should be strongly recommended in severe infections requiring hospitalization and when risk factors for MRSA are present. Available antimicrobials, however, possess some limitations for the use in clinicl practice.

Vancomycin still represents the most used antimicrobial with anti-MRSA activity worldwide[26-27]. However, in a recently published prospective, multicenter, observational study treatment failure and acute kidney injury were reported, respectively, in 18% and 26% of hospitalized adult patients with MRSA bacteremia treated with vancomycin. Moreover, higher vancomycin exposures did not confer a lower treatment failure risk but were associated with more acute kidney injury[28]. Due to the well-known correlation between plasmatic vancomycin concentrations and the development of nephrotoxicity, Therapeutic Drug Monitoring should be considered, particularly among older patients with pre-existing renal failure, co-administration of nephrotoxic drugs or multiple comorbidities[29].

Moreover, vancomycin requires a twice-daily intravenous administration, not allowing the treatment of outpatients.

Daptomycin represents a good alternative to vancomycin for the treatment of the majority of MRSA infections (with the exception of pneumonia due to the inactivation of daptomycin by the pulmonary surfactant) and is widely used in clinical practice due to the rapid bactericidal activity, the good tolerability profile and the once-daily intravenous administration[30]. The use of high daptomicin doses (8-10 mg/kg) is currently well established and is recommended to improve clinical outcomes while minimizing the risk of resistance selection[31-32]. However, due to the need for a once-daily intravenous administration, daptomycin does not represent the ideal option for early-discharge policies and for the treatment of outpatients. Although daptomycin is commonly used as monotherapy in majority of clinical settings, recent data support an investigational use of daptomycin in combinations with new antimicrobials (e.g. caftaroline) for the treatment of MRSA bacteremia, but further studies are needed[33].

Linezolid currently represents a good option for the treatment of MRSA infections, particularly pneumonia and skin and soft tissue infections[34-35].

Major limitations for the use of linezolid in clinical practice are the potential risk of hematological side effects, mainly thrombocytopenia, which is particularly relevant in patients with plasmatic exposure above 8 mg/liter[36]; for this reason, Therapeutic Drug Monitoring might probably be useful in majority of patients[37]. Moreover, due to the inhibition of mono-amino-oxydase enzymes, linezolid is contraindicated in association with drugs with serotoninergic activity for the risk of development of serotoninergic syndrome[38].

To face off the threat of methicillin-resistant Staphylococcus aureus (MRSA), many new therapeutic options with a peculiar activity against MRSA have been recently developed and approved. New agents are characterized by peculiar issues in terms of spectrum of activity, pharmacokinetics, risk of drug-drug interactions and toxicity, with potential main advantages that should be considered in everyday clinical practice.

Eravacycline

Eravacycline is a novel fluorocycline in Phase 3 clinical development for cIAI and cUTI. Eravacycline is structurally similar to tigecycline but is not subjected to the mechanisms that are responsible for tetracycline resistance, such as efflux pumps and ribosomal protection protein[39]. The most attractive characteristic of eravacycline is the broad- spectrum activity against both Gram-positive and Gram-negative resistant pathogens, including MRSA, enterococci (included vancomycin-resistant Enterococci) and Enterobacteriacae expressing resistance genes from different classes of β-lactamases (particularly ESBL, KPC and OXA), with a 2- to 4-fold greater activity than tigecycline[40-41]. Moreover, eravacycline currently represents the most potent antibiotic against MDR A.baumanii, with a fourfold higher activity compared with tigecycline, including strains resistant to sulbactam, imipenem/meropenem, levofloxacin and amikacin/tobramycin[42]. Eravacycline exerts also a potent activity against anaerobic pathogens[43]. As tigecycline, eravacycline is not effective against P. aeruginosa[44].

Together with the broad-spectrum activity, another attractive characteristic of eravacycline is the availability of both intravenous and oral formulations, making eravacycline a potential option for early oral shift and early discharge in patients with infections due to MDR Gram-negative bacteria[45]. In a recent Phase 3, randomized, double-blind, multicenter study eravacycline was found to be non-inferior compared to ertapenem for the treatment of patients with cIAI (Clinicaltrials.gov, Identifier NCT01844856)[46]. No studies investigating eravacycline efficacy for the treatment of respiratory tract infections are currently ongoing; however, a Phase 1 study conducted in 20 healthy adult volunteers analyzed eravacycline safety and pulmonary concentration after the administration of 1 mg of eravacycline/kg intravenously every 12 h for a total of seven doses over 4 days. Eravacycline was found to achieve 6-fold and a 50-fold higher concentrations in the ELF and alveolar macrophages than in plasma respectively, supporting its potential role for the treatment of respiratory tract infections. Moreover, eravacycline was well tolerated, with no serious adverse events and no treatment

discontinuations[47]. Promising data for the use of eravacycline for the treatment of pneumonia comes from a study by Grossmann et al, showing eravacycline to be as effective as linezolid in a neutropenic MRSA mouse lung infection model[48]. These data make eravacycline an attractive option for the treatment of respiratory tract infections due to resistant pathogens, including MRSA, beta-lactamase producing Enterobacteriacae and MDR A.baumanii and for oral step-down therapy.

Tedizolid

Tedizolid belongs to the class of oxazolidinones and is currently approved for the treatment of ABSSSIs. Tedizolid is characterized by a potent in vitro activity against Gram-positive pathogens, with a four- to eight-fold greater activity than linezolid; moreover, tedizolid is active against linezolid-nonsusceptible strains[49].

Tedizolid might represent a promising option for the treatment of MRSA pneumonia because of many advantages over linezolid, including: lower risk of myelotoxicity[50-51]; lower risk of drug – drug interactions with selective serotonin reuptake inhibitors (SSRIs), compounds with serotonergic activity, and adrenergic agents due to its weak and reversible in vitro inhibition of the monoamine oxidase pathway[52]; high bioavailability (>80%), with in vivo half-life value approximately twofold greater compared with linezolid, allowing once daily administration[53].

Moreover, PK/PD studies showed that tedizolid achieves approximately 40-fold higher concentration in ELF relative to free plasma ones, supporting the use of tedizolid in the setting of pneumonia[54].

The role of tedizolid for the treatment of MRSA respiratory tract infections is only investigational so far. However, promising data supporting the use of tedizolid for the treatment of respiratory infections come from a study conducted in an in vivo murine pneumonia model, showing tedizolid to be as effective as linezolid and more effective than vancomycin for the treatment of MRSA pneumonia[55].

A Phase 4 study designed to characterize the pharmacokinetics of intravenous and oral tedizolid in patients with cystic fibrosis in currently ongoing (Clinicaltrials.gov, Identifier NCT02444234).

A Phase 3, randomized, double blind study comparing tedizolid (200-mg intravenous once daily for 7

days, or 14 days in bacteremia) versus linezolid (600 mg intravenous every 12 h for 10 days, or 14 days for bacteremia) for the treatment of patients with presumed Gram-positive HAP or VAP is currently recruiting (Clinicaltrials.gov, Identifier NCT02019420).

Telavancin

Telavancin belongs to the class of new lipoglycopeptides and exerts a rapid, concentration-dependent, bactericidal activity against a broad-spectrum of Gram-positive pathogens, including MRSA and S. pneumoniae[56-57]. This drug is characterized by the presence of a lipophilic side chain that attaches to the bacterial membrane showing increased affinity compared with old glycopeptides. Telavancin acts through two different mechanisms of action: inhibition of bacterial wall synthesis (transglycosylation and transpeptidation) and disruption of bacterial membrane function[58].

PK/PD studies demonstrated that telavancin achieves good concentrations in ELF in healthy volunteers, with a median AUC_{ELF} approximately 75% of the free AUC_{plasma}[59].

Non-inferiority of telavancin (10 mg/kg every 24 h) versus vancomycin (1 g every 12 h) for the treatment of HAP has been demonstrated in two Phase 3, randomized, double-blinded studies (ATTAIN studies)[60]. A systematic review and meta-analysis of data coming from ABSSSI and HAP studies on telavancin, however, suggested a higher risk of nephrotoxicity and serious adverse events among telavancin-treated patients compared to vancomycin[61]. Particularly, an increased mortality in patients with HAP and moderate-to-severe renal impairment treated with telavancin compared to vancomycin was reported[62]. A post hoc analysis of data from the two Phase 3 ATTAIN trials demonstrated that, in the subset of patients without severe renal impairment or preexisting acute renal failure, clinical and safety outcomes were similar in the telavancin and vancomycin treatment groups[63]. Telavancin is currently approved by EMA for the treatment of adult patients with HAP (including VAP) only for MRSA known or suspected infections and other alternative treatments are not suitable. Moreover, it is strongly suggested to restrict the use of telavancin only to patients with normal renal function[64].

Delafloxacin

Delafloxacin belongs to the class of fluoroquinolones and exerts a potent anti-MRSA activity together with a broad-spectrum activity against both Gram-positive (including penicillin-sensitive, penicillin-resistant, and levofloxacin-resistant S. pneumoniae, Streptococcus pyogenes and Enterococci) and Gram-negative pathogens (Escherichia coli, Klebsiella spp., Haemophilus influenzae, Moraxella catharralis, and quinolone- susceptible P. aeruginosa)[65-66-67]. Moreover, delafloxacin is active against anaerobes and atypical respiratory tract pathogens (e.g., Legionella, Chlamydia, and Mycoplasma)[68-69-70].

Due to the peculiar dual mechanism of DNA target inhibition (DNA gyrase and topoisomerase IV), delafloxacin is characterized by a reduced probability for the selection of resistant in vitro mutants[71].

In a neutropenic murine lung infection model delafloxacin demonstrated a high penetration into the lung compartment, as epithelial lining fluid concentrations were substantially higher than plasma ones[72]. The potential role of delafloxacin for the treatment of respiratory tract infection has been evaluated in two Phase 2 studies, with promising results. In a double-blinded, randomized, Phase 2 study, 309 outpatients affected by CAP were treated with once-daily oral administration of delafloxacin at different dosages (100, 200, and 400 mg) for 7 days, with overall clinical and bacteriological cure rates demonstrated in up to 87% of patients. Furthermore, pathogen eradication rates were higher than 90% for H. influenzae, H. parainfluenzae and other atypical bacteria, and achieved 100% for S. aureus and S. pneumoniae[73]. The second study investigated the safety and efficacy of delafloxacin in patients with acute bacterial exacerbation of chronic bronchitis. Four different regimens were tested (100, 200, 400, and 500 mg, given orally every 24 h); clinical response was similar in the four treatment groups, with clinical and microbiological cure rates higher than 70%[74]. Data coming from studies on the use of delafloxacin for the treatment of ABSSSI demonstrate that delafloxacin at the dose of 300 mg every 12h is well tolerated, with diarrhea being the most

common adverse event [111]. Moreover, in healthy volunteers doses up to 900 mg were well tolerated, without any effect on QTc prolongation[75].

Due to the broad-spectrum activity including MRSA, the availability of an oral formulation, the reduced probability for resistance selection and the good tolerability profile, delafloxacin could represent a promising option for the treatment of respiratory tract infections.

A Phase 3 study comparing delafloxacin to moxifloxacin for the treatment of adult patients with CAP (DEFINE-CABP) is currently ongoing (Clinicaltrials.gov, Identifier NCT02679573).

Iclaprim

Iclaprim is related to trimethoprim, as an inhibitor of bacterial dihydrofolate reductase, but is active against Gram-positive bacteria that are resistant to trimethoprim. Notably, iclaprim does not have to be combined with a sulphonamide, which is commonly associated with adverse events. Iclaprim has rapid in vitro bactericidal activity in time-kill studies in human plasma[76], including against MSSA/MRSA. Using clinical S. aureus isolates from US and Europe (2015-16), the MIC50/MIC90 was 0.06/0.06 for MSSA (n=304) and 0.03/0.12 for MRSA (n=314)[77]. The clinical development programme for iclaprim has been protracted, reflecting changes to regulatory guidance, financial constraints by the original company (Arpida) developing the antibiotic, and then the transfer of the development rights to Motif Bio.

Two phase 3 clinical trials of iclaprim (REVIVE-1 and -2)[78-79], using a fixed dosage (80 mg IV twice daily for ? days), have recently been completed in ABSSSI; these are in addition to the original phase 3 studies, in which a weight-based dosage was employed. No oral formulation of iclaprim is available. The recent clinical trials showed that iclaprim achieved early clinical response rates comparable with

vancomycin 15 mg/kg IV every 12 hours (79.6% versus 78.8%; treatment difference 0.75%, 95% CI -3.84 to 5.35%)[80]. Clinical cure rates at test of cure were also very similar (80.4% and 82.5% for patients in the iclaprim and vancomycin groups, respectively; treatment difference -2.04%, 95% CI -6.44% to 2.36%). S. aureus was the most commonly isolated pathogen (n = 595), of which 45.9% were MRSA. The MIC50/MIC90 values for iclaprim and vancomycin for S. aureus isolates were 0.12/0.5 mg/L and 1/1 mg/L, respectively.

In a phase II, double-blind, multicenter study in patients with nosocomial pneumonia suspected or confirmed to be caused by Gram-positive pathogens (NCT00543608), subjects were randomized (1:1:1) to iclaprim (0.8 mg/kg IV q12h, n = 23; or 1.2 mg/kg IV q8h, n =24), or vancomycin 1 g IV q12h, n =23) for 7-14 days. The trial was ended early due to financial resource limitations, but the primary endpoint, clinical cure in the intent-to-treat (ITT) population at test of cure (TOC; 7 ± 1 days post treatment) visit, was achieved in 73.9%, 62.5%, and 52.2% of the three treatment groups, respectively. The adverse event profile of both iclaprim dosaging regimens were similar to that of vancomycin.

Motif Bio submitted a New Drug Application (NDA) for iclaprim in 2018 for the treatment of ABSSSI. The FDA has recently stated that it requires an additional clinical trial to be performed, as it has concerns about possible liver toxicity associated with iclaprim. Motif Bio has also stated its desire to develop iclaprim for hospital acquired bacterial pneumonia (HABP), including ventilator associated bacterial pneumonia (VABP), and possibly also for the treatment of S. aureus infection in cystic fibrosis, but new clinical trials in these indications have not commenced.

Oritavancin

Oritavancin is a lipoglycopeptide with three described mechanisms of action: inhibition of transglycosylation, inhibition of transpeptidation and disruption of cell membrane integrity. These actions likely explain the faster killing activity of oritavancin against S. aureus, including MRSA (at

least 99.9% killing in vitro within 1 hour; i.e. similar to that achieved by daptomycin), compared with vancomycin (similar level of kill, but requiring 24 hours)[81]. For clinical isolates recovered in Europe and USA between 2010-16, oritanvancin inhibited 99.7-99.8% of S. aureus at ≤0.12 mg/L (oritavancin $MIC_{50/90}$, 0.03/0.06 mg/L)[82]. The other key attribute of oritavancin is its very long half life (~ hours), which means that one IV 1.2g dose provides sufficient blood concentrations of antibiotic to exceed the MIC of staphylococci and streptococci over at least 10 days.

Hence, a single iv dose of oritavancin is (FDA/EMA) approved for the treatment of adult patients with cSSSI/ABSSSI caused or suspected to be caused by Gram-positive microorganisms, including MRSA. Approval of oritavancin was based primarily on the two phase 3 (SOLO-I and -II) clinical trials in ABSSSI, where a single dose of oritavancin had comparable efficacy and safety compared with 7-10 days of twice-daily vancomycin[83-84]. In a pooled analysis of the results from these trials, there were 1959 patients, of whom 1067 had at least one baseline Gram-positive pathogen and 405 had MRSA[85]. In these MRSA cases, at post-therapy evaluation (days 14–24), clinical success was achieved in 170/204 (83.3) and 169/201 (84.1) treated with oritavancin and vancomycin, respectively. In a real world registry of patients treated with oritavancin, almost 80% of the 112 patients (from 8 sites) had MRSA infections[86]. A positive clinical response was seen in 92.8% of patients, and microbial eradication occurred in 90.0%. Only 4 (3.6%) patients were hospitalized for failure of treatment of the index infection within 28 days following oritavancin administration. Five (4.5%) patients had ≥1 possible drug-related AEs, but no drug-related serious AEs were reported. Notably, therefore, single dose treatment with oritavancin can avoid the need for hospital admission or shorten the length of stay.

Ceftaroline/avibactam

Ceftaroline belongs to the new class of fifth generation cephalosporins, and is characterized by a potent activity against MRSA, due to the high binding affinity for the penicillin binding protein (PBP)-2a[87]. Avibactam is a new non-beta-lactam beta-lactamase inhibitor and broadens the spectrum of

activity of ceftaroline, restoring antimicrobial activity against Gram-negative pathogens expressing Ambler class A, C and some class D beta-lactamases[88]. In a Phase 1 study aiming to evaluate safety, tolerability and pharmacokinetics of ceftaroline/avibactam, the compound was found to be safe and was well tolerated at total daily doses of up to 1,800 mg of each compound. Adverse events (AEs), mainly represented by diarrhea, dry mouth and headache, were mild to moderate in severity. Infusion-site reactions were the most common AEs reported after multiple intravenous dosing[89]. A Phase 1 study analyzing pharmacokinetic profiles of ceftaroline and avibactam following intravenous administration of ceftaroline/avibactam in adults with augmented renal clearance has been completed (NCT01624246). A Phase 2 study comparing treatment with ceftaroline/avibactam versus doripenem for the treatment of adult patients with complicated urinary tract infections has recently been completed and results are pending (NCT01281462). Moreover, two studies investigating the potential effect of ceftaroline/ avibactam on QT interval prolongation and on intestinal flora have been completed and results are awaiting (NCT01290900 and NCT01789528).

Due to the broad-spectrum activity, including both MRSA and carbapenemases-producing Enterobacteriacae, ceftaroline/avibactam might represent an interesting option for the treatment of infections due to MRSA, particularly when a concomitant empiric or targeted treatment against ESBL- or KPC- producing Enterobacteriacae is required.

Omadacycline

Omadacycline is a semisynthetic antibiotic structurally related to tetracyclines, and has been approved by U.S. FDA on October 2018 for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Currently approved schedule consists in a loading dose (200 mg single dose intravenously or 100 mg every 12 hours intravenously) followed by 100 mg every 24 hours intravenously or 300 mg orally once a day for 7-14 days for both ABSSTIs and CAP. For the treatment of ABSSSIs an oral loading dose of 450 mg orally once a day for two days is feasible.

Omadacycline is characterized by a broad-spectrum activity including anaerobes and difficult-to-treat aerobic pathogens, in particular MRSA, vancomycin-resistant Enterococcus faecium (VRE), ESBL- and carbapenemase-producing Enterobacteriaceae, MDR Acinetobacter spp., Moraxella catharralis and Stenotrophomonas maltophilia[90-91]. Safety and pharmacokinetics of both oral and intravenous formulations have been evaluated in a Phase 1 study including 24 healthy subjects. The absolute bioavailability of the tablets was approximately 34.5% compared with intravenous formulation (a 300-mg dose of the tablet formulation produced a total exposure equivalent to that of a 100-mg intravenousdose), with a consistent inter-subject variability. Overall, omadacycline was well tolerated, with dizziness, nausea and vomiting being the most frequently reported adverse events[92].

In a recently published, double-blind trial, omadacycline has been found non-inferior to linezolid for the treatment of acute bacterial skin and skin-structure infections, with favorable response rates at 48-72 hours of 84,8% and 85,5%, respectively[93]. Omadacycline displays also a good penetration into both ELF and alveolar cells, with an overall magnitude of systemic exposure of omadacycline approximately 3-fold higher than that of tigecycline in plasma, ELF and alveolar cells[94]. In a recently published double-blinded, phase III trial, omadacycline was found to be non-inferior compared with moxifloxacin for the treatment of community-acquired bacterial pneumonia in adults, with favorable early clinical response rates at 48-72 hours of 81,1% and 82,7%, respectively[95]. In both studies omadacycline was administered at the dose of 100 mg given intravenously every 12 hours for two doses, then 100 mg given intravenously every 24 hours with an option to transition to oral omadacycline 300 mg every 24 hours after 3 days. A similar safety profile was described for the two compounds, with adverse events, mainly represented by gastrointestinal symptoms, reported in up to 45% of patients[96-97].

Moreover, omadacycline is currently under evaluation for the treatment of urinary tract infections. In a recently published 1b, open label study omadacycline was administered to 31 women with cystitis for 5 days; there groups with ascending doses (group 1: 200 mg intravenously on day 1, then 300 mg orally every 24 h [q24h]; group 2: 300 mg orally every 12 h [q12h] on day 1, then 300 mg orally q24h;

group 3: 450 mg orally q12h on day 1, then 450 mg orally q24h) were evaluated. A good excretion of omadacycline in urine was reported, with favorable clinical outcomes at end of treatment in 94% of cases[98]. A phase-2 study evaluating safety and efficacy of omadacycline compared to levofloxacin for the treatment of acute pyelonephritis is currently recruiting [NCT03757234].

Plazomicin

Plazomicin is a next-generation aminoglycoside that was approved by the FDA in June 2018 for the treatment of cUTIs, including pyelonephritis. Compared with the other aminoglycosides, plazomicin has been structurally modified to prevent inactivation by plasmid-borne aminoglycoside-modifying enzymes, which represent the main resistance mechanism impairing the activity of traditional aminoglycosides. For this reason, plazomicin exerts a potent in vitro bactericidal activity against MDR Enterobacteriacae, including aminoglycoside-resistant pathogens that encode aminoglycoside-modifying enzymes, and retains activity against most carbapenemease-producing strains, including metallo-beta-lactamase producing isolates[99-100]. Plazomicin was tested against 4,825 clinical isolates collected during 2014 and 2015 in 70 U.S. hospitals as part of the ALERT (Antimicrobial Longitudinal Evaluation and Resistance Trends) program, and was found to be able to inhibit 99.2% of Enterobacteriaceae isolated at ≤4 μg/ml. Moreover, plazomicin, as well as other aminoglycosides, is effective against P.aeruginosa and A.baumanii[101]. Regarding Gram-positive pathogens, plazomicin displays a good activity against staphylococci (both methicillin-susceptible and methicillin-resistant strains), but possess a limited activity against S.pneumoniae and Enterococci[102]. In vitro synergy between plazomicin and piperacillin/tazobactam or ceftazidime has been reported against MDR Enterobacteriacae, suggesting a potential role of plazomicin both as monotherapy and as combination therapy for the treatment of serious infections due to this class of pathogens[103]. Moreover, synergy with carbapenems for the treatment of both MDR A.baumanii and MRSA has been reported[104-105]. Plazomicin at the dose of 15 mg/kg once daily for 5 days was found to be effective in the treatment of adults with cUTIs and acute pyelonephritis (including patients with antibiotic-resistant

Enterobacteriaceae) in a double-blind, Phase 2 study comparing plazomicin with levofloxacin[106]. In a recently published Phase 3 plazomicin (15 mg/kg daily) was found non-inferior to meropenem (1 g every 8 hours, with the option to switch to oral levofloxacin after at least four days) for the treatment of cUTIs and acute pyelonephritis caused by Enterobacteriacae, including multidrug-resistant strains. To note, a higher percentage of patients in the plazomicin group than in the meropenem group were found to have microbiologic eradication, and fewer patients in the plazomicin group than in the meropenem group had microbiologic recurrence (3.7% vs. 8.1%) or clinical relapse (1.6% vs. 7.1%)[107]. In a multicenter, randomized, open-label trial tried to evaluate safety and efficacy of plazomicin compared to colistin, both in combination with tigecycline or meropenem for the treatment of serious infections (including HAP, VAP, bloodstream infections, cUTIs and acute pyelonephritis) due to carbapenem-resistent Enterobacteriacae. Unfortunately, the study was stopped prematurely because of slow enrollment. Overall, 39 patients have been enrolled; among these, 18 were randomized in the plazomicin arm and 21 in colistin arm. Owing the small sample size, no formal hypothesis testing was performed. However, the primary end-point event, represented by death forma any cause at 28 days, occurred 4/17 (24%) patients receiving plazomicin and 10/20 (50%) patients receiving colistin, with serious adverse events reported less frequently in plazomicin arm compared to colistin arm[108].

Lefamulin

Lefamulin (formerly known as BC-3781) is the first in class pleuromutilin antibiotic and exhibits a unique mechanism of action through inhibition of protein synthesis by binding to the peptidyl transferase center of the 50S bacterial ribosome, thus preventing the binding of transfer RNA for peptide transfer[109]. Lefamulin exherts a potent activity against both Gram-positive pathogens (including MRSA and VRE) and atypical organisms associated with CAP (e.g. Mycoplasma pneumoniae, Legionella pneumophila, and Chlamydophila pneumoniae). Addictionally, lefamulin retains activity against multidrug-resistant Neisseria gonorrhoeae and Mycoplasma genitalium[110].

Both population pharmacokinetic models and murine models demonstrated a high and rapid penetration into ELF, irrespective of the route of administration (intravenous or oral)[111-112]. In a recently published Phase 3, multicenter, randomized, double blind trial, lefamulin at 150 mg intravenously every 12 hours (with the option to switch to oral treatment after 6 doses) was found non inferior to moxifloxacin at 400 mg intravenously every 24 hours for the treatment of community-acquired bacterial pneumonia[113]. Due to the peculiar spectrum of activity, lefamulin might represent an interesting option for the treatment of community acquired pneumonia, particularly in patients presenting with risk factors for MRSA infection.

Conclusions

A number of new drugs for the treatment of MRSA infections has been recently approved or are in advanced stage of development (**Table 1**). The most attractive characteristic of new drugs is represented by the broad spectrum of activity against multi-drug resistant pathogens; moreover, new compounds in most cases are characterized by favorable toxicity profiles compared with old drugs currently used in clinical practice. Some of the new antimicrobials will be also available as oral formulations, with the potential for oral shift even in infections due to resistant pathogens.

Expert opinion

The spread of MRSA in the last decades has inevitably changed the therapeutic approach to this infection. Most β-lactams (with the exception of fifth-generation cephalosporins) have become ineffective against proven MRSA, as well as potentially ineffective in the empirical treatment of infections in patients with risk factors for MRSA. Fortunately, several alternatives are now available for suspected or proven MRSA, consisting of the abovementioned fifth-generation cephalosporins combinations and various non-β-lactam antibiotics (e.g., oxazolidinones, glycopeptides, lipopeptides, lipoglycopeptides, delafloxacin). Furthermore, MRSA may remain susceptible to SMX/TMP, tetracyclines, and/or clindamycin.

Since noninferiority was frequently the rule in phase-3 RCT evaluating the efficacy of the anti-MRSA agents mentioned above in the treatment of MRSA infections, other factors may become preeminent when selecting the appropriate antibiotic on a patient-by-patient basis: (i) history of hypersensitivity reactions; (ii) availability of oral formulation for out-patient treatment; (iii) possibility of switch from intravenous to oral therapy and early discharge; (iv) spectrum of activity (e.g., for suspected or proven polymicrobial infections); (v) safety profile of the different therapeutic options in light of the patient's baseline comorbidities and risks for toxicity. Very importantly, with regard to this latter point (toxicity), adequate knowledge of the peculiar safety profile of each drug is essential for guiding monitoring and management of AE, in turn reducing any possible unfavorable impact of toxicity on patients' outcomes.

Data regarding the safety and the efficacy of newer molecules for the treatment of MRSA infections in particular conditions/populations (e.g. liver failure, renal disease, pregnancy, diabetic, children, elderly) are scant, thus dedicated studies are warranted. In our opinion, novel antibiotics with reduced toxicity could be an important option in the elderly (considering the usually non-negligible burden of comorbidities in this population) and in discharged patients. Two examples may be those of well-tolerated fifth-generation cephalosporins in hospitalized patients with impaired renal function, to avoid additional nephrotoxicity due to glycopeptides, and of tedizolid in non-closely monitored discharged patients, by possibly enabling earlier discharge with also a lower risk of thrombocytopenia in comparison with linezolid.

The increasing challenge of antimicrobial dosing for the treatment of MRSA infections in the obese population is also worth mentioning. Notably, the majority of the newly approved molecules does not provide specific indications for dosing in this patient population. In our opinion, drugs with a weight-driven dosage should be preferred. Whenerver a β lactam is required, continuous/extended infusions, higher doses, or more frequent dosing should be considered, together with TDM to avoid underexposure. Dose adjustments in obese patients are not recommended for novel, long acting

molecules. However, very limited data have been published to date, and the results of a phase I study evaluating the pharmacokinetics of telavancin in obese subjects are pending.

In diabetic patients, moxifloxacin and delafloxacin could be among the options to be considered for diabetic foot infections, owing to their high penetration in the perinecrotic tissue and the bone, and their good oral bioavailability.

In the next five years, we expect to witness a continuous refining of therapeutic algorithm for maximizing the cost-effectiveness of the treatment of MRSA infections, in which, considering the similar efficacy of novel treatment, potential toxicity will play a critical role in establishing the best available therapy for each specific patient, together with consideration regarding the possibility of avoiding hospitalization or allowing switch from intravenous to oral therapy and early discharge. Against this backdrop, it will be

interesting to define also the specific place in therapy of other novel agents that could be available in the future, by accurately considering and weighing their safety data from currently ongoing RCT for MRSA infections.

Disclosures

Outside the submitted work, MB has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, Bayer, Basilea, Biomerieux, Cidara, Gilead, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, Melinta, Shionogi, Tetraphase, VenatoRx and Vifor and has received study grants from Angelini, Basilea, Astellas, Shionogi, Cidara, Melinta, Gilead, Pfizer and MSD.

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