A focus on the newer antibiotics targeting Gram-positive bacteria

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Key words: antibiotics, Gram-positive, multi-drug resistant, daptomycin, tigecycline, linezolid

The incidence of antimicrobial resistance has continued to rise with a threat to return to the "pre-antibiotic" era. This has included a sharp increase in multi-drug resistant organisms, which may cause life-threatening infections. Efforts have been made to develop new antibiotics with novel modes of action, aimed at acting against these multi-drug resistant strains. This review aims to focus on newly available and investigational antibiotics targeting Gram-positive organisms. It is likely that these antibiotics will be used mainly in a secondary care setting; however primary care health care professionals also need to have an understanding of these antibiotics, since patients may be discharged home on them.

Introduction

Antimicrobial resistance and the threat this brings with it have long been recognised. Inherent antimicrobial resistance existed even before antimicrobials were introduced into medicine; in 1940, Abraham and Chain recognised acquired antimicrobial resistance when, during the development of penicillin, they isolated an enzyme (now termed penicillinase) that destroys penicillin.[1] Due to the international and fast spread of microorganisms in this era of mass travel and global trade, the problem of antimicrobial resistance no longer remains a national one. Rather it is a European and global problem requiring international cooperation and a global strategy to avoid returning to the "pre-antibiotic" era. The inferior quality of poorly formulated or manufactured antimicrobials in the less developed world, where medications are often used after their expiry date, adds to the complexity of the problem.[2] This has been further compounded by factors in secondary care including hospital over-crowding leading to cross-infection, immunosuppression (due to disease or its treatment) and the use of more invasive techniques which provide access for easy entry of bacteria into the patient's body.[3]

Despite improvements in immunization, infection control policies and medical practice amongst others, the rate of emergence of resistant strains has continued to rise, with a nearly 25% increase in resistance among Gram- positive pathogens in the United States over a ten year period.[4] The most common drug resistant Gram-positive pathogens are staphylococci, enterococci and streptococci with meticillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Staphylococcus aureus* (VRSA) and vancomycin resistant *Enterococcus* species (VRE) offering the greatest challenge to health care and causing potentially life-threatening infections. Multi-drug-resistant *Streptococcus pneumoniae* has also been reported.[5] Reports indicate that more than 25% of *Staphylococcus aureus* infections in Europe are caused by MRSA, with most of these isolates being multi-drug resistant.[6] The European Union has voiced its concern about this alarming increase in antibiotic resistance and has launched a surveillance programme, the European Antimicrobial Resistance Surveillance System (EARSS). A recent report summarising trends over the past seven years (1999 to 2006), has indicated that there continues to be a loss of antimicrobial effectiveness which does not seem to have slowed down, with resistance and a reduction in antimicrobial effectiveness reported both in community and in hospital-based care.[7]

The purpose of this review is to describe some of the newer compounds targeting mainly Gram-positive organisms, including multi-drug resistant strains. The review will also briefly describe some compounds in various stages of clinical development.

Daptomycin

Daptomycin is a fermentation product produced by *Streptomyces roseosporus*. It was originally discovered by Eli Lilly in the 1980s and given the name deptomycin, which was later changed due to potential

confusion with the names of other compounds such as streptomycin. Following Phase I and Phase II trials, Lilly abandoned the development of daptomycin; this was then taken up by Cubist Pharmaceuticals in 1997 primarily as a response to the increasing threat of resistance by Gram-positive bacteria.[5]

Daptomycin is a cyclic lipopeptide antibiotic with a unique structure, giving it an equally unique mode of action on the bacterial cell wall. Its proposed mechanism of action involves the insertion of the lipophilic tail into the bacterial cell membrane causing formation of a channel in the presence of calcium, resulting in depolarisation of the membrane. This results in potassium efflux causing inhibition of protein, DNA and RNA synthesis and subsequently cell death.[4,6] It is bactericidal with activity against most Gram-positive bacteria; this includes both antibiotic-susceptible and resistant strains. In the US, it has been licensed for treatment in adults of complicated skin and skin-structure infections (cSSTI) associated with *Staphylococcus aureus,* streptococci and vancomycin-susceptible *Enterococcus faecalis*.[6] More recently, it has also been licensed for treatment of *Staphylococcus aureus* bloodstream infections including right-sided endocarditis.[8] In the UK it is licensed only for use in cSSTI in adults.[9] It has no activity against Gram-negative bacteria since it is unable to penetrate the bacterial cell wall. Consequently, it should not be administered as monotherapy where mixed infections are suspected. When compared to vancomycin, linezolid and quinipristin-dalfopristin, daptomycin had a greater bactericidal activity against *Staphylococcus* and *Enterococcus* species.[4] It has shown *in vitro* synergy with aminoglycosides and rifampicin.[6] Despite limited availability on the market, reduced susceptibility to daptomycin by *Staphylococcus aureus* has been observed and was associated with prolonged use and the presence of foreign devices that could not be removed.[8]

The dose giving maximum efficacy and safety is 4mg/kg daily as a once daily intravenous infusion, possibly due to the prolonged post-antibiotic effect of more than 6 hours. In healthy volunteers it has a half life of 8 hours. It is excreted renally and consequently the dosage interval should be increased to every 48 hours in renal impairment where the creatinine clearance is <30ml/min or in patients on haemodialysis or continuous ambulatory peritoneal dialysis, where the half life increases to 28 hours.[9] Since it is not hepatically metabolised, it does not cause any interactions related to the cytochrome P-450 enzyme system.[4,6] It does not cross the blood brain barrier or enter the cerebrospinal fluid in normal individuals. Bone penetration is poor and daptomycin should therefore not be used in central nervous system or bone infections.[10] It has also not been effective in pneumonia, primarily due to daptomycin inactivation by lung surfactant.[8]

Myopathy has been reported with higher plasma concentrations and is associated with the release of creatine phosphokinase (CPK) by skeletal muscle. This is not progressive and is reversible on withdrawal of the drug. To ensure safe administration, it is recommended to measure plasma CPK at baseline and at least once weekly during therapy in all patients; this should be done more often in patients with increased risk of developing myopathy such as patients with renal impairment. Caution should also be exercised when daptomycin is co-administered with medications that may increase the risk of myopathy (including HMG-CoA reductase inhibitors, fibrates and ciclosporin). Peripheral neuropathy has also been reported, and daptomycin should be stopped in any patients reporting symptoms of this condition.[9] Safety in pregnancy, lactation and children has not yet been established.[4]

Compared to other newer agents, one of the main advantages of daptomycin is that it is bactericidal. Besides, it is the first drug with bactericidal activity against *Enterococcus* and may offer an alternative to vancomycin-resistant *Enterococcus* endocarditis, though more evidence on this is needed.[10] The myopathy it produces as an adverse effect is dose-dependent and is not expected at the recommended dose, unlike quinipristin-dalfopristin where myopathy may occur at therapeutic doses.[10] It offers advantages over vancomycin in that it is administered once daily and does not require any therapeutic drug monitoring.[4]

Linezolid

Linezolid is the first of a new class of antibacterial agents called oxazolidinones.[11] Its antibacterial activity is due to an inhibitory effect on protein synthesis. It disrupts the interaction of fMet-tRNA onto the bacterial ribosome which is important for the initial phase of protein translation.[12] Hence, it has no effect on bacterial replication or transcription of DNA to RNA.

Linezolid is bacteristatic. It has good activity against Gram-positive bacteria, including MRSA, glycopeptide-intermediate *Staphylococcus aureus* (GISA), VRE and penicillin-resistant *Streptococcus pneumoniae*. Moreover, it is also active against anaerobes, such as *Clostridium perfringens* and *Peptostreptococcus* species.[11]

The drug is available in both oral and intravenous forms.[13] The oral dose is 600mg bd. Bioavailability following oral administration is 100% and absorption is not affected by food.[11] Elimination half life of the drug is 4.5 to 5.5 hours after a steady state has been reached.[11]

Although bacteristatic, linezolid has an important role in the treatment of serious Gram-positive infections. Its use is mainly in cases of multi-drug resistant infections such as MRSA, GISA and VRE. Hence, it is more likely to be used in the hospital setting. Currently, the approved indications for use of linezolid include hospital-acquired pneumonia (especially ventilator-associated pneumonia) and cSSTI.[13]

A number of trials have been carried out in order to assess the efficacy of linezolid compared to other well established treatment regimens, including a randomized control trial comparing linezolid with vancomycin in the treatment of cSSTI.[14] The results showed that the two drugs were equivalent in the intention-to-treat analysis. However, linezolid was noted to be superior where MRSA was isolated and in those patients with abscesses and surgical site infections secondary to MRSA. The authors of this paper suggest that the better outcome with linezolid could be due to better penetration of the drug into skin and subcutaneous tissue.

In an anaylsis of two double-blind randomised trials of patients with MRSA-documented hospital-acquired pneumonia, linezolid was noted to have a higher rate of cure and a lower mortality than vancomycin.[15] There was no difference between the two for meticillin-sensitive *Staphylococcus aureus* (MSSA) infections. As with cSSTI, it is thought that linezolid penetrates lung tissue better than vancomycin. As a result of this study and two others based on tissue penetration of linezolid, the American Thoracic Society's guidelines on the treatment of hospital-

acquired pneumonia suggest that patients with documented MRSA pneumonia could be treated with either vancomycin or linezolid, but the latter should be preferred if patients have renal impairment or are at risk of nephrotoxicity.[16]

There are also case reports of linezolid being used in other disease states, such as infective endocarditis[17], central nervous system infections[18] and bone/joint infections[19], but its use has been hampered by a lack of safety data on long term use.

Adverse events associated with linezolid use include anaemia, neutropaenia, thrombocytopaenia, deranged liver function, headaches and gastrointestinal disturbances.[20] It is recommended that patients who are on linezolid should have their full blood count checked every week whilst on treatment, especially if the duration of the antibiotic continues beyond the recommended maximum of 28 days.[13]

Linezolid is an inhibitor of monoamine oxidase inhibitors (MAOI). Hence, it should be avoided in patients on MAOIs unless it is given under close supervision.[13] There have also been reports of the serotonin syndrome when the antibiotic was administered with serotonin reuptake inhibitors (SSRI); this can occur early during treatment in young patients but later in older patients.[21]

Although linezolid is a novel antibiotic with a different site of action than any other antibiotic, resistance has been seen in some cases. Most of the cases have been noted in patients who have either indwelling prosthetic devices or have been receiving prolonged courses of the antibiotic.[22]

Tigecycline

Tigecycline belongs to a class of drugs, closely related to tetracycline, called glycylcyclines. It inhibits protein synthesis by binding to the 30S ribosomal subunit and preventing the addition of transfer RNA molecules required for the elongation phase.[23]

Tigecycline is a bacteristatic drug.[24] In this respect, it is similar to linezolid. Its antibacterial spectrum is however much more extensive, with excellent activity not only against Gram-positive organisms but also against Gram-negatives. It is very potent against MRSA, VRE, meticillin-resistant *Staphylococcus epidermidis* and streptococci (including penicillin-resistant strains). Moreover, it is active against many Gram-negatives including Enterobacteriaceae and multidrug resistant *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*. On the other hand, it has reduced activity against *Proteus* and *Pseudomonas aeruginosa*.[25]

Tigecycline is only available as an intravenous preparation because oral bioavailability is poor.[23] The currently recommended dose is a 100mg loading dose followed by 50mg twice daily. The half life in humans ranges between 37 and 67 hours. It is widely distributed in the body with concentrations in skin and lungs reaching three times that of plasma in experimental rats.[26] Tigecycline circulates as unchanged drug in serum. It is eliminated through the gut and hence, does not need any dose adjustment in patients with renal failure.[27]

The current indications for tigecycline are cSSTI and complicated intra-abdominal infections.[24] In the case of cSSTI, results from two phase 3 randomised, double-blinded studies were pooled and analysed.[28] Patients were treated with either tigecycline monotherapy or vancomycin plus aztreonam for up to 14 days. The results showed that tigecycline was as effective as the comparator arm. On the other hand, in the case of complicated intra-abdominal infections both Gram-positive and Gram-negatives are important in the pathogenesis of this disease. In a pooled analysis from two Phase 3 studies between tigecycline monotherapy versus imipenem-cilastatin in 1642 adults with complicated intra-abdominal infections, it was shown that tigecycline was non-inferior to the comparator arm.[29]

Tigecycline is very well tolerated. The most frequent adverse events reported to date include nausea and vomiting, resulting in discontinuation of treatment in 5% of cases.[30] Other relevant events are transient elevations of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase, which are all markers of hepatic function.

There are very few drug interactions of clinical significance, when administering tigecycline. Since it is not metabolised by the liver there is no effect on drugs acting on the cytochrome P450 enzyme system.[23] Although tigecycline may prolong both prothrombin time and activated partial thromboplastin time, there is no evidence to suggest that this may result in a significant change in the INR. However, it is advisable that patients on warfarin should be more closely monitored if they are administered tigecycline concurrently.[24]

Currently, resistance to tigecycline is not a major problem. It is known that tigecycline binds more avidly to ribosomes than tetracycline and hence can overcome the resistance methods employed against the latter. However, resistance can emerge in microorganisms that are able to express the multi-drug efflux pump normally associated with Gram-negatives.[31]

Other antibiotics under development

With the emergence of ever more drug resistant microorganisms, the need for developing more active drugs is a real emergency. The antibiotics mentioned above have all been approved for specific clinical indications. There are other investigational drugs which are at different stages of development. Their main target is multi-drug resistant bacteria.

- **Dalbavancin** is a semisynthetic glycopeptide with a similar mode of action to vancomycin. It has potent activity against Gram-positive organisms including MRSA.[32] This drug is remarkable for its long half life of 8.5 days and can therefore be used once weekly. In a number of trials involving this drug, it was administered on day 1 and day 8 only for cSSTI.[33,34] This drug could be very useful in the outpatient treatment of cSSTIs. Its long half-life may be a major drawback since if there is a drug related reaction, its effects will last for a number of days and cannot be reversed by simply stopping the drug.
- Other semisynthetic glycopeptides used against Gram-positive organisms including MRSA are under investigation. **Telavancin** is rapidly bactericidal and exists as an intravenous preparation to be given once daily. Its current indication is in cSSTI.[35] **Oritavancin** is still in a Phase 3 study. Its indications are likely to include cSSTI, catheter-associated infections and endocarditis. Because of a long half life, it is likely that it will be dosed on a daily or alternate day schedule.[32]
- **Ceftobiprole** is a novel bactericidal cephalosporin being developed for the treatment of Gram-positive organisms, including MRSA, whilst maintaining the Gram-negative cover of the third generation cephalosporins. At the time of writing, the drug is in a Phase 3 trial and the indications are thought to include cSSTI.[36]

- **Iclaprim** is a new dihydrofolate reductase inhibitor belonging to the same class of antibiotics as trimethoprim. Its Gram-positive cover is very promising with potent activity against MRSA, VISA and VRSA. It is currently in development as an intravenous agent; however, oral bioavailability is good and there are Phase I trials with an oral preparation which would allow intravenous-to-oral switch.[37]

Practice Points

- New antibiotics are being produced to target multi-drug resistant bacteria.
- Most of these drugs are aimed at the in-patient management of serious infections.
- Pharmacists should be aware of the interactions and adverse effect profiles of these new drugs as their use is likely to increase in the future.
- Prudent and optimal use of antibiotics may help to limit the development of resistance; pharmacists should play a vital role to ensure optimal prescribing of antibiotics, both in hospital and community environments.

Conclusion

As more resistant organisms are being seen in clinical practice, there is an urgent need for more potent antibiotics. There are only a few drugs which belong to a completely novel class; the rest are only a development of old and existing classes. If we do not take good care of the existent antibiotics by responsible prescribing, we will be at risk of losing even these more efficacious antibiotics.

References

1. Abraham EP, Chain E. An enzyme from bacteria able to destroy penicillin. *Rev Infect Dis* 1988; 10(4):677-8.
2. *Emerging and other communicable diseases: antimicrobial resistance.* World Health Organization Bill 51.17 Fifty-first World Health Assembly.
3. World Health Organization. *WHO Global Strategy for containment of antimicrobial resistance.* Switzerland: World Health Organization; 2001.
4. Tedesco KL, Rybak MJ. Daptomycin. *Pharmacotherapy.* 2004; 24(1):41-57.
5. Schiever CA, Fernandez C, Rodvold KA, Danziger LH. Daptomycin: a novel cyclic lipopeptide antimicrobial. *Am Journal Health-Syst Pharm* 2005; 62:1145-58.
6. Steenbergen JN, Alder J, Thorne GM, Tally FP. Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 2005; 55:283-8.
7. European Union. *Eurosurveillance weekly release.* [homepage on the Internet]. 2007 March 15 [cited 2007 March 24]; Available from: URL: http://www.earss.rivm.nl/
8. Paterson DL. Clinical experience with recently approved antibiotics. *Curr Opin Pharmacol* 2006; 6:486-90.
9. Novartis Pharmaceuticals UK Ltd. *Cubicin powder for concentrate for solution for infusion.* [homepage on the Internet]. 2006 November 20 [cited 2007 March 21]; Available from: URL: http://emc.medicines.org.uk/
10. Pham PA. *FDA approves daptomycin, a new cyclic lipopeptide antibiotic, for the treatment of resistant gram positive organisms.* [homepage on the Internet]. John Hopkins Division of Infectious Diseases Antibiotic Guide 2001-2004 [cited 2007 March 21]; Available from: URL: http://hopkins-abxguide.org/show_pages.cfm?content=F40_100803_content.html
11. Perry CM, Jarvis B. Linezolid: a review of its use in the management of serious Gram-positive infections. *Drugs.* 2001; 61(4):525-51.
12. Aoki H, Ke L, Poppe SM, Poel TJ, Weaver EA, Gadwood RC, *et al.* Oxazolidinone antibiotics target the P site on *Escherichia coli* ribosomes. *Antimicrob Agents and Chemother* 2002; 46(4):1080-5.
13. Pharmacia Limited. *Zyvox 600mg film-coated tablets, 100mg/5ml granules for oral suspension, 2mg/ml solution for infusion.* [homepage on the Internet]. 2007 updated March 09 [cited 2007 April 5]. Available from: URL: http://emc.medicines.org.uk
14. Weigelt J, Itani K, Stevens D, Lau W, Dryden M, Knirsch, C and the linezolid CSSTI Study Group. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. *Antimicrob Agents Chemother* 2005; 49(6):2260-6.
15. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with meticillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest.* 2003; 124:1789-97.
16. American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171(4):388-416.
17. Drees M, Boucher H. New agents for *Staphylococcus aureus* endocarditis. *Curr Opin Infect Dis* 2006; 19:544-50.
18. Viale P, Pagani L, Cristini F, Stefini R, Bergomi R, Colombini P, et al. Linezolid for the treatment of central nervous system infections in neurosurgical patients. *Scand J Infect Dis* 2002; 34(6):456-9.
19. Falagas ME, Siempos II, Papagelopoulos PJ, Vardakas KZ. Linezolid for the treatment of adults with bone and joint infections. *Int J of Antimicrob Agents* 2007; 29(3):233-9.
20. Bishop E, Melvani S, Howden BP, Charles PGP, Grayson ML. Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. *Antimicrob Agents Chemother* 2006; 50(4):1599-602.
21. Morales-Molina JA, Mateu-de Antonio J, Marin-Casino M, Grau S. Linezolid-associated serotonin syndrome: what we can learn from cases reported so far. *J Antimicrob Chemother* 2005; 56:1176-8.
22. Hancock REW. Mechanisms of action of newer antibiotics for Gram-positive pathogens. *Lancet Infect Dis* 2005; 5:209-18.
23. Zhanel GG, Karlowsky JA, Rubinstein E, Hoban DJ. Tigecycline: a novel glycylcycline antibiotic. *Expert Rev Anti-Infect Ther* 2006; 4(1):9-25.
24. Wyeth Pharmaceuticals. *Tygacil 50mg powder for solution for infusion.* [homepage on the Internet]. 2006 May 26 [cited 2007 April 05]; Available from: URL: http://emc.medicines.org.uk
25. Hawkey P, Finch R. Tigecycline: in-vitro performance as a predictor of clinical efficacy. *Clin Microbiol Infect* 2007; 13:354-62.
26. Wilcox MH. Tigecycline and the need for a new broad-spectrum antibiotic class. *Surg Infect* 2006; 7(1):69-80.
27. Meagher AK, Ambrose PG, Grasela TH, Ellis-Grosse EJ. The pharmacokinetic and pharmacodynamic profile of tigecycline. *Clin Infect Dis* 2005; 41:S333-40.
28. Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E, for the Tigecycline 300 and 305 cSSSI Study Groups. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis* 2005; 41(S341):S353.
29. Babinchak T, Ellis-Grosse E, Dartois N, Rose GM, Loh E, for the Tigecycline 301 and 306 study group. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. *Clin Infect Dis* 2005; 41(S354):S366.
30. Stein GE, Craig WA. Tigecycline: A critical analysis. *Clin Infect Dis* 2006; 45:518-24.
31. Frampton JE, Curran MP. Tigecycline. *Drugs.* 2005; 65(18):2623-35.
32. Drew RH. Emerging options for treatment of invasive multidrug-resistant Staphylococcus aureus infections. *Pharmacotherapy.* 2007; 27(2):227-49.
33. Seltzer E, Dorr MB, Goldstein BP, Perry M, Dowell JA, Henkel T and the dalbavancin and skin and soft-tissue infection study group. Once weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. *Clin Infect Dis* 2003; 37:1298-303.
34. Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis* 2005; 41:1407-15.
35. Stryjewski ME, O'Riordan WD, Lau WK, Pien FD, Dunbar LM, Vallee, M. et al. Telavancin versus standard therapy for treatment of complicated skin and soft-tissue infections due to Gram-positive bacteria. *Clin Infect Dis* 2005; 20:1601-7.
36. Chambers HF. Ceftobiprole: in-vivo profile of a bactericidal cephalosporin. *Clin Microbiol Infect* 2006; 12(Supp 2):17-22.
37. Hawser S, Lociuro S, Islam K. Dihydrofolate reductase inhibitors as antibacterial agents. *Biochem pharmacol* 2006; 71:941-8.