Tedizolid: A Novel Oxazolidinone for Gram-Positive Infections

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Despite the concerted efforts of modern medicine, infections due to gram-positive bacteria, such as skin and soft tissue infections, pneumonia, bacteremia, and endocarditis, continue to pose many challenges to achieving successful treatment outcomes. A good case in point is found in the emergence and spread of methicillin resistance in Staphylococcus aureus. The first strains of methicillin-resistant S. aureus (MRSA) were discovered a half-century ago in a hospital in London, just 2 years after the first clinical use of methicillin [1]. During the ensuing 50 years, these organisms have spread worldwide despite extensive attempts to control them. In some of the Scandinavian countries and the Netherlands, “search and destroy” efforts in hospitals have been successful in controlling infections caused by MRSA. This was aided by the fact that most MRSA infections were hospital acquired. That situation, however, began to change in the early 1990s, when infections due to MRSA were noted in patients without previous inpatient healthcare exposure across 6 different continents, including Australia, where several outbreaks were detected in Western Australia and the Northern Territory [2, 3]. Community-acquired (or community-associated) MRSA (CA-MRSA) subsequently spread throughout North America, where one particular clone (USA-300) quickly established dominance. Not surprisingly, these strains have also spread to Europe, where they have caused significant problems due to the fact that European guidelines for infection control have been geared to inpatient rather than outpatient acquisition of methicillin-resistant strains [4].

However, MRSA is not the only gram-positive organism causing major problems because of the development of antibiotic resistance. Macrolide-resistant group A streptococci and pneumococci as well as multiresistant enterococci (including strains of Enterococcus faecium resistant to virtually all currently available antimicrobial agents) are becoming greater and greater problems throughout the world. The development of resistance in these organisms is not surprising. Most antimicrobial agents in clinical use are antibiotics, which are antimicrobial substances produced by a variety of microorganisms in nature, presumably to secure their ecologic niches. Resistance genes are, of course, found in antibiotic producers to prevent them from essentially committing suicide due to the toxic substances they themselves emit. Such genes have thus been present in nature for millions, if not billions, of years before the clinical use of antibiotics. A number of studies have demonstrated the presence of this type of genetic material among bacteria found in isolated human populations who had never received therapeutic antibiotics [5]. Recently, D’Costa and coworkers reported on finding resistance genes among core samples obtained from Late Pleistocene permafrost sediments collected east of Dawson City, Yukon. Those were estimated to be 25 000 to 30 000 calendar years old by radiocarbon dating and contained genes coding for β-lactamases related to TEM enzymes, tetracycline resistance genes (tetM), and even more strikingly, vancomycin resistance genes (vanA) [6]. Given these findings, it is not surprising that the clinical and nonclinical (such as inclusion in livestock feed) use of antimicrobial agents has rapidly selected resistant bacterial isolates. In this
context, it is disturbing to note that antibacterial agents have been employed for only about 70 years in humans, but this has proven sufficient to select for resistance among bacteria that have had several billion years to acquire resistance genes in nature.

Since the initial deployment of antimicrobial agents in humans, the problem of resistance has been attacked by finding and developing novel antimicrobials. However, this process has slowed rapidly over recent years for a variety of reasons, including the fact that all of the intuitive molecular targets for antimicrobial agents have essentially been exploited [7, 8]. Because genes encoding resistance to true antibiotics are ubiquitous in nature, one obvious solution to the problem would be to develop nonantibiotic antimicrobial agents (such as entirely synthetic chemical entities). Only a very small handful of effective, currently available antibacterial agents are chemical entities not produced by microorganisms or semisynthetic derivatives of such entities.

Oxazolidinones represent a most interesting class of nonantibiotic antibacterials with good antimicrobial activity [8, 9]. It was discovered that these compounds, originally synthesized as monoamine oxidase inhibitors for the treatment of depression, had antimicrobial properties, and E. I. DuPont de Nemours and Company developed the first of these agents in the late 1970s for the control of various plant diseases [9]. Unfortunately, the early oxazolidinones, although active against plant pathogens and exhibiting good activity against gram-positive bacteria, also exhibited lethal toxicity (likely due to myelosuppression) in experimental animals and were initially not further developed for use in humans [10]. Scientists at Upjohn Laboratories eventually began work on oxazolidinones and carried out chemical modifications of the original oxazolidinone nucleus. These efforts led to the discovery of a number of agents that exhibited good antimicrobial activity and decreased toxicity compared with the earlier DuPont compounds. Among these were eperezolid and linezolid [8]. Although eperezolid exhibited significantly better in vitro activity, linezolid was chosen for clinical development because of its superior bioavailability [11].

Linezolid has proven to be a highly effective drug and has been widely used for the therapy of gram-positive infections, including those due to MRSA. However, it does have certain liabilities, such as the fact that it can produce reversible thrombocytopenia (and bone marrow suppression) when given for prolonged periods of time [12]. In addition, linezolid can cause serotonin syndrome in patients with depression who are taking selective serotonin reuptake inhibitors, but this complication appears to be fairly rare. Resistance against linezolid has been very slow to develop, because bacteria have 4–6 copies of the gene encoding the 23S ribosomal RNA binding site, which is the target for linezolid. It requires multiple mutations, therefore, for resistance to develop. Resistance due to mutations in genes encoding ribosomal proteins L3 or L4, which are found on the 50S subunit, is much less frequent, and there is evidence that at least some of the resultant mutants may be less fit than their susceptible relatives [13]. A recent disturbing (and surprising) development has been the discovery of the cfr gene, which conveys resistance not only to linezolid, but also to chloramphenicol, the lincosamides, the pleuromutilins, and streptogramin B. The cfr gene encodes a methylase that modifies the ribosomal binding sites in such a fashion that they no longer present suitable targets for these agents [14]. Moreover, cfr is carried by a transmissible plasmid, which means that there is considerable potential for spread of these genes among gram-positive species in the clinical setting [15]. So far, the only outbreaks of resistance due to this mechanism have been described in Madrid, Spain [16], but the potential for more widespread dissemination is concerning.

Tedizolid (previously known as TR-700 or torezolid) is a novel oxazolidinone, the properties of which are clearly outlined in the subsequent articles in this supplement. As will be seen, tedizolid has enhanced in vitro activity compared with linezolid, and data from comparative clinical trials suggest that tedizolid has less toxicity. Perhaps more important, tedizolid appears to be effective against staphylococci containing the cfr gene, which will make it particularly useful should this gene spread more widely among this group and other gram-positive organisms. A successful expedited review of the new drug application submitted to the US Food and Drug Administration (FDA) would make tedizolid the first oxazolidinone to be developed and approved for clinical use since linezolid in 2000.

The first article in this supplement, by Andrew F. Shorr and Kamal M. F. Itani, provides up-to-date information on US FDA guidance for the conduct of clinical trials for acute bacterial skin and skin structure infections. These new guidelines are most important, because recent uncertainty concerning the stance of regulatory agencies in the United States has served to make the conduct of clinical trials of antibiotics considerably more difficult. The new guidelines go a long way toward solving this problem.

Martin E. Stryjewski and G. Ralph Corey discuss the origins and global epidemiology of MRSA in hospital and community settings. They also provide valuable data on the emergence of resistance to vancomycin and other glycopeptides, as well as related antimicrobials.

The therapy of MRSA infections is the subject of the contribution by Keith A. Rodvold and Kevin W. McConeghy. These authors discuss the potential utility of presently available agents and provide valuable information concerning several new antimicrobial agents that are currently undergoing or have recently completed phase 3 trials in patients with acute bacterial skin and skin structure infections caused by MRSA.

Current dosing recommendations for tedizolid have been developed through the use of pharmacokinetic and pharmacodynamic systems analysis, which provides a powerful tool for
choosing the appropriate dosing regimen for drugs such as tedizolid. This process is described in detail in the article by Thomas P. Lodise and George L. Drusano.

The in vitro activity of tedizolid against clinically significant wild-type and resistant gram-positive pathogens is outlined in the paper by Jeffrey B. Locke, Gary Zurenko, Karen J. Shaw, and Kenneth Bartizal. Included in the discussion of the in vitro activity are data on the mechanism through which tedizolid exhibits greater activity against cfr-containing strains than linezolid.

William O’Riordan, Sinikka Green, Purvi Mehra, Carisa De Anda, Edward Fang, and Philippe Prokocimer provide an excellent summary of the efficacy of tedizolid in phase 2 dose-ranging and phase 3 comparative trials. The phase 2 trials allowed the selection of an appropriate dose regimen for the subsequent comparative trials that demonstrated noninferiority to linezolid.

Finally, an extensive safety summary of tedizolid is provided in the article by Debadiya Das, Paul M. Tulkens, Purvi Mehra, Edward Fang, and Philippe Prokocimer. The data available thus far reflect a very favorable adverse event profile, which may facilitate the clinical deployment of this new oxazolidinone antimicrobial agent, if approved.

Notes
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