Clinical outcome with oral linezolid and rifampin following recurrent methicillin-resistant *Staphylococcus aureus* bacteremia despite prolonged vancomycin treatment

Jon-David Schwalm MD¹, Philippe El-Helou MD¹, Christine H Lee MD²

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Drug-resistant Gram-positive bacteria, especially *Staphylococcus aureus*, are emerging as the predominant organisms involved in both nosocomial and community-acquired infections. Since the 1980s, vancomycin has been the first-line antibiotic used to treat methicillin-resistant *S aureus*. However, allergy and intolerance to vancomycin, the increasing number of vancomycin clinical failures and the existence of vancomycin intermediate-susceptible isolates of *S aureus* suggest that new antibiotics are needed. This paper reports the only known case of a successful clinical outcome with long term oral linezolid and rifampin therapy in the management of recurrent and persistent methicillin-resistant *S aureus* bacteremia with metastatic infections despite prolonged vancomycin use. More than two years since the initiation of linezolid and rifampin, the study patient has been clinically well with no evidence of adverse drug reactions including cytopenia and hepatic toxicities. Physicians must be aware of the novel developments in antibiotic therapy to treat drug-resistant bacterial infections.

Key Words: Linezolid; MRSA bacteremia; Osteomyelitis; Vancomycin

Résultats cliniques de l'association de liné-zolide et de rifampine par voie orale, consécutive à une bactériémie récidivante au staphylocoque doré résistant à la méthicilline malgré un traitement prolongé à la vancomycine

Les bactéries Gram-positives, résistantes aux médicaments, en particulier le staphylocoque doré, apparaissent maintenant comme les germes les plus souvent mis en cause dans les infections tant nosocomiales qu'extrahospitalières. La vancomycine s'avère, depuis les années 80, l'antibiotique de première intention pour traiter les infections à staphylocoque doré résistant à la méthicilline (SARM). Toutefois, les allergies et l'intolérance au médicament, le nombre croissant d'échecs de traitement à la vancomycine et l'existence d'isolats de SARM plus ou moins sensibles à la vancomycine justifient la recherche de nouveaux antibiotiques. Le présent article fait état du seul cas déclaré jusqu'à maintenant de résultats cliniques favorables de la bithérapie orale, de longue durée, au liné-zolide et à la rifampine pour le traitement d'une bactériémie récidivante et persistante au SARM, accompagnée d'infections métastatiques, et ce, malgré l'utilisation prolongée de vancomycine. Plus de deux ans après l'amorce de la bithérapie, le patient à l'étude se porte bien au point de vue clinique et ne montre pas de signes de réactions indésirables aux médicaments, notamment de cytopénie et d'hépatotoxicité. Les médecins doivent être au fait des derniers progrès réalisés en matière d'antibiothérapie pour le traitement des infections bactériennes résistantes aux médicaments.

According to the National Nosocomial Infection Surveillance System, Gram-positive pathogens, especially *Staphylococcus aureus*, are emerging as the predominant organisms involved in both nosocomial and community-acquired infections (1). *S aureus* is spread via contact and is a common cause of numerous infections including soft tissue infections (cellulitis and impetigo), wound infections, bacteremia with metastatic infections (osteomyelitis, septic arthritis and acute infective endocarditis) and toxic shock syndrome (2-4).

Since the introduction of antibiotics in the 1940s, *S aureus* has been most effective in its ability to develop resistance to antimicrobial agents, thus evoking significant concern in both the public and the health care communities. For example, one year following the introduction of methicillin for the treatment

of penicillin-resistant *S aureus*, the first strain of methicillin-resistant *S aureus* (MRSA) was identified (5).

Over the past two decades, MRSA rates have increased dramatically in both the community and hospital settings, to the point that this pathogen is now endemic in many American centres (5). Methicillin resistance is associated with significant morbidity and mortality. Bacteremia due to MRSA, when compared with methicillin-susceptible *S aureus*, has a two- to threefold increase in mortality (6-7).

Vancomycin was initially introduced in the middle 1960s but gained significant recognition in the early 1980s as the treatment of choice for MRSA (8). While this antibiotic is principally used for the treatment of MRSA infections today, it has a relatively high clinical failure rate (9,10). Various reasons

¹Department of Medicine; and ²Department of Pathology & Molecular Medicine, McMaster University, Hamilton, Ontario
Correspondence: Dr Christine H Lee, Infectious Diseases and Microbiology, St Joseph's Hospital, 50 Charlton Avenue, Hamilton, Ontario L8N 4A6. Telephone 905-521-6143, fax 905-521-6083, e-mail clee@mcmaster.ca
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Figure 1 Febrile illness in relation to antibiotic therapy (*Temperature approximated to represent presence or absence of fever). Vanco Vancomycin

for the decreased clinical efficacy of vancomycin despite the in vitro sensitivity of MRSA to the antibiotic have been suggested. First, vancomycin has decreased bactericidal activity against *S aureus* (11). Second, its low tissue concentration prevents effective eradication of virulent Gram-positive pathogens (12,13).

In July 2002, the first case of infection due to vancomycin-resistant *S aureus* (VRSA, minimum inhibitory concentration [MIC] greater than 128 µg/mL) related to catheter exit site infection in a Michigan patient was reported (14). There have also been several worldwide reports of glycopeptide-intermediate *S aureus* (GISA), defined as an MIC of 8 to 16 µg/mL. The first case of GISA was reported in Japan in 1996 (5). Since then, strains of GISA, also resistant to methicillin, were reported from Italy, the United Kingdom, France and the United States (2,15-21). Prolonged intermittent vancomycin use has been associated with the development of GISA and VRSA strains (14,16).

Current antimicrobial agents routinely used to treat antibiotic-resistant Gram-positive organisms, especially MRSA, have limitations in terms of their efficacy. With the emergence of the aforementioned resistant strains, newer antimicrobial agents must be considered.

This paper reports the only known case of a successful clinical outcome and no adverse drug reactions with long term linezolid and rifampin therapy in the management of recurrent and persistent MRSA bacteremia with metastatic infections despite prolonged vancomycin use.

CASE PRESENTATION

The case of a 66-year-old woman with a significant medical history of type II diabetes mellitus and severe chronic obstructive lung disease requiring long term use of systemic corticosteroids is presented (Figure 1).

The patient was initially admitted to the study facility with MRSA bacteremia and metastatic infections involving her left ankle and bilateral acromioclavicular joints.

Vancomycin was initiated at approximately 15 mg/kg intravenously every 12 h; serum vancomycin levels were not assessed because the patient had a calculated creatinine clearance greater than 60 mL/min. The patient's course in the hospital was further complicated by two chronic obstructive pulmonary disease exacerbations requiring her to remain on high dose systemic corticosteroids.

Three months following admission, the patient was discharged from the hospital and closely followed as an outpatient. Vancomycin was discontinued one month later because there was no evidence of persistent infection.

However, shortly after the discontinuation of vancomycin, the patient was readmitted to the study facility with a two-day history of fever, chills, left shoulder and ankle pain, left arm swelling and general malaise. Vancomycin was empirically initiated given the patient's past medical history, again at a dose of approximately 15 mg/kg intravenously every 12 h. Twelve hours later, the patient developed septic shock and was transferred to the intensive care unit. MRSA was isolated from blood, synovial fluid and several tissue biopsies. The organism was resistant to oxacillin (MIC greater than 4 µg/mL; measured by MicroScan [Dade Behring Inc, USA]) and was only sensitive to vancomycin (MIC up to 2 µg/mL; measured by MicroScan). Despite a six-week course of vancomycin, the patient continued to be ill. She remained febrile and the blood cultures were persistently positive for MRSA. The isolate remained susceptible to vancomycin (MIC up to 2 µg/mL). During this period, the patient underwent debridement and synovectomy of her affected joints and bones to help subdue the infectious burden. An indium chloride-labelled white blood cell scan confirmed the diagnosis of osteomyelitis of the left calcaneus. Transthoracic and transesophageal echocardiograms were negative for vegetations or cardiac involvement. Rifampin (300 mg/day orally) was then added to the vancomycin, however, the patient remained febrile for approximately another two weeks. Given the patient's poor response to vancomycin, a twice daily oral regimen of linezolid 600 mg was added. Vancomycin was discontinued shortly thereafter and the linezolid and rifampin were continued.

Following the initiation of linezolid, the patient dramatically improved and defervesced, and subsequent blood cultures remained sterile. The patient was discharged two months later to a long term care facility. She was continued on linezolid and rifampin for 14 months. While on the antibiotics, she remained afebrile and fully ambulatory, and the repeat indium chloride-labelled white blood cell scan showed resolution of osteomyelitis. Based on these findings, the antibiotics were discontinued.

Approximately three weeks after discontinuing the antibiotics, the patient developed recurrent fever, fatigue and anorexia. Levofloxacin was initiated by her family physician but she continued to experience constitutional symptoms as well as fever. After repeating the blood cultures, chest x-ray, erythrocyte sedimentation rate and complete blood counts, linezolid and rifampin were reintitiated. While no organism or source of infection was identified, five days after reinstating antibiotics the patient defervesced and showed improvement of appetite and mobility. She has remained well since the reintroduction of linezolid and rifampin.

Currently, more than 24 months since her admission for recurrent MRSA bacteremia, the patient's quality of life has been restored. She is walking independently and there has been no further admission to an acute care hospital. The patient has been treated with linezolid and rifampin for over 24 months and her weekly complete blood counts, serum alanine transferase and creatinine levels remain normal.

DISCUSSION

While vancomycin is a standard antimicrobial agent used to treat MRSA infections, this case report demonstrates its potential lack of clinical efficacy despite laboratory-proven sensitivity to MRSA. Novel classes of antibiotics such as linezolid, quinupristin-dalfopristin, daptomycin and the ketolides

have been developed and studies have shown their in vitro and in vivo activities against resistant Gram-positive bacteria. Considering our patient clinically failed vancomycin alone, as well as combined vancomycin and rifampin, and her successful clinical outcome coincided with the initiation of linezolid for her severe MRSA infection, this paper will focus on the characteristics of this oxazolidinone class of antibiotic.

Linezolid was released in the United States in May 2000 and in Canada in May 2001. Linezolid has been shown to be clinically effective in the treatment of nosocomial and community-acquired pneumonia as well as skin and soft tissue infections caused by Gram-positive organisms, including resistant strains (ie, MRSA, GISA [in vitro], methicillin-resistant *Staphylococcus epidermidis*, vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae*) (21-25). Linezolid has also demonstrated in vitro activity against various anaerobic bacteria including *Clostridium perfringens*, *Clostridium difficile* and *Bacteroides fragilis* (24).

Multiple in vitro and in vivo studies have demonstrated that linezolid is either more potent or as active in the eradication of Gram-positive cocci when compared with traditional antimicrobial agents such as vancomycin or other novel antibiotics, eg, quinupristin-dalfopristin (27-29). The causes for its superior efficacy compared to vancomycin are yet to be determined. Both vancomycin and linezolid have similar half-lives of 6 to 8 h (21,29-30) and postantibiotic effects of 1 to 2 h (31,32). Vancomycin has lower minimum inhibitory concentrations for many Gram-positive cocci compared with linezolid. In vitro, the majority of *S aureus* and *S epidermidis* are highly susceptible to vancomycin, with MICs of up to 2 µg/mL (33). In comparison, the MIC of linezolid for *S aureus* ranges between 2.0 and 3.6 µg/mL (34,35). Perhaps linezolid is more efficacious than vancomycin due to its better tissue penetration (12,13,36).

Linezolid has a unique mechanism of action from other protein translation inhibitors and therefore does not share cross-resistance with other classes of antimicrobial agents. Linezolid binds to the bacterial 23s ribosomal RNA of the 50s subunit with secondary interaction with the 30s subunit. This blocks formation of the initiation complex, thus effectively inhibiting the initiation of protein translation during the early stage of the ribosome cycle (24). Linezolid has 100% oral bioavailability with an elimination half-life of 5 to 7 h (22). Because metabolism of linezolid does not involve the cytochrome P450 system or the kidneys, dose adjustment is not required for hepatic or renal dysfunction (22).

While linezolid has been demonstrated to be an effective antibiotic against resistant Gram-positive pathogens, it has three potential drawbacks. First, adverse reactions to linezolid are rare but include the following: diarrhea, nausea, headache, vomiting, skin rash and increased liver enzymes (23,25). The most serious adverse reaction includes mild, reversible bone marrow suppression in approximately 2% of patients (23,25). It is therefore suggested to monitor the patient's complete blood count every two weeks. The patient described in this report has been tolerating linezolid therapy at 600 mg orally, twice a day, for more than two years with no evidence of adverse reactions.

Second, linezolid has a significantly higher cost of therapy compared with other antibiotics. However, considering the case described in this paper, the costs of multiple hospitalizations secondary to MRSA infections despite long-term vancomycin therapy, outweighs the cost of oral linezolid.

Finally, while linezolid has been shown to be an excellent alternative to vancomycin, there have been various cases of linezolid-resistant bacteria reported in literature. The initial seven cases involved linezolid-resistant *Enterococcus faecium* (37), while a more pertinent case, involving linezolid-resistant MRSA in a patient with peritoneal dialysis-associated peritonitis and a hypersensitivity to vancomycin (38), has been reported. These reports are not unexpected, because there has been a steady emergence of multiple drug resistance in many pathogens over the past five decades. This stresses the importance of the judicious use of antimicrobials to minimize resistance problems and provide optimal patient care.

While this case represents a successful clinical outcome with long term oral linezolid and rifampin therapy in the management of recurrent and persistent MRSA bacteremia, it also highlights potential limitations of this novel antibiotic. Considering the patient's recurrence of fever shortly after discontinuing the linezolid and rifampin and the need for continuing antibiotic therapy, this case demonstrates the role of linezolid in suppression of the replication of the organisms rather than complete eradication of the bacteria.

CONCLUSION

Drug-resistant Gram-positive bacteria, especially *S aureus*, are emerging as the predominant organisms involved in both nosocomial and community-acquired infections. Treatment of these antibiotic-resistant pathogens is becoming increasingly difficult because clinicians are restricted to a select few antimicrobial agents with limited efficacy. It is essential for clinicians to be aware of newer or investigational antimicrobial agents to maximize the treatment options for drug-resistant pathogens. Linezolid may be effective when used alone or in combination with other antibiotics such as rifampin for treatment of MRSA infections.

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