

Salvage Therapy For Methicillin- Resistant Staphylococcus Aureus (MRSA) And Methicillin- Resistant Staphylococcus Epidermidis (MRSE) Infected Total Knee Arthroplasty (TKA) Using Telavancin. An Alternate Option.

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Citation

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Abstract

Introduction: Prosthetic joint infections (PJI) occur in about 2% of knee arthroplasties (TKA), resulting in significant morbidity, mortality, and associated medical costs. Current treatments consist of antibiotic therapy and surgical management via the one-stage joint revision or, the more common, two-stage joint revision.

Case Presentation: We present the case of a patient with methicillin- resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermis (MRSE) positive prosthetic knee joint infection who was successfully treated by an incision and drainage and change of polymer along with intravenous telavancin, a novel bactericidal lipoglycopeptide. Follow-up at 6 months revealed no evidence of a recurrence of infection.

Conclusion: Further studies involving clinical trials testing the use of telavancin in methicillin- resistant Staphylococcal PJI's are needed to develop official guidelines and protocols, and establish its overall efficacy.

BACKGROUND

As the overall number of total hip and knee arthroplasties have increased over the years, so have prosthetic joint infections [1]. Prosthetic joint infections remain the major and most serious complications of total hip and knee arthroplasties. The most common causative organism of prosthetic joint infection is reported to be Staphylococcus aureus, followed by coagulase-negative Staphylococci [2]. However, the emergence of methicillin-resistant strains of Staphylococci has made treatment of prosthetic joint infections more challenging. Vancomycin has been used as the first-line treatment for MRSA but increased resistance has emerged over the years necessitating newer treatments. Telavancin is a lipoglycopeptide antibiotic that has a dual mechanism of action on bacterial cell wall synthesis and disruption of the barrier function of the cell membrane [3]. Telavancin has been shown to be more effective at bacterial eradication of MRSA as compared to vancomycin [4].

While there is considerable literature advocating the usage of vancomycin for PJI's, minimal literature exists regarding telavancin [8, 27]. We present a case of MRSA and MRSE infection of a prosthetic knee joint which was successfully treated by an incision and drainage along with intravenous telavancin for 6 weeks.

CASE PRESENTATION

A 74 year-old Hispanic female with a history of hypertension and osteoarthritis underwent a TKA of the left knee 6 years ago. Over the course of her illness, she had 5 surgeries with MRSE positive cultures at every occasion. Since then, she was treated twice with a two- stage revision along with suppressive Trimethoprim-Sulfamethoxazole for 4 months after IV antibiotic treatment. Six months after her last revision, she presented with pain and tenderness to the knee.

Upon examination, she had a temperature of 97.2 F, blood pressure of 110/70 mm Hg, and pulse of 88 bpm. The

physical exam was significant for previous surgical scars along with mild erythema and tenderness of the knee. There was also the presence of a small effusion. Lastly, there was significant restriction of the range of motion.

Laboratory findings were significant for an erythrocyte sedimentation rate (ESR) 98 mm/hr and C-reactive protein (CRP) of 5.6mg/dL. Aspiration of the knee revealed MRSE. Additionally, the cultures done intra-operatively grew MRSE with a minimum inhibitory concentration (MIC) of 0.5µg/mL and MRSA with MIC of 1.0µg/mL.

She refused to have the TKA removed but allowed a wash out and replacement of the polymer. Due to repeated failures in the past with vancomycin as well as daptomycin, we elected to try telavancin as salvage therapy.

She was treated with intravenous telavancin 10 mg/kg for 6 weeks, followed by Trimethoprim-Sulfamethoxazole Double Strength twice daily for 2 months. The ESR and CRP finally decreased to 14 mm/hr and <0.5 mg/dL, respectively, at the end of 6 months of therapy. There was no evidence of renal dysfunction during or after her therapy. At her 6-month follow-up visit post-surgery she presented with no signs of infection.

DISCUSSION

Data suggests that 23-25% of revision procedures following total knee arthroplasties are a result of PJI's [2]. PJI's are most likely to occur within the first two years following arthroplasty, with the highest incidence within the first six month [5].

Pathogenesis of PJI's involving bacterial adhesion on artificial joint surfaces with subsequent development of biofilm that prevents penetrance of antibiotics [5,7]. Intraoperative contamination, contiguous spread from overlying skin and soft tissue, as well as hematogenous spread from varying anatomical locations account for the possible means of acquiring PJI's [5].

Staphylococci are responsible for more than half of the cases of prosthetic hip and knee infections. Polymicrobial infections account for approximately 20% of cases while culture-negative infections in the setting of previous antibiotic therapy account for 7% of cases [1]. Non-Staphylococcal species commonly causing PJI's include, Enterococcus, Pseudomonas, E.Coli, Enterobacter,

Streptococci, and Proteus [2]. In this patient, there was polymicrobial infection with clinical suspicion of not only PJI, but also deep tissue infection as well as osteomyelitis of the adjoining long bones that could have accounted for her chronic infection. In addition, the presence of extensive biofilm may have prevented penetration of the previous antibiotics [5].

Overall treatment options for infected TKA include irrigation and debridement with component retention that can be done with or without polymer exchange, one-stage revision, two-stage revision, antibiotic mediated suppression, resection arthroplasty, less commonly arthrodesis, and amputation as the last resort [6].

Antibiotics used for PJI's should generally be bactericidal, orally-bioavailable, penetrable within bone and joint tissues, and effective against surface- adhering-biofilm-producing microorganisms [10]. While evidence remains limited for use-specific antibiotics in the context of PJI's, most studies have explored the treatment of Staphylococcal infection due to its wide prevalence. Additionally, no clear evidence exists over the superiority of oral versus intravenous route of antibiotic administration [11]. An initial IV regimen allows for maximum plasma concentration in the shortest duration. However, switching to oral antibiotics following initial IV regimen decreases financial burden, lowers risks associated with catheterization, and promotes home therapy for patients [9].

Early switch to oral antibiotics after 2 weeks of IV antibiotics have shown excellent outcomes using rifampicin and ciprofloxacin combination therapy, with no relapses in Gram-positive mono-bacterial infections in both one and two stage exchanges [32, 33]. While the Infectious Disease Society of America (IDSA) supports highly bioavailable, pathogen-specific oral antibiotics as alternatives for IV antibiotics in some cases of PJI's, no literature is conclusive for exclusive oral antibiotic therapy in the setting of PJI's, especially prior to reimplantation [9]. Moreover, oral therapy also carries its disadvantages due to increased gastrointestinal side effects, need for selection based on bioavailability, and the possibility of decreased compliance and adherence as a result of unsupervised therapy [34].

As a result of inadequate confirmatory studies, current treatment options are largely based on tradition, personal experience, and factors related to the different specialists involved in PJI care [10]. Use of intra-articular

antibiotics has now been used with around 87% success [30-31]. In our patient, this approach was not used as the optimum dose of intra- articular telavancin could not be calculated with much confidence.

According to practice guidelines of the IDSA, recommendations for Staphylococcal PJI following one-stage exchange includes, two-6 weeks of IV microbial therapy, specific to presenting pathogen, combined with rifampin 300-450mg orally twice daily, followed by rifampin plus a companion oral drug for a total of 3 months. Companion drugs for rifampin include ciprofloxacin and levofloxacin. First- line options for susceptible Staphylococci include nafcillin, cefazolin, or ceftriaxone. Mainstay treatment for resistant Staphylococci includes Vancomycin IV 15mg/kg q12 hr with daptomycin or linezolid serving as substantial alternatives [12]. While adequate evidence for specific antibiotic therapy targeting gram negative joint infection is currently lacking, use of ciprofloxacin may be associated with better outcomes [10,13]. Culture-negative joint infections can be empirically treated with a glycopeptide and/or cephalosporin [10,14].

However, it is MRSA, which remains problematic as current protocols have inferior results when compared to protocols for the treatment of other organisms causing PJI's [15]. Additionally, MRSA has shown higher failure rates in PJI treatments when compared to MSSA [16]. While first-line treatment of methicillin resistant Staphylococci in PJI's remains limited to vancomycin with a few other alternatives such as daptomycin and linezolid, novel antibiotics such as telavancin and oritavancin can aid and broaden treatment measures to decrease the burden of methicillin- resistant Staphylococci in PJI's [12,17, 29].

Telavancin, a lipoglycopeptide antibiotic with rapid concentration-dependent bactericidal effects, is derived from vancomycin [3, 18-19]. However, unlike vancomycin, telavancin has a dual mechanism of action. Firstly, like vancomycin, telavancin inhibits peptidoglycan polymerization and cross-linking by binding to D-alanyl-D-alanine which results in the overall inhibition of bacterial cell wall synthesis. The second, newer mechanism of action of telavancin is mediated by its attachment to the cell wall precursor, lipid II, which, in turn, disrupts the functional integrity of the bacterial membrane [18, 24-25].

Telavancin has shown lower MICs than vancomycin against *S.aureus* and *S.epidermidis* in both methicillin

resistant and susceptible strains. It has also demonstrated overall potent activity against streptococci, enterococci, anaerobic gram-positive organism, and *Cornebacterium* [5, 23]. Administered intravenously over a 24-hour period, the drug possesses a half- life of 7-9 hours and extended post-antibiotic effect of 4-6 hours; whereas, vancomycin has a post-antibiotic effect of 1 hour [20, 23]. Telavancin is excreted renally, therefore, dose adjustments are necessary for patients with renal impairment [28]. Most commonly reported adverse reactions of telavancin include taste disturbance and nausea followed by vomiting, and foamy urine [26].

Telavancin 10mg/kg given once daily has been shown to be effective in complex gram positive bacterial skin and soft tissue infection, particularly involving MRSA [18, 20, 23]. Moreover, it is currently being investigated for its potential use in nosocomial pneumonia and bacteremia [23]. In vitro studies comparing the activity of telavancin and vancomycin against MRSA grown in planktonic culture and biofilms, demonstrated increased efficacy of telavancin indicating its potential value in the treatment of biofilm-mediated infections [21-22]. While adequate literature exists regarding the usage of telavancin in skin and soft tissue infections, only one other case report exists, till date, exhibiting the successful usage of telavancin in MRSE prosthetic joint infection [27]. Telavancin, in that case, was also used as salvage therapy for an MRSE culture positive infection, unresponsive to vancomycin, after repeated debridement of a prosthetic knee joint [27]. In our case, telavancin was used for a combined MRSA and MRSE prosthetic joint infection. Advantages of using telavancin include its bactericidal action and once-daily dosing. Disadvantages include lack of availability of oral administration and possible renal toxicity in studies that have looked at bone penetration in osteomyelitis and biofilms.

CONCLUSION

In conclusion, total joint arthroplasties are interventions facilitating improvements in pain, functionality, and the overall quality of life. Prosthetic joint infections associated with them, however, can be significantly debilitating with respect to health burden, time involved, and overall associated costs. As mentioned above, Staphylococcal PJI's, particularly involving methicillin-resistant strains, continue to cause a major burden on patients undergoing joint arthroplasties [15-16].

While a rough protocol exists for the treatment of such PJI's, extensive research as well as confirmatory randomized controlled clinical trials are needed to allow for a uniform approach towards PJI management [10-12].

Televancin provides an alternative approach to the treatment of MRSA/MRSE PJIs. Further studies involving clinical trials testing the use of televancin in methicillin-resistant Staphylococcal PJI's is needed to develop official guidelines and protocols, and establish its overall efficacy. Future research could possibly be directed towards televancin as a potential intra-articular antibiotic in the treatment of PJIs.

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