

G89: is there a role for the administration of newer and long-acting antibiotics such as Dalbavancin, Oritavancin, Fosfomycin, or 5th generation Cephalosporins?

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Response/ Recommendation:

There may be a role for administration of newer and long-acting antibiotics, as a safe and effective alternative treatment for PJI. At the present time there is more evidence around Dalbavancin use than Oritavancin use, but there is scant evidence regarding Fosfomycin use and unfortunately no clinical data for 5th generation Cephalosporins for the treatment of PJI. Consequently, more research is needed to clarify the role of these agents in the treatment of PJI.

Level of Evidence: Limited

Delegate Vote:

Rationale:

Novel antimicrobials are welcomed with excitement, particularly at a time when the emergence and spread of antimicrobial resistance is considered a global public health threat. (13) Some of these novel antibiotics have been developed with the intention of treating complex soft tissue and bone infections. Orthopaedic implant-related infections require prolonged antibiotic treatment to eradicate biofilm and intracellular bacteria that are frequently involved in these infections (7).

In attempts to shorten or avoid hospitalization without increasing overall health care costs, two long-acting lipoglycopeptides, Oritavancin and Dalbavancin, have been approved for use in acute bacterial skin and skin structure infections (ABSSSIs). Some studies have also included complicated infections such as periprosthetic joint and osteomyelitis. The use of these agents for longer courses of therapy, were beneficial for resistance and would not only potentially decrease hospital admissions, but also prevent the need for prolonged intravenous catheterization, which in turn could decrease line complications. (11,)

The role of newer and long-acting antibiotics such as Dalbavancin, Oritavancin, Fosfomycin and 5h-generation Cephalosporins have been researched through a systematic review carried through Covidence by reviewing identified studies added from 2 databases, PubMed (274 studies) and Scopus (106 studies). The inclusion criteria were studies of clinical cases of periprosthetic joint infections (PJIs) treated with systemic newer and long-acting antibiotics. Reviews were not included. Only one study met the inclusion criteria. Therefore, we re-evaluated all available studies that included clinical applications of PJI treated with the targeted antibiotics and manually identified studies by reviewing the references of the studies. This resulted in 16 studies with clinical use of Dalbavancin, Oritavancin and Fosfomycin. During data extraction, PJI cases were extracted from a mixed series of other infections. Dalbavancin was the most investigated drug, with 11 clinical studies identified. Only 3 studies on Oritavancin, 2 on Fosfomycin and none on 5th generation cephalosporins were identified.

Dalbavancin:

There were 11 studies, published between 2017 and 2023, that discussed the use of Dalbavancin for the treatment of PJIs. (1,3-7,9,10,12,13,16) One study was prospective, the rest being retrospective, with 6 multicentre and 5 single institution studies. A total of 675 patients were treated with intravenous injection of Dalbavancin, of whom 245 were for PJI. The majority of patients were hips (89 patients) and knees (63 patients) and a few shoulders (4 patients) and ankles (1 patient). There were many different microorganisms treated, with the majority being Staphylococci (MRSA, MSSA, MRSE and Coa N. staph), Enterococci, Streptococci, Corynebacteria and polymicrobial as well as culture negatives. Dalbavancin was administered intravenously with different dose regimens varied from short courses of a starting dose of 1500mg followed a week later with another 1500mg administration, to longer courses starting with either 1500mg or 1000mg followed by 500mg weekly. One regimen started with 1500 mg followed by 1000 biweekly and another one started with 750mg followed by 750mg with renal adjustments of the dose. There was also a significant variation in the length of treatment from a short course of one to two doses up to 3 months. Surgical interventions were also not clearly identified but included DAIR, single or two stage procedures and excision arthroplasties and Girdle stones. The results of treatment of Dalbavancin were assessed based on clearance of infection but for various periods of time in different studies. With the exception of one study (3) where there was infection clearance in 8/17 (47%) with 2 PJI-related deaths, 4 relapses and 3 antibiotic suppression, the results of favourable outcome ranged from 75% to 90% but with different periods of follow up from as short as 90 days to more than one year. Adverse drug reactions have also been reported; however, due to the small number of cases, meaningful conclusions could not be established, with the incidence of ADRs ranging from 3% to 13%, including rash, tachycardia, leucopenia, and impaired renal function.

Oritavancin:

There were 3 studies, published between 2017 and 2020 that discussed the use of Oritavancin in a small number of cases (11,14,15). Among 576 patients receiving Oritavancin, only 29 were being treated for PJI; 2 patients in one study, 3 in the second and 24 in the third study. The majority of microorganisms were *S. aureus* with MRSA, MSSA and one case of MRSE. The dose regimens were variable, with one consisting of 1200mg twice every 2 weeks, one starting with 1200mg followed by 800mg weekly and the third 1200mg every 10 days. There were no specifications about the surgical intervention except in one study where 2 case were treated with a one stage procedure. The infection clearance rate was 2/3 after 30 days in one study, 2/2 after 6 months in the second study and 20/24 (83.3%) in the last study at 3 and 6 months. Adverse drug reactions were reported for the total group of infections, varying between 3.7% and 6.6%, but not specified among the PJI cases.

Fosfomycin:

There were 2 studies published in 2019 discussing the use of Fosfomycin in the treatment of PJI. (2,8) Among 95 PJI patients, 54 received Fosfomycin in combination, mainly with Vancomycin and Daptomycin. There were 55 hips, 35 knees, 2 elbows, 2 shoulders and one ankle. Isolated organisms included *Enterococcus faecalis*, *Enterococcus faecium* and *Enterococcus casseliflavus* in one study, as well as *Enterobacter cloacae* in the second. The administration regimen was not identified in one study and consisted of 5gm intravenously every 3 hours in the second study, with a mean duration of treatment of 14 days (3 to 90 days). Different surgical interventions were used including DAIR, one and two stages with 2 cases of arthrodesis. Against *Enterococcus* species, the infection clearance was 85% (a cure

rate of 95% for the group with added Fosfomycin compared to 80% cure rate for the group without Fosfomycin.) ($p = 0.621$). No specific adverse drug reactions were reported for Fosfomycin.

5th generation cephalosporin:

Although Ceftaroline and Ceftobiprole have proved effectiveness against both gram positive and gram negative organisms in various reports, we could not identify clinical studies addressing treatment of PJI with 5th-generation cephalosporins.

Conclusion and Remarks:

Only few studies have investigated the use of long acting antibiotics or fosfomycin and 5th generation cephalosporins in the treatment of PJI. Most of the current studies include retrospective small cohort studies (extracted from a mixed series of infections) and case reports. Long term follow up was not available in most cases. The decision of their use, as well as choice of surgical plan, was primarily individualized by physicians with no uniform criteria of use.

The few studies of Dalbavancin suggested that its administration allowed earlier discharge, reduced hospital stay with a potential for outpatient treatment, and seemed to be safe, effective and cost saving, and can even be used as a salvage therapy. (1,3)

Regarding the very scant data on the use of Oritavancin, it appeared at this juncture to be a safe and effective alternative to daily antibiotic infusions to treat complicated Gram-positive infectious disease processes.

With little available evidence, Fosfomycin was found to be of value as an additive agent to other antibiotics. No evidence on clinical use of 5th generation Cephalosporin could be found in PJI patients.

Still, the current information could provide a starting point for performing new well-structured studies evaluating these new compounds.

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