G90

Given recent warnings regarding the use of fluoroquinolones: is there a role for these antibiotics in the management Gram-negative and staphylococcal peri-prosthetic joint infections treated with implant retention (DAIR), when other alternative antibiotic options are available?

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Response/Recommendation:

Based on their efficacy and the low absolute risk for serious adverse events, fluoroquinolones have a role in the management of Gram-negative and staphylococcal periprosthetic joint infections treated with debridement, antibiotics and implant retention (DAIR). Relevant pre-treatment investigations, screening of medication list, patient information, and careful monitoring during treatment should be considered in patients at risk for serious adverse events.

Level of evidence:

Weak

Delegate Vote:

Background:

FQs are commonly used in the oral treatment phase of periprosthetic joint infections (PJIs) caused by Gram-negative bacteria and staphylococci[1-6]. Due to reports of significant adverse events such as tendinopathy, neuropathy, dysglycemia and aortic aneurysm, regulatory agencies have issued warnings on the use of FQs[7-12]. While these warnings do not specifically target PJIs, caution is recommended, particularly in certain patient categories. This review summarizes the risks and benefits of using FQs in PJI treatment.

Fluoroquinolone use in PJIs:

Gram-negative PJIs (GNB-PJIs)

Seven cohort studies compared FQ-containing regimens to alternative treatments. Of these, four studies reported a benefit associated with FQs[13-16]. A pooled analysis of data from 187 patients across five studies[14-18], found a statistically significant increase in treatment success with FQ therapy (reported cure 87% vs. 62%, $p=0.0005$). In contrast, a recent prospective cohort containing 100 patients did not find any significant advantage in using FQs in GNB-PJIs[19].

Staphylococcal PJIs Treated with DAIR

Twelve observational studies compared FQ-containing antibiotic regimens to other regimens in staphylococcal PJIs treated with DAIR[14,20-30]. Most found no statistically significant difference in outcome. However, in a pooled analysis of unadjusted data from eight studies[14,20-26], a FQ-based regimen showed an association with improved treatment success (reported cure 87% vs 75%, $p<0.0001$).

Several studies detected a positive effect of FQs in the univariate but not multivariate analysis[25-27]. Shabana *et al.* found that resistance to FQs was an independent risk factor for clinical failure in multivariate analysis[30] while Senneville *et al.* reported FQ/rifampin therapy independently predicted remission[22]. A meta-analysis suggests that FQ/rifampin combinations were more effective than other rifampin-containing antibiotic strategies[31].

Review of potential adverse events during fluoroquinolone therapy:

Tendinopathy

Animal models demonstrate FQ-induced tendon lesions[32], and observational studies in humans have evaluated the risk of tendon injury/rupture associated to FQ treatment[33-46]. An increased incidence of tendinopathy has been reported in connection with FQ use; in one large, population-based study, the incidence of tendinitis was 6.61 per 10^5 person-years for FQ treated patients compared with 3.64 for controls[42-44]. An elevated risk of levofloxacin compared to ciprofloxacin or moxifloxacin was reported in several studies[33-36], but a focused systematic review did not confirm this differential risk[47]. FQ therapy with ciprofloxacin or levofloxacin within three months of surgical tendon repair for achilles or rotator cuff injury was associated with higher revision rates within two years[33]. Various comorbidities and patient factors may increase the risk of FQ-associated tendinopathy[37-42].

QT Prolongation and Arrhythmia

FQs can prolong the QT interval[48,49]. A small, uncontrolled retrospective cohort study reported that ventricular tachycardia occurred in 0.2% of patients with long QTc at baseline treated with levofloxacin[50]. While some studies link moxifloxacin to a higher risk of arrhythmia[51,52], other studies found no significant differences compared with other antibiotics[49,51-53]. Studies of levofloxacin have likewise yielded mixed results[51,52,54-56]. Large population studies, such as those by Polgreen *et al.* and Ellenardottir *et al.,* did not find an excess risk of ventricular arrhythmia or out-of-hospital cardiac arrest with FQs[57,58].

Aortic Aneurysm and Dissection (AA/AD)

FQ-induced collagen degradation is hypothesized to occur in vascular walls and may increase the risk of AA/AD[59]. However, the relationship between FQs and AA/AD remains controversial. Epidemiological studies report divergent results regarding the relationship between FQs and AA/AD[36,45,53,60-74], and only two of these reported stratified data on the different FQs[36,69]. Aortic mortality was higher in FQ users with pre-existing AA/AD[60,75]. Dong *et al.* demonstrated an association between infectious conditions and AA/AD[74]. The association of AA/AD to FQs with amoxicillin as comparator initially found by Gopalakrishnan *et al*. did not retain significance when patients without baseline imaging were excluded[67]. Five systematic reviews all report increased risk for AA after FQ use when compared to other antibiotics or no antibiotic treatment[75-79]. However, two reviews found no association to AD[77,78], and one reported no higher risk for AA /AD when comparing with other broad-spectrum antibiotics[78].

Peripheral Neuropathy and CNS Toxicity

FQ use has been associated with peripheral neuropathy, exacerbation of myasthenia gravis, and CNS neurotoxicity[80-83]. Three case-control studies report an elevated risk of peripheral neuropathy during/after FQ use compared to controls[84-86]. Morales *et al.* reported increased risk for peripheral neuropathy persisting up to 180 days after FQ exposure[86]. Regarding CNS toxicity, Ellis *et al*. reported a HR of 1.08 (95%CI 1.05-1.11) [84].

Retinal detachment (RD)

Eleven studies investigating whether FQ associated collagen degeneration could lead to RD were found[87-97]. Etminan *et al.* showed an increased RR of 4.50 (95%CI 3.56-5.70) for current use of FQs and RD and found no risk with recent or past use[89], but these results could not be replicated in another setting[90]. Other studies likewise report conflicting results, including some reporting associations with multiple other antibiotics as well as FQ [93-96]. Two systematic reviews did not support an association between FQ use and RD[98,99].

Dysglycemia

Dysglycemia, including hypoglycemia and hyperglycemia, has been documented during FQ therapy[100-104]. This was seen particularly for patients with diabetes, where

moxifloxacin[100,103] or levofloxacin[102,104] were used, and when combined with insulin or sulfonylurea[104].A systematic review concluded that caution must be taken when using FQs in diabetic patients, and that ciprofloxacin may be the FQ least likely to cause dysglycaemia[105].

Conclusion:

Available data suggest, with moderate certainty, a potential independent benefit in treating Gram-negative periprosthetic joint infection (GNB-PJI) managed with debridement, antibiotics and implant retention (DAIR) with fluoroquinolones (FQs). For staphylococcal PJI treated with DAIR, there is some evidence for improved clinical outcomes when combining FQs and rifampin compared with other rifampin combinations and non-rifampin-based regimens.

Current evidence suggests that FQ use is associated with an increased risk of tendinopathy, peripheral neuropathy and dysglycemia in diabetics, even though the absolute risk is low. There is conflicting evidence for an association between FQs and cardiac arrhythmia, aortic aneurysm and dissection, and retinal detachment.

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