Tasman JOURNALS
tasmanjournals.com
Open access medical and scientific journals from Down Under

TASMAN MEDICAL JOURNAL
ISSN 2652-1881
Volume 3(1): 64-68; (2021)

FIONA STANLEY HOSPITAL AND SOUTH METROPOLITAN HEALTH SERVICE (PERTH, AUSTRALIA) SPECIAL EDITION

CASE REPORTS

Re-introduction of biological DMARDs for rheumatoid arthritis during active antibiotic therapy for prosthetic joint infections

Kylan Pathmanathan, Graeme J. Carroll, Helen I. Keen

Department of Rheumatology, Fiona Stanley Hospital, Murdoch, WA 6150, Perth, Australia.

Abstract

***Objectives*:** To examine the safety of early re-introduction of biologic DMARD (bDMARD) therapy for rheumatoid arthritis (RA) during antibiotic treatment for prosthetic joint infections (PJI).

***Methods*:** Medical records of three RA patients with PJI were reviewed. During antibiotic treatment, all patients were recommenced on bDMARD therapy due to worsening disease activity. Details recorded include causative organism, timing of bDMARD re-introduction and infection risk factors.

***Results*:** *Case 1:* A 67-year-old female with RA developed a *Staphylococcus Schleiferi* PJI three weeks after an elbow replacement. Etanercept was re-commenced three months later with long term prophylactic antibiotics. After five years, no recurrence of infection had occurred.

Case 2: A 67-year-old male with RA developed a *Staphylococcus aureus* PJI 15 months after total knee replacement (TKR). Etanercept was recommenced at two months and switched to abatacept at five months. Antibiotics were ceased at seven months, however recurrence of MSSA PJI was confirmed two months later. Abatacept was ceased. Synthetic DMARDs were reintroduced with no further PJI identified over the following four years despite addition of Baricitinib in early 2020.

Case 3: A 74-year-old male with RA experienced a *Finegoldia magna* PJI eight weeks after TKR. Etanercept was restarted one-month later. No further joint infections occurred during the next 10 years.

***Conclusions*:** One of three RA patients experienced re-activation of PJI with an organism of high virulence. Two with low virulence organisms remain PJI free at five- and 10 years post infection. Treatment considerations should include organism virulence, risk factors for infection, RA disease activity off bDMARDs and patient preference.

Tasman Medical Journal 2020: 3(1); 64-68.

Introduction

Re-introduction of biological Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) for rheumatoid arthritis (RA) following prosthetic joint infection (PJI) remains a matter of conjecture. The requirement for long-term antibiotic suppressive therapy and adequate source control specifically for PJIs creates added complexity. Management in this particular scenario is currently based on consensus rather than evidence.

Joint replacement surgery is common in RA. bDMARD use is associated with a modest increased risk of native septic arthritis and post-operative infection following orthopaedic surgery in RA patients.[1,2] Conversely, in a Danish cohort study, corticosteroid exposure and high inflammation but not bDMARD therapy was associated with PJI risk at one year.[3]

The safety of bDMARDs in the setting of a PJI is unclear, especially where the prosthesis remains *in situ*. Reactivation of a PJI on re-introduction of bDMARDs may be difficult to detect, possibly due to the presence of a bacterial biofilm on implanted material resulting in the masking or obfuscation of typical signs for joint infection.[4] In the five published cases describing outcomes in bDMARD treated persons with PJI, three further infections but no recurrent PJIs were reported.[5,6] Further evidence is required to guide clinical decision-making.

In this report, three cases in which bDMARDs were re-commenced following a PJI are described. Details include rheumatoid disease activity and concentrations of mannose-binding lectin (MBL). MBL has been implicated in risk for serious infections in RA patients are presented.[7,8]

Case 1

A 67-year-old female developed an elbow PJI in September 2015 on a background of long-standing RA treated with leflunomide, etanercept and prednisolone 5 mg daily. There was no prior history of serious infections and mannose-binding lectin concentrations were undetectable (<56ng/mL).

An elbow replacement was performed in August 2015 and was complicated by purulent discharge after three weeks. Orthopaedic management involved washout and debridement with implant retention. Joint cultures grew *Staphylococcus schleiferi*. Intravenous flucloxacillin (8g daily) and rifampicin (450mg b.i.d.) were administered for six weeks, followed by ciprofloxacin and rifampicin for two weeks. Etanercept was ceased prior to the initial operation and remained on hold. Due to drug tolerance issues and potential future interactions with rheumatoid medications, long-term cephalexin (500 mg Q.I.D.) was commenced following review of documented sensitivities.

The patient's RA progressively deteriorated whilst off etanercept. Three months after the start of the infection, it was recommenced after consultation with specialist infectious diseases physicians. Considerations included low organism virulence, apparent absence of ongoing infection, and the patient's poor functional status due to active RA. Due to the patient's reluctance to discontinue antibiotics because of concerns over reactivation of infection, prophylactic cephalexin 500 mg twice daily was continued long-term. Five years later, no infection recurrence has been identified.

Case 2

A 67-year-old overweight male with seropositive RA treated with methotrexate 20 mg weekly, leflunomide 10mg daily and etanercept 50mg weekly underwent a left knee replacement for osteoarthritis in August 2014. He was not receiving corticosteroids, had no history of serious infections and had a normal MBL concentration (2550 ng/ml).

In December 2015, he experienced malaise and fevers followed by knee pain and swelling. Joint aspirates and blood cultures grew methicillin-sensitive *S. aureus* (MSSA). He was admitted and underwent debridement and modular component exchange operation whereby the lining of the prosthetic joint components were replaced, but with implant retention. Gallium scanning was consistent with septic arthritis in the prosthetic knee and suggested osteomyelitis of the medial femoral condyle. Cephazolin and rifampicin were administered for four weeks followed by oral ciprofloxacin and rifampicin. Etanercept was ceased at presentation of infection. Methotrexate 20 mg weekly and leflunomide 10 mg daily were withheld on admission and restarted on discharge.

Clinical and biochemical improvement were apparent five weeks later, but a rheumatoid flare was evident in other joints. Etanercept was re-commenced at two months, and ciprofloxacin and rifampicin were continued. Due to secondary RA non-response, etanercept was changed to abatacept three months later. Following discussion with the patient, antibiotics were ceased seven months after the start of the infection.

After nine months, the patient re-presented with acute knee pain, swelling and rigors. PJI recurrence was confirmed and MSSA was grown in blood cultures and intra-operative samples. DMARD treatment (methotrexate, leflunomide and abatacept) was discontinued. First stage revision was undertaken, with insertion of vancomycin impregnated spacers. Cephazolin was administered for six weeks prior to a planned second stage revision. One month later, a rheumatoid flare occurred and was managed by reintroduction of methotrexate and leflunomide at previous doses. The patient now remains on lifelong prophylactic cephalexin therapy (500mg b.i.d.). No further PJIs have been identified in the subsequent 4 years. A bacterial pneumonia occurred in February 2020, shortly after baricitinib was added for deteriorating RA disease activity despite use of combination methotrexate and leflunomide. Baricitinib has been continued with excellent control of RA disease activity with no further serious infections.

Both PJIs in this patient identified MSSA organisms on culture, but these differed in specific sensitivities, raising the possibility of infections with different strains of the same species.

Case 3

A 74-year-old male developed a left knee PJI on a background of severe RA complicated by peripheral neuropathy and foot vasculitis. The rheumatoid disease had been managed with prednisolone 7.5 mg daily and etanercept 50 mg weekly. There had been two previous infections, notably diverticulitis requiring partial colectomy and subsequent urosepsis in 2009. MBL was undetectable (<56ng/ml). A previous right knee replacement was uncomplicated.

Left knee replacement was performed in October 2010. PJI was confirmed at eight weeks after surgery. A sinus was present, and *Finegoldia magna* was grown from peri-operative samples. Washout was undertaken, with liner replacement. Clinical and biochemical improvement was observed following six weeks treatment with ticarcillin/clavulanate (12.4 g per 24 hours) followed by oral amoxicillin/clavulanic acid 875/125 mg twice daily. Etanercept was withheld on initial presentation and re-commenced one month after washout due to increased rheumatoid disease activity. Once re-commenced, the patient improved. Prednisolone was continued at the 7.5mg daily maintenance dose throughout.

In July 2011, a left knee wound sinus excision was undertaken. *Enterobacter cloacae* was cultured from the surgical specimens. Amoxicillin/clavulanic acid was switched to oral ciprofloxacin. Review in October 2011 indicated full resolution of the sinus with no superficial infection, and ciprofloxacin was dis-continued. No PJI has been identified over the past nine years. The patient continues to receive etanercept and prednisolone 5mg daily.

Discussion

Re-introduction of bDMARD therapy during active PJI has been reported only infrequently. Manolios *et al.* described a case of *S. pneumoniae* septicaemia with bilateral knee PJI.[6] The patient was receiving etanercept, methotrexate and prednisolone 5mg daily. The PJI was treated with antibiotics, washout and retention of the prosthetic implant. Anti-tumour necrosis factor (anti-TNF) therapy was commenced five months after infection with no PJI recurrence after five years.

Hirano *et al* reported four comparable cases.5 Biologic DMARD therapy was ceased in three cases due to serious infections not related to PJI re-activation.[5] Case 1 was a culture-negative knee PJI in a 55-year-old female. Anti-TNF therapy was commenced over four years following onset of infection. Immunosuppressive therapy (infliximab plus tacrolimus) was subsequently ceased due to disseminated tuberculosis. Case 2 was a *S. aureus* hip PJI in a 34-year-old female with multiple orthopaedic complications. Etanercept was permanently discontinued due to *Pneumocystis jiroveci* pneumonia. Case 3 describes a *S. aureus* elbow PJI infection in a 67-year-old male with implant removal. Methotrexate and infliximab were recommenced, but ceased 24 months later due to interstitial pneumonia. Case 4 describes a knee PJI in a 69-year-old female with *Capnocytophaga* growth from synovial specimens. No PJI was reported following methotrexate and etanercept re-introduction. Short-term or maintenance corticosteroid requirements either prior to or during active treatment for PJI were not documented in any of the above cases.

In our case series, one of three patients experienced PJI re-activation, and two with low virulence organisms remain free of infection five and nine years later, respectively. Amongst the eight cases collectively now reported (five published plus this case series), only one patient has experienced PJI recurrence with a highly virulent organism after 18 patient-years of follow-up.[5,6] The following aspects are raised for consideration: organism virulence, patient risk factors for severe infections and treatment options.

<u>*Organism virulence*</u>

Organism identification is crucial for diagnostic confirmation and antibiotic guidance. All three cases had convincing clinical and microbiological evidence of PJI. *S. schleiferi* (case 1) is considered to have low virulence and pathogenicity. Thus it was considered unlikely to reactivate after antibiotic treatment. *S. aureus* (case 2) is one of the leading causes of PJI and typically has high virulence.[9] *Staphylococci* (in particular *S. aureus* and *S. epidermidis*) are the most frequent biofilm-forming bacteria, which potentially accounts for their high frequency amongst PJI cases.9 Importantly, a 35% recurrence of *S.aureus* PJI in RA patients over the subsequent two years has recently been described.[10] The recurrence of *aureus* in Case 2 may have been foreseen given this moderately high statistical risk. *F. magna* (case 3) is an anaerobic commensal organism mostly found in skin flora, but also in the gastrointestinal and urogenital tracts. It is considered an opportunistic pathogen resulting in bone/joint, prosthetic valve and wound infections.[11]

<u>*Patient factors*</u>

PJI risk factors include male gender, obesity, diabetes, age, inflammatory arthropathy such as RA and bacteraemia in the past year.[12,13] Case 1 experienced no prior septic episodes and underwent multiple previous uneventful arthroplasties, complicated only by a solitary wound infection. Case 2 developed a subsequent serious infection (pneumonia). Case 3 was particularly

susceptible to significant infections as demonstrated by multiple previous serious infections. This patient was also receiving 7.5 mg of prednisolone, which confers an increased serious infection risk.[1,3,8]

MBL is a component of the innate immune system and is commonly low in auto-immune disorders including RA. MBL binds to carbohydrate motifs on the surface of pathogens, damaged host cells and immune complexes. Undetectable MBL has been implicated in serious infections in RA including septic arthritis.[7,8,14] Two of our three cases had undetectable MBL. The measurement of MBL concentrations may inform SI risk stratification, particularly in RA, however further research is required.

The findings of Hirano *et al* as described above together with the previous paragraph support the argument that a propensity to serious infections in general may confer increased risk for PJIs in particular.

Treatment options

Treatment aspects such as choice of bDMARD, timing of reintroduction, source control and alternative management options are all relevant. The total duration of antibiotics (including the possibility of long-term prophylaxis) and crossover period will likely remain contentious and may need to be decided on an individual basis. Consultation with infectious diseases specialists is recommended to optimise antibiotic selection which needs to take account of biofilm activity and treatment duration.[15]

PJI rates were found to be comparable for non-biologic DMARD and bDMARD recipients in the British Society for Rheumatology Biologics Register (BSRBR) study in 47 patients (HR=1.2, 0.4-3.4).[1] Accordingly, bDMARDs are unlikely to contribute significantly to the initial development of PJI. Studies have also reported no difference in risk of SIs between different bDMARDs.[16] Recent observational studies have shown mixed findings, but tend to favour an equal risk profile across anti-TNF agents.[17,18] Our PJI cases all occurred in etanercept recipients. Two of our cases were included in the cohort by Carroll *et al,* who observed that amongst bDMARD recipients in a moderate sized cohort, joint infection occurred exclusively in etanercept recipients.[8] A trend toward higher frequencies of septic arthritis in those patients taking etanercept was also observed in the RABBIT and BSRBR cohorts, but in all of these studies, confounding factors such as marketing dates in specific jurisdictions and prescribing tendencies may be responsible for this bias.[1,19]

It remains to be determined whether etanercept disproportionately increases native septic arthritis or PJI risk. Furthermore, it remains unclear which, if any bDMARD may confer greatest safety when reintroduced post-joint sepsis.

The outcome of PJIs is also influenced by infection source control, including the choice of orthopaedic intervention.[20] Whilst implant retention may be preferable to both surgeon and patient alike, especially in cases of short duration infection, revision procedures are generally considered the gold standard.[4,20] The possibility of suboptimal infection control should always be considered especially in those patients with implant retention and the potential for ongoing biofilm activity. In all three cases described here, etanercept was restarted given previous successful responses. The American College of Rheumatology, based on low level evidence, has conditionally recommended abatacept over anti-TNFs following previous serious infections.[21] This was prior to the wide availability of targeted synthetic DMARDs. Long-term bDMARD safety in respect to serious infections and in particular, site-specific infections still requires ongoing scrutiny.

In the context of an RA flare following bDMARD cessation, corticosteroids are an alternative option. According to Cordtz *et al* glucocorticoid use (especially >7.5mg daily) and ongoing inflammation (high DAS-28 score) but not bDMARD treatment were associated with increased risk of PJI recurrence after 1 year. We note the small sample size for the bDMARD group, and hence low statistical power to identify a difference.[3] Where there is disease relapse and maximal synthetic DMARDs have proved inadequate, re-commencing low-dose bDMARD monotherapy is likely to be safer than using prednisolone at doses above 5mg daily.

Conclusions

1. Cautious re-introduction of bDMARD therapy for active RA in the setting of antibiotic therapy for PJI should be considered. Such treatment may be safer than new/escalating corticosteroid exposure.
2. Until definitive clinical trials and guidelines are available, ongoing therapy after PJIs should consider known risk factors for serious infections.

Provenance: Internally reviewed
Funding: Not required
Conflicts of interest: HK has received consultancy fees from Roche and AbbVie and reimbursement of professional travel costs from Pfizer.
Ethics Approval: Not required

Corresponding author: Dr Kylan Pathmanathan, Department of Rheumatology, Fiona Stanley Hospital, Murdoch, Perth, WA 6150, Australia. Email: kylan.pathmanathan@health.wa.gov.au.

References

1. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Ustianowski AP *et al*. Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011; 70(10): 1810–4.
2. Mabille C, Degboe Y, Constantin A, Barnetche T, Cantagrel A, Ruyssen-Witrand A. Infectious risk associated to orthopaedic surgery for rheumatoid arthritis patients treated by anti-TNFalpha. Joint Bone Spine. 2017; 84(4): 441–5.
3. Cordtz RL, Zobbe K, Højgaard P, Kristensen LE, Overgaard S *et al*. Predictors of revision, prosthetic joint infection and mortality following total hip or total knee arthroplasty in patients with rheumatoid arthritis: a nationwide cohort study using Danish healthcare registers. Ann Rheum Dis. 2018; 77(2): 281–8.
4. Davidson DJ, Spratt D, Liddle AD. Implant materials and prosthetic joint infection: the battle with the biofilm. EFORT Open Rev. 2019 Nov 5;4(11):633–9.
5. Hirano Y, Kojima T, Kanayama Y, Shioura T, Hayashi M, Tsuboi S, *et al*. Anti-tumor necrosis factor therapy in rheumatoid arthritis patients with a history of deep prosthetic joint infection: a report of four cases. Mod Rheumatol Jpn Rheum Assoc. 2011; 21(5): 542–7.
6. Manolios N, Burneikis A, Spencer D, Howe G. Failure of anti-TNF therapy to reactivate previously septic prosthetic joints. BMJ Case Rep 2013; 2013: bcr2013009827.
7. Nisihara R, Skare T, Capeletto CM, Moreira L, Goeldner I *et al*. Mannose binding lectin deficiency and susceptibility to infections in patients with rheumatoid arthritis. Rheumatol Oxf Engl 2016; 55(5): 951–2.
8. Carroll GJ, Makin K, Garnsey M, Bulsara M, Carroll BV *et al*. Undetectable Mannose Binding Lectin and Corticosteroids Increase Serious Infection Risk in Rheumatoid Arthritis. J Allergy Clin Immunol Pract. 2017; 5(6): 1609–16.
9. Lentino JR. Prosthetic Joint Infections: Bane of Orthopedists, Challenge for Infectious Disease Specialists. Clin Infect Dis. 2003; 36(9): 1157–61.
10. Singh N, Nair R, Goto M, Carvour ML, Carnahan R *et al*. Risk of Recurrent Staphylococcus aureus Prosthetic Joint Infection in Rheumatoid Arthritis Patients - a Nationwide Cohort Study. Open Forum Infect Dis. 2019; 6(11).
11. Frick I-M, Karlsson C, Mörgelin M, Olin AI, Janjusevic R *et al*. Identification of a novel protein promoting the colonization and survival of *Finegoldia magna*, a bacterial commensal and opportunistic pathogen. Mol Microbiol. 2008; 70(3): 695–708.
12. Aslam S, Reitman C, Darouiche RO. Risk factors for subsequent diagnosis of prosthetic joint infection. Infect Control Hosp Epidemiol. 2010; 31(3): 298–301.
13. Kong L, Cao J, Zhang Y, Ding W, Shen Y. Risk factors for periprosthetic joint infection following primary total hip or knee arthroplasty: a meta-analysis. Int Wound J. 2017; 14(3): 529–36.
14. Holdaway J, Deacock S, Williams P, Karim Y. Mannose-binding lectin deficiency and predisposition to recurrent infection in adults. J Clin Path 2016; 69(8): 731–6.
15. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W *et al*. Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013; 56(1): e1–25.
16. Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS *et al*. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2017; 76(6): 1101–36.
17. Chen SK, Liao KP, Liu J, Kim SC. Risk of Hospitalized Infection and Initiation of Abatacept Versus Tumor Necrosis Factor Inhibitors Among Patients With Rheumatoid Arthritis: A Propensity Score–Matched Cohort Study. Arthritis Care Res. 2020; 72(1): 9–17.
18. Mori S, Yoshitama T, Hidaka T, Sakai F, Hasegawa M, Hashiba Y, *et al*. Comparative risk of hospitalized infection between biological agents in rheumatoid arthritis patients: A multicenter retrospective cohort study in Japan. Kuwana M, editor. PLOS ONE. 2017; 12(6): e0179179.
19. Listing J, Strangfeld A, Kary S, Rau R, Hinueber U von, Stoyanova-Scholz M, *et al*. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum. 2005; 52(11): 3403–12.
20. Sousa R, Abreu MA. Treatment of Prosthetic Joint Infection with Debridement, Antibiotics and Irrigation with Implant Retention - a Narrative Review. J Bone Jt Infect. 2018; 3(3): 108.
21. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR *et al*. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2016; 68(1): 1–26.