Periprosthetic Joint Infection in Patients Receiving TNFα Antagonists


Abstract

Tumor necrosis factor-α antagonists (anti-TNFα) have become increasingly more common as a treatment for rheumatoid arthritis (RA). However, there has been an increased incidence of severe infections in patients taking anti-TNFα therapy.

We present a case series of RA patients treated with anti-TNFα therapy that had previously underwent TJA and subsequently developed periprosthetic infections.

All patients had a well-functioning implant for a period of 1 to 14 years prior to the development of infection. Each patient underwent two to five different joint replacements, and four patients developed infection in multiple sites. The infections proved difficult to eradicate with four patients requiring multiple procedures, and one patient ultimately requiring a hemipelvectomy.

This study suggests that periprosthetic infections acquired by patients on anti-TNFα therapy are challenging to eradicate and treat; highlighting the need for the establishment of guidelines for perioperative and long-term management of anti-TNFα therapy, and infection monitoring in joint replacement patients.

Periprosthetic joint infection (PJI) is one of the most significant and costly problem facing adult reconstruction surgeons. A recent review of total hip arthroplasties (THA) performed in the Medicare population showed an incidence of PJI of 1.63% within 2 years of surgery and of 0.59% between 2 and 10 years postoperatively.1 A similar review of total knee arthroplasties (TKA) found that within 2 years of surgery the incidence of PJI was 1.55%, and at 2 to 10 years postoperatively the incidence was 0.46%.2 An analysis of the economics of PJI3 showed that the average total costs in 2009 for a revision of an infected hip was $93,600 and $74,900 for a knee. The total cost to the health care system of PJI in 2009 was $566 million and is projected to reach $1.62 billion by 2020.

Since their introduction in the late 1990s, biologic agents, such as tumor necrosis factor-α (TNFα) antagonists, have been an increasingly used modality for treating RA, especially RA that is recalcitrant to management with conventional disease modifying anti-rheumatic drugs (DMARDs). Multiple randomized controlled trials have confirmed the efficacy of TNFα antagonists in RA, demonstrating reduced disease activity and radiographic progression, with multiple meta-analyses confirming these findings.4-6 This gives hope that the need for multiple TJAs in RA patients will be somewhat muted by these newer agents.7

However, there has been concern with the potential for increased malignancy and infection in patients with anti TNFα therapy.8-10 A review of the literature finds that there is evidence of increased occurrence of serious infections (usually defined as needing a prolonged antibiotic course or hospitalization) in patients undergoing anti TNFα therapy.8,11-14 This is in contrast to evidence that there is no increased risk of serious infections for certain DMARD agents.15 One study comparing patients before and after initiation of TNFα therapy found that the rate of serious infections in these patients more than doubled after initiation
of TNFα therapy, and that the only significant predictor (in a multivariate analysis) for developing an infection was a prior joint procedure (arthroplasty or arthrodesis). Furthermore, there is limited evidence discussing the infection risk for patients, treated with anti TNFα therapy, after orthopaedic procedures, with no studies examining the change in risk for late onset PJI for patients started on TNFα DMARDs. We present a retrospective chart-review case series of nine RA patients treated with TNFα antagonists after previous TJA that went on to develop periprosthetic infections, followed by a review of the current literature on TNFα antagonists, infection, and TJA.

Methods and Materials

Study Design and Selection Criteria

This retrospective case series was performed after IRB approval. Using the NYU Hospital for Joint Diseases Arthroplasty Registry, a retrospective review was conducted of nine consecutive patients who presented to our tertiary care medical center. All patients with previous hip or knee arthroplasty and who had a history of periprosthetic joint infections combined with a history of TNFα treatment were included in this case series.

During this 9-year period, nine cases of late PJI after the start of TNFα treatment were found. Eight patients were treated with etanercept (Enbrel®, Amgen, Thousand Oaks, CA, USA) and one patient with infliximab (Remicade®, Janssen Biotech, Titusville, NJ, USA).

Data Collection

Information regarding RA disease course, RA medications, previous total joint arthroplasty, previous periprosthetic joint infections, and microbiological data were collected. Demographic and patient data were collected for all cases.

Results

We have found nine patients that met our inclusion criteria of late PJI after starting TNFα treatment. Patients had an average of 6.3 years (range: 1.5 to 14 years) of successful implantation prior to diagnosis of infection, with only one patient developing infection less than 2 years following arthroplasty. All of the patients had an average of three TJAs (range: two to five TJAs) at the time of being diagnosed with infection, and four of the nine patients had infection in multiple joints. All infections were considered hematogenous in etiology due to the symptom free period prior to presentation. The immunosuppressive treatment that the patients were receiving hindered our ability to establish an exact date of infection seeding. Among the nine patients, average age at infection was 54 (range: 36 to 65 years), average body mass index was 26.2 kg/m² (range: 19.5 to 34.7), and eight were female (Table 1).

All patients had been diagnosed with RA at a mean of 22.2 years (range: 5 to 36 years), prior to their primary joint replacement surgery. Eight patients had been treated with etanercept, and one patient was treated with infliximab (Table 1).

Among the 9 patients, there were 17 (8 knees, 6 hips, 2 ankles, and 1 shoulder) prosthetic joint infections, as several patients presented with polyarticular PJI. At presentation, patients had an average white blood cell count of 8.4 x 10⁹/L (range: 6.2 to 10.5 x 10⁹/L), erythrocyte sedimentation rate of 82.9 mm/hr (range: 30 to 120 mm/hr), and a C-reactive protein level of 93.4 mg/L (range: 12 to 158 mg/L). The most common identified bacterial organism was methicillin resistant Staphylococcus aureus, which was found in four patients, Streptococcus viridians in two patients, and methicillin sensitive Staphylococcus aureus in one patient. Two patients had polymicrobial infections with Enterobacter cloacae, Morganella morganii, Enterococcus, and alpha-hemolytic Streptococcus (Table 1).

TNFα treatment was stopped when PJI was diagnosed and held during the entire treatment course for all patients. Two patients (three joints) were treated successfully with irrigation and debridement alone, three patients (five joints) were treated successfully with a two-stage revision, and two

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient Demographics and Periprosthetic Joint Infection Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
</tr>
</tbody>
</table>

Average: 6.3, 3

PJI = periprosthetic joint infection, RA = rheumatoid arthritis, MRSA = methicillin resistant Staphylococcus aureus, MSSA = methicillin sensitive Staphylococcus aureus.
patients (two joints) had a successful two-stage revision after a failed irrigation and debridement. Some patients have proven to be more refractory to conventional two-stage revisions: one patient failed two two-stage revisions and required a resection arthroplasty, two patients failed a two-stage revision and multiple irrigation and debridement attempts, which required a resection arthroplasty for one and hip disarticulation for the other, and one patient continued to have chronic infection, which needed suppressive antibiotic treatment.

Discussion

TNFα therapy in patients undergoing TJA and in patients with previous joint replacement can have serious consequences. A recent study16 has shown that patients with multiple lower limb TJAs that get infected in a single joint have a 20% chance of becoming infected in another of their prosthetic joints, with an average time to second infection of 2 years. An older study17 of patients with PJIs and multiple TJAs found a 19% incidence of additional PJI. This study also found that rheumatoid arthritis (RA) patients had more total joint arthroplasties (TJAs) on average than osteoarthritis (OA) patients, and that RA was highly associated with development of a second PJI, making this population particularly at risk. In one study spanning from 1974 to 1997, it was estimated that 25% of RA patients underwent one TJA within 22 years of disease onset, and of those, 50% had an additional TJA within 7 years.18 In addition to being more susceptible to a second PJI, RA patients have had an increased occurrence of initial PJI compared to the patients with OA, with studies identifying RA as an independent risk factor for this complication.19 A recent study using data from the Norwegian Arthroplasty Registry,20 of 108,786 THAs and TKAs performed on 6,629 patients with RA and 102,157 patients with OA, found that for THA, there is no increase in revision surgery for PJI in the first 6 years of implantation for RA compared with OA patients, but that after 6 years, there is a relative risk of 4.1 for revision surgery among the RA patients. For TKA, there was an initial increase in risk of PJI for the first postoperative year, which was not present for the next 5 years. The relative risk of revision for TKA for patients with RA was 5.4 after 6 years when compared with OA patients. This highlights the potential for late onset presentation of infection in patients with RA.

Furthermore, no recommendation exists on proper follow up protocol for patients who start TNFα therapy and have had a joint replacement. The most relevant publication to our patient experience is a case report by Yurube and coworkers.21 They present the case of a 54-year-old woman with RA. Infliximab therapy was started 3 years and 8 months after having undergone bilateral TKA. One week after the third administration of infliximab, the patient suffered sudden left knee pain and infectious clinical symptoms. The knee joint was found to be infected by MSSA. Plain radiographic film of the knee also showed multiple lytic lesions around the tibial component that had not been present prior to the onset of treatment. The investigators postulated that the patient might have been suffering from a chronic subclinical infection for a long time, and that the administration of anti-TNFα therapy allowed this to exacerbate into a serious infection.

Much more has been written about the use of these agents in the perioperative period. However, despite this, currently, there is no consensus in the literature on the length of the suspension period of the medication prior to surgery. Some patients undergo TJA without suspending TNFα treatment at all. Previous studies have not clearly demonstrated risk with immune modulators and orthopaedic surgery. Recently the American College of Rheumatology released recommendations for the use of biologics in the perioperative period.22 The consensus was that biologic DMARDs should be suspended for at least 1 week prior to and after surgery. However, according to the report, this should be adjusted according to the agent being used and according to infection risk with no guidelines given as to how this should be done. The 2013 International Consensus Group on Periprosthetic Joint Infection proposed a guideline based on medication half-life (Table 2).

Talwalkar and colleagues23 presented a case series of 11 patients (10 RA, 1 PA) that underwent 16 orthopaedic op-

<table>
<thead>
<tr>
<th>Biological Response Modifiers</th>
<th>Half Life of Drug*</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>4.3 days</td>
<td>Hold for at least 1.5 weeks prior and after</td>
</tr>
<tr>
<td>Infliximab</td>
<td>8-10 days</td>
<td>Hold for 3 weeks prior and after</td>
</tr>
<tr>
<td>Golimumab</td>
<td>12-14 days</td>
<td>Hold for 1 month prior and after</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>12-14 days</td>
<td>Hold for 1 month prior and after</td>
</tr>
<tr>
<td>Abatacept</td>
<td>12-14 days</td>
<td>Hold for 1 month prior and after</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12-14 days</td>
<td>Hold for 1 month prior and after</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>12-14 days</td>
<td>Hold for 1 month prior and after</td>
</tr>
<tr>
<td>Rituximab</td>
<td>21 days</td>
<td>Hold for 2 months prior and after</td>
</tr>
</tbody>
</table>

*Recommendations adapted from the 2013 Periprosthetic Joint Infection International Consensus Meeting."
erations ranging from hand operations to TJA. All patients were receiving etanercept, adalimumab, or infliximab. The operations were subdivided into 2 groups. Group A included four patients where there was no interruption in anti-TNFα therapy, and Group B included 12 patients in which therapy was halted for 2 weeks (adalimumab and etanercept) or 4 weeks (infliximab) prior to the procedure. The investigators found no difference in infection rates between the two groups in this small case study.

Gilson and associates published a case control study using cases from the French Ratio (Research Axed on Tolerance of Biotherapies) registry and a retrospective control group from a tertiary care center. Twenty patients who underwent TJA (12 knee, 5 hip, 2 shoulder, and 1 ankle) who were on anti-TNFα therapy and suffered infection were matched with 40 controls (each case was matched with 2 controls) that were on anti-TNFα therapy with a TJA and did not develop infection. The investigators analyzed risk factors for inquiring an infection. It was found that increased steroid intake, primary TJA within the last year, and revision of an infected prosthesis within the last year were all risk factors for a PJ. The investigators also showed a trend that if anti-TNFα therapy was not interrupted for 5 drug half-lives prior to surgery, there was an increased rate of infection. However, this trend did not reach statistical significance.

A study by Bongartz and coworkers included all patients with RA who underwent THA and TKA at the Mayo Clinic during a period of 8.5 years. This included 462 patients with 657 total hip and knee arthroplasties. A matched control cohort with osteoarthritis (OA) was also assembled. At 5-year follow up, this study showed that the infection rate for patients with RA was 4.2%, and for those with OA, it was 1.4%. In examining the patients that were on anti-biologic therapy at the time of TJA, they found that there were 3 infections in the 38 patients that did not suspend anti-TNFα therapy prior to surgery and none in the 12 patients that did suspend the treatment. However, this difference was not found to be statistically significant.

Hayata and colleagues studied 52 patients on infliximab therapy that had undergone orthopaedic surgery (including not only arthroplasty surgery but also spine surgery, arthroscopic synovectomy, ankle arthrodesis, hand surgery, and fracture care). For the subset of arthroplasty patients, there were five THA in three patients, seven TKA in six patients, two TSA in two patients, two TEA in two patients, and two toe arthroplasties in two patients. At 1 year, the investigators reported only 2 superficial infections in the entire 52 patients (1 toe arthroplasty, 1 spine surgery) with no deep infections. The investigators concluded that there was no significant effect of time between last infusion of infliximab and surgery. However, it should be noted that the mean time between last infusion and surgery was 4 weeks, and no range data was provided in the paper.

Ruyssen-Witrand and associates published a retrospective case study of 92 patients with RA receiving infliximab, etanercept, or adalimumab. The cohort underwent 127 surgical procedures. Patients were divided into five groups based on the risk of infection: three orthopaedic groups including low risk (such as arthrodesis, synovectomy, tendon surgery), moderate risk (such as primary TJA, and spinal fusion), and high risk (such as TJA revision); septic orthopaedic surgery; and all emergency surgery. The study examined the issue of interruption of TNFα DMARD therapy and found no statistically significant difference in total complication rate (infectious and non-infectious) between the patients whose therapy was interrupted for ≥ 5 drug half-lives versus those whose therapy was not interrupted or interrupted for a shorter amount of time prior to surgery. This non-significance continued when the threshold for withholding was lowered to ≥ 2 drug half-lives, although a trend appeared toward an increased complication rate in the non-interrupted group. However, the investigators did state that the orthopaedic complication rate for patients on anti-TNFα therapy (12% overall, 5.6% infectious) was higher than the rates reported in the literature for patients on conventional DMARDs.

Kawakami and coworkers conducted a retrospective pair matched case control study of 64 patients on anti-TNFα therapy and 64 matched controls on exclusively non-biologic DMARDs. Anti-TNFα therapy was withheld for 2 or 4 weeks prior to surgery for etanercept and infliximab, respectively. There were two branches of the study, one examining infections and one examining risk of DVT. Infection was defined using the CDC definition for surgical site infection: superficial infection within 30 days of surgery or deep infection within 30 days or within 1 year if an implant was left behind and the infection appears related to the implant. For the infection arm, the procedures included were TSA, TEA, MCP arthroplasty, wrist arthroplasty, TAA, THA, and TKA. The TNFα group experienced seven superficial surgical site infections and one deep infection requiring ROH. The non-biologic DMARD group only suffered one superficial infection. Multivariate analysis showed that disease duration, prednisone dosage, and anti-TNFα therapy were all risk factors for surgical site infection. Additionally, in the DVT wing of the study (which used a slightly different group of patients) it was shown that anti-TNFα therapy increased risk of DVT.

Momohara and colleagues performed a retrospective single center review of 420 TJAs in RA patients. There were 81 THAs with 11 of those performed on patients on biologic DMARDs and 339 TKAs with 37 being performed on patients on biologic DMARDs. Patients taking biologic DMARDs included three anti-TNFα drugs, such as infliximab, etanercept, and adalimumab, and one anti-IL-6, such as tocilizumab. Of the 420 procedures, there were 24 superficial infections and three PJIs that required removal of hardware. Multiple logistic regression was used and found that both biologic DMARD use and duration of RA were significant risk factors of infection. The odds ratio for biologic DMARD use and sustaining a surgical site infection...
compared with conventional DMARDs was 5.69. Given the difficulty and the severity of our cases presented in this case series, with one requiring a hemipelvectomy, it is important to appreciate the increased risk and clinical outcome of late infection among this patient group. Another difficulty in treating this patient group is accurately identifying the onset of the PJI and correctly differentiating between acute and chronic hematogenous PJI. Furthermore, if such patients incur a PJI, the outcomes of treatment of the PJI seem to be inferior to results of PJI treatment in patients that are not treated with anti-TNFα therapy. When consulting the patient, it is important to discuss the high chance of failure of irrigation and debridement alone, and the possibility of needing multiple procedures in order to eradicate the infection and achieve a good outcome.

TNFα antagonists are powerful agents that can result in significant clinical improvement for some RA patients. However, this does come with increased risk for patients with previous total joint replacements of late infection, and further research is needed to quantify this risk so that appropriate protocols can be developed and so patients with total joint replacements can be appropriately counseled before initiating treatment with these agents.

Disclosure Statement
None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References


