

# Risk factors for late deep infection after total hip arthroplasty in patients with rheumatoid arthritis

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## ABSTRACT

**Objective:** Postoperative infections, a serious complication of orthopedic surgery, occur 2–4 times more frequently in patients with rheumatoid arthritis (RA) without adjustment for medication. Some studies have demonstrated a similar risk of postoperative infection following orthopedic surgery regardless of whether patients underwent tumor necrosis factor- $\alpha$  (TNF) inhibitor therapy; however, other studies have reported a higher risk with TNF inhibitor use. However, few reports have focused on the correlation between TNF inhibitor use and postoperative late infection. Therefore, we investigated the correlation between TNF inhibitor therapy and serious postoperative late infection in patients with RA who underwent total hip arthroplasty (THA).

**Methods:** Ninety-nine patients with RA who were enrolled in our institution's and Konan Kakogawa Hospital's THA registry between January 2003 and December 2012 were eligible to participate. Data collected included clinical parameters and medications, including biological drugs, disease-modifying antirheumatic drugs, and glucocorticoids. Logistic regression analysis was performed to examine the association between clinical parameters, medications, and the development of postoperative late infection.

**Results:** One risk factor was identified in the multivariate analysis. TNF inhibitor therapy was found to be significantly associated with the development of late infection after THA (biological drugs: OR: 9.5, 95% CI: 1.0–88.8; TNF inhibitor: OR: 11.7, 95% CI: 1.2–109.7).

**Conclusion:** Biological drug therapy, especially TNF inhibitors, may be associated with an increased rate of

late deep infection after THA. When the use of TNF inhibitor therapy is considered, rheumatologists must be attentive to patients after THA.

**Keywords:** Hip arthroplasty; Infection; anti-TNF therapy.

## INTRODUCTION

Postoperative infections, such as periprosthetic septic arthritis and deep infections, are serious complications of orthopedic surgery. Such infections cause disability, prolonged hospitalization, additional surgical procedures, and delayed rehabilitation. Furthermore, there is a three-fold increase in mortality in cases of orthopedic procedures complicated by joint sepsis or osteomyelitis<sup>1</sup>. Improvements in surgical techniques, perioperative routines, and prophylactic measures have reduced the overall incidence of postoperative orthopedic infections to 1–2%<sup>2</sup>. However, this rate is two to four times higher in patients with rheumatoid arthritis (RA) than in patients without RA<sup>3</sup>.

The efficacy of tumor necrosis factor (TNF) inhibitor therapy is well established in patients with RA<sup>4</sup>. Consequently, these drugs are frequently prescribed. However, several reports have indicated that anti-TNF therapy is associated with a significantly greater risk of serious infection compared with non-biological agent treatment, such as conventional disease-modifying anti-rheumatic drugs (DMARDs), because of the risk of immunosuppression<sup>5</sup>.

Some published studies have demonstrated a similar risk of postoperative infection following orthopedic surgery regardless of TNF inhibitor use<sup>6-8</sup>, whereas other studies have reported a higher risk in the presence of TNF inhibitor use<sup>3,9</sup>. These surgical-site infections have most often occurred within four weeks of surgery, and most are focused on perioperative surgical sites.

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Few studies have evaluated late deep infections, especially those occurring >1 year postoperatively. To address this clinically important issue, we investigated the correlation between TNF inhibitor therapy and serious postoperative late deep infection in patients with RA who underwent total hip arthroplasty (THA).

## PATIENTS AND METHODS

### PATIENT SELECTION

This was a retrospective cohort study. The medical records of 99 patients with RA who fulfilled the criteria of the American College of Rheumatology<sup>10</sup> in our institution and who were enrolled in the Konan Kogawa Hospital THA registry between January 2003 and December 2012 were analyzed. Institutional review board approval was received and informed consent was obtained. The start date of 2003 was chosen because it approximated the date of the commercial introduction of TNF inhibitors.

Collected data included age at the time of the operation and RA duration. RA medications and doses at the last rheumatology clinic visit prior to the index date were recorded as well, including prednisolone; non-biological DMARDs (methotrexate [MTX] and tacrolimus); biological DMARDs, including TNF inhibitors (etanercept, infliximab, and adalimumab); and other biological drugs. THA-related infections occurring more than 2 years after implantation were defined as late deep infections in this study<sup>11</sup>. We collected data from the medical records of all patients at the end of 2014. The minimum follow-up duration was 2 years after THA, unless the patient developed a late deep infection, which was defined as the endpoint. At that time, the medication data were collected.

### STATISTICAL ANALYSIS

Differences in age at the time of surgery, RA duration, MTX dose, tacrolimus dose, and glucocorticoid dose with the development of a postoperative late deep infection were assessed using an unpaired-t test for continuous variables and Fisher's exact test for categorical variables. To identify risk factors for late deep infection after THA, we performed a multivariate analysis to test the association between clinical factors (age at the time of surgery, RA duration) and drugs (all biologicals, TNF inhibitors, and non-biological DMARDs) with the development of late deep infections after THA. The risk factor was identified using this multivariate

analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. The data were analyzed using SPSS version 19 J (IBM Japan, Tokyo, Japan).

## RESULTS

### PATIENT CHARACTERISTICS

The characteristics of the 99 patients are summarized in Table I. None had a perioperative infection; however, five (5.0%) developed late deep infection during the study period. There were no significant differences in age at the time of surgery or RA duration between the groups with and without infection. We did not find any significant difference in non-TNF inhibitor, non-biological DMARD, or tacrolimus use between the two groups. However, we did find significant differences in biological drug use ( $p=0.032$ ), TNF inhibitor use ( $p=0.022$ ), MTX use ( $p=0.005$ ), MTX dose ( $p<0.001$ ), tacrolimus dose ( $p=0.02$ ), prednisolone use ( $p=0.019$ ), and prednisolone dose ( $p=0.01$ ).

### RISK FACTORS OF LATE INFECTION AFTER THA

We showed that biological drug therapy, especially TNF inhibitor therapy, was significantly associated with the development of late deep infection after THA (biological drugs: OR: 9.5, 95% CI: 1.0–88.8; TNF inhibitor: OR: 11.7, 95% CI: 1.2–109.7) (Table II).

### PROGNOSIS OF PATIENTS WITH LATE DEEP INFECTION

Table III demonstrates the prognosis of patients with late deep infection. Four patients were administered TNF inhibitor therapy (infliximab in one, etanercept in three) after primary THA among five patients who experienced late deep infection postoperatively, and three of four patients experienced the infections in the first 3 months of TNF inhibitor therapy (Table III). All four patients were treated with conventional synthetic DMARDs prior to the introduction of TNF inhibitor therapy. When a deep infection occurred, open debridement was performed immediately for all patients. The patients were treated with intravenous antibiotics for at least six weeks. One patient was successfully treated with open debridement (Table III, case 1). However, the infection was not cured in four other patients (Table III, cases 2–5). Therefore, removal of the prosthesis, and insertion of an antibiotic-impregnated, cemented spacer was performed, and a revision

**TABLE I. DEMOGRAPHIC AND CLINICAL PARAMETERS OF PATIENTS WITH OR WITHOUT LATE TOTAL HIP ARTHROPLASTY INFECTION**

	No infection	Infection	P-value Ns, non-significant p
Number of cases	94	5	
Age at operation (y.o.)	66.3+8.5	63.8+8.9	N.S.
Duration of RA (years)	18.3 +11.6	22.8+8.6	N.S.
Follow-up duration (years)	8.2+5.8	3.5+0.8	<0.001
Duration of anti-TNF therapy	6.3+3.8	0.7+1.0	<0.001
Biological drugs (cases)	27	4	0.032
TNF inhibitor (cases)	24	4	0.022
Non TNF inhibitor (cases)	8	0	N.S.
DMARDs except MTX, TAC (cases)	54	3	N.S.
MTX (cases)	64	0	0.005
Dose of MTX (mg/week)	4.4+3.6	0	<0.001
Tacrolimus (cases)	6	0	N.S.
Dose of tacrolims (mg/day)	0.1+0.5	0	0.020
Prednisolone (cases)	70	5	0.019
Dose of prednisolone (mg/day)	3.6+2.7	5.8+1.3	0.010

DMARDs: disease-modifying anti-rheumatic drugs; MTX: methotrexate; RA: rheumatoid arthritis; TAC: tacrolimus; TNF: tumor necrosis factor

**TABLE II. RISK FACTORS OF LATE TOTAL HIP ARTHROPLASTY INFECTION IN PATIENTS WITH RHEUMATOID ARTHRITIS**

	P-value	Odds ratio	95%CI
Biological drugs	0.049	9.5	1.0-88.8
TNF inhibitor	0.032	11.7	1.2-109

TNF: tumor necrosis factor

THA was performed following 2-6 months of open debridement therapy.

All patients were treated with tacrolimus or prednisolone after deep infection. The disease entered remission after treatment in four patients (Disease Activity Score 28, C-reactive protein [DAS28 CRP] <2.3). However, the condition of one patient (Table III, case 4) was not well controlled (DAS28 CRP = 5.8), and that patient ultimately died following a cardiac infarction one year after the revision THA.

## DISCUSSION

Most studies combined the surgery types and calculated the infection rates in TNF inhibitor use. However,

the surgical site circumstances (muscle, subcutaneous tissue) and the patients' backgrounds differed among the surgery types, which may bias the statistical analysis. Therefore, we focused only on THA in this study.

Most studies in this area have focused on perioperative surgical site infections. Total joint arthroplasty-related infections occurring >2 years after implantation are often referred to as late deep infections and can be attributed to hematogenous seeding. In contrast, early infections generally occur as a result of contamination during surgery<sup>12</sup>. Patients with RA are considered susceptible to late infections around the implant<sup>13</sup>. Schramma *et al.* demonstrated an increased risk of revision for late infection in both THA and total knee arthroplasty in patients with RA from approximately six years postoperatively onward compared to patients with osteoarthritis<sup>14</sup>. Therefore, evaluating the rate of late deep infection in RA patients is critical.

In this study, we identified a significant association between TNF inhibitor use and the development of postoperative late deep infection after THA. This association persisted after being adjusted for other risk factors, such as age, RA duration, non-biological DMARDs use and dose, and prednisolone use and dosage. The rate of serious infections during TNF inhibitor treatment observed in daily practice is reportedly much higher<sup>15</sup>. Studies focusing on the risk of postoperative

**TABLE III. DEMOGRAPHIC PARAMETERS OF PATIENTS WITH LATE DEEP INFECTION**

No. sex	Age	TNF inhibitor	DMARDs prednisolone	Duration for TNF inhibitor	Duration after THA	Pathogen	Surgical procedure	Treatment of RA after infection
1 F	74	etanercept	Sulfasalazine prednisolone 5mg	2 month	3 year	<i>E.coli</i>	open debridement	tacrolimus prednisolone 5mg
2 F	62	etanercept	Sulfasalazine prednisolone 5mg	1 month	3 year	MRSA	1. removal of implant 2. revision THA	tacrolimus
3 F	61	none	prednisolone 5mg		4 year	MRSA	1. removal of implant 2. revision THA	prednisolone 5mg
4 F	59	infliximab	prednisolone 9mg	3 month	2.5 year	MRSE	1. removal of implant 2. revision THA	tacrolimus prednisolone 10mg
5 F	53	etanercept	prednisolone 5mg	2 year	4 year	MRSE	1. removal of implant 2. revision THA	prednisolone 5mg

DMARDs: disease-modifying anti-rheumatic drugs; MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; THA: total hip arthroplasty; TNF: tumor necrosis factor

deep infection and TNF inhibitor therapy over four weeks after surgery are rare<sup>7,16</sup>. Several papers have shown that postoperative continuation of TNF inhibitor therapy was not an important risk factor for surgical site infection within one year<sup>17</sup> or three months<sup>18</sup>. However, Giles *et al.* first showed a significant association between TNF inhibitor therapy and postoperative deep infection >1 year postoperatively (OR: 4.6, 95% CI: 1.1–20)<sup>3</sup>. Scherrer *et al.* demonstrated a significantly increased late deep infection rate after the use of TNF inhibitors (OR 2.54, 95% CI 1.08–5.97)<sup>19</sup>. In particular, the risk of late deep infection was greatest in the first year of TNF inhibitor therapy<sup>3,20</sup>. In this study, three of four patients developed infections in the first three months of TNF inhibitor therapy. This result is attributable to the strong immunosuppressive effect of TNF inhibitor therapy. When we focused on the pathogens in patients with late deep infection, the pathogen in case 1 was *E. coli*, but the infections in the other four patients were caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) or Methicillin-resistant *Staphylococcus epidermidis* (MRSE). These differences in pathogen might affect the surgery procedures.

Gilson *et al.* demonstrated that daily glucocorticoid intake ( $\geq 5$  mg/day) was a risk factor of postoperative infection (OR: 5.0, 95% CI: 1.1–21.6)<sup>21</sup>. We found that the rate or dosage of glucocorticoid intake was signifi-

cantly higher in patients with late deep infection. However, we did not find that daily glucocorticoid intake was a risk factor for postoperative late deep infection on multivariate analysis.

We demonstrated here that the MTX dosage and use rate and the tacrolimus dosage in patients with late deep infection were significantly lower than those in patients with no infection. In this study, 80% of patients with late deep infections had used biological drugs. This rate was much higher than that in patients with no infection. One possible reason is that patients treated with MTX or tacrolimus only may have lower RA disease activity. However, we did not have data concerning disease activity; therefore, the reason for this was not confirmed. Therefore, we need to analyze the associations between RA disease activity and the occurrence of late deep infections in a future study. The study limitation is that the cohort was likely not large enough to enable a full evaluation of the associations with medication use. We analyzed the associations of comorbidities, such as diabetes mellitus, malignant tumors, post-stroke condition, hepatitis, tuberculosis, and renal dysfunction, with the development of postoperative late deep infection. However, we did not find any significant association. Furthermore, we did not find any significant association with infection rate in each biological drug. The small number of patients may have in-

fluenced the result of this analysis. However, the results of the present study suggest that TNF inhibitor therapy has a higher risk of postoperative late deep infection in patients after THA, this requires confirmation in larger prospective studies.

## CONCLUSION

In conclusion, biological drug therapy, especially TNF inhibitors, may be associated with an increased rate of late deep infection after THA. When the use of TNF inhibitor therapy is under consideration, both rheumatologists and orthopedic surgeons need pay attention to patients with RA who undergo THA. We propose that the patients should be monitored frequently by blood examination in order to avoid late deep infection following initiation of TNF inhibitor therapy.

## CORRESPONDENCE TO

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