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Perioperative Surgical Site Infections and Complications in Elective Orthopedic Surgery in Patients with Rheumatoid Arthritis Treated with Anti-Tumor Necrosis Factor-Alpha Agents – Discontinue or Not, Clinical Dilemma

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Additional information is available at the end of the chapter

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1. Introduction

Rheumatoid arthritis (RA) is characterized by the destruction of peripheral joints in which articular cartilage and subchondral bone are destroyed by chronic proliferative synovitis. This damage often leads to significant loss of joint function and impairs the ADL of patients with RA.

Most patients with RA are in use of traditional disease modifying antirheumatic drugs (DMARDs) to control disease activity, and among the traditional, non-biological DMARDs (nbDMARDs), methotrexate (MTX) is a first line and an anchor drug for the treatment of RA. Currently introduced biologic agents, especially anti-tumor necrosis factor-alpha (TNF- α) agents, have revolutionized the treatment of RA. TNF- α triggers the inflammatory cascade and stimulates the production of matrix degradable proteinases such as matrix metalloproteinases, which well known to play a major role in the proteolytic degradation of extracellular matrix macromolecules of cartilage and bone, which is a key step in joint destruction in RA. Anti-TNF- α agents are now in routine use for RA patients who have failed to respond to nbDMARDs, and have been demonstrated to improve the clinical symptoms and delay joint destruction dramatically. Unfortunately, despite of the administration of nbDMARDs and/or biologic agents, complete prevention of the destruction of the affected joints is still not achieved. Over the course of their lifetime, many patients with RA may re-

quire orthopaedic surgical interventions, such as total joint arthroplasty (TJA), arthrodeis, reconstructive surgeries, cervical stabilization, and so on.

For orthopaedic surgeons, post-operative surgical site infections (SSI) and delayed wound healing are major concerns, especially in TJA. Prosthetic infection is associated with prolonged antibacterial therapy and hospitalization, functional decline, depression, shorter prosthesis durability, which have great impact on morbidity, mortality and quality of life. The baseline infection risk is increased 13-fold in individuals with RA when compared with the general population [1]. In addition, receiving anti-TNF- α agents showed an increased risk of serious infections. Delayed wound healing or wound dehiscence is also believed to occur more frequently in patients with RA. Patients with RA are already predisposed to impaired wound healing as a result of reduction in skin thickness above that which is due to steroid use. Furthermore TNF- α is required for normal wound healing, and in experimental settings anti-TNF- α has been linked to poor wound healing [2]. Thus careful management of anti-rheumatic agents and their adverse effects in a perioperative period is essential. Among nbDMARDs, only MTX has been investigated prospectively and randomized manner, and demonstrated that continuation of MTX treatment did not increase the risk of either infections or surgical complications in elective orthopaedic surgery in patients with RA [3]. As for biologic anti-TNF- α agents, current national guidelines suggested that treatment with biologic agents should be discontinued during the perioperative period. Although discontinuation of anti-TNF- α agents during the perioperative period may have a positive effect on SSI and wound healing rates, but this is at the expense of increased risk of RA flare that could affect postoperative rehabilitation. However, there are no prospective clinical trials and few studies assessing the use of anti-TNF- α agents during the perioperative periods in RA patients undergoing elective orthopaedic surgery. In this chapter, we review the available literature related to perioperative complications, especially SSI, delayed wound healing and RA flare in elective orthopaedic surgery in patients with RA treated with anti-TNF- α agents, and discuss the perioperative management of anti-TNF- α agents, the clinical dilemma whether discontinue or not.

2. Risk of septic arthritis (SA) in RA patients

Individuals with RA are at an inherently increased risk of infection [1, 4]. Edwards et al. [1] reported that the incidence rate for SA was 12.9 times higher in subjects with RA than those without [95% confidence interval (CI) 10.1-16.5]. Doran et al. [4] performed a retrospective longitudinal cohort study and reported that the overall rate of infection per 100 person-years was higher in RA patients (19.64) than in non-RA patients (12.87), and the rate ratio for developing infections in patients with RA was 1.53 (95% CI 1.41-1.65). Infection sites that were associated with the highest rate ratio were the joints (rate ratio for SA 14.89 [95% CI 6.12-73.71]), bone (rate ratio for osteomyelitis 10.63 [95% CI 3.39-126.81]), and skin and soft tissues (rate ratio 3.28 [95% CI 2.67-4.07]) [4]. SA is a serious and severe condition for patients that can lead to irreversible joint destruction, and the incidence of SA in the general population is around 4-10/100,000/person-years [5, 6]. SA is lethal around 10% of a death

rate [7]. In fact, infections requiring hospitalization were significantly more frequent in RA patients (9.57/100 person-years) than in non-RA patients (5.09/100 person-years) with rate ratio 1.88 (95% CI 1.71-2.07), and SA was also associated with a highest rate ratio of 21.66 (95% CI 7.37-257.61) [4].

Accumulated data indicate that the risk factors for SA are increasing age, comorbidities (diabetes mellitus, chronic renal failure, chronic cardiac failure), joint prosthesis, skin infection and pre-existing joint damage [1, 8-10], but whether RA treatment with nbDMARDs, corticosteroids and biologics including anti-TNF- α agents increases the risk of SA is still unclear. DMARDs and biologics including anti-TNF- α agents are generally believed to be immunosuppressive and likely to increase the incidence of SA in patients with RA. But the data on these are very limited and sparse. Edwards et al. [1] performed a retrospective study using the United Kingdom General Practice Research Database to analyze the effect of DMARDs on developing SA in patients with RA. There was significantly increased risk of SA in individuals with RA prescribed DMARDs compared with those not prescribed DMARDs. The incidence rate ratios (IRR) for developing SA in the patients receiving DMARDs compared with receiving no DMARDs were different for different medications. Penicillamine (adjusted IRR 2.51, 95% CI 1.29-4.89, $P=0.004$), sulfasalazine (adjusted IRR 1.74, 95% CI 1.04-2.91, $P=0.03$) and prednisolone (adjusted IRR 2.94, 95% CI 1.93-4.46, $P<0.001$) were associated with an increased incidence of SA when compared with receiving no DMARDs [1]. The use of other DMARDs (including MTX) not showed such effect [1]. There was a number of individuals with RA developed SA without receiving DMARDs, thus they considered that the immune dysfunction associated with RA and the coexistent joint damage are more important risk factors than immunomodulatory therapies with DMARDs [1].

There is very limited information regarding the effect of anti-TNF- α therapy on the risk of SA. Galloway et al. [11] conducted a prospective observational study to evaluate the risk of SA in patients with RA treated with anti-TNF- α agents. They reported that incidence rates for SA were anti-TNF 4.2/1000/patient years (95% CI 3.6-4.8) and nbDMARDs 1.8/1000/patient years (95% CI 1.1-2.7). The adjusted hazard ratio (HR) for SA in the anti-TNF cohort was 2.3 (95% CI 1.2-4.4). The risk did not differ significantly between the three agents: infliximab (IFX), etanercept (ETN) and adalimumab (ADA). The hazard for SA in the anti-TNF cohort was greatest in the early months of therapy, as well as data from other cohorts [12], and the risk then decreased steadily over the remainder of the follow-up period [11]. One of the potential explanations for early increased risk is that it may reflect a true reduction in risk of joint infection in patients who achieve better control of their RA [11].

In summary of this section, patients with RA are at an increased risk of SA irrespective of therapy. Some DMARDs and corticosteroid increase the risk of SA. Exposure to anti-TNF therapy is also associated with an increased risk of SA and this risk was greatest in the first year of treatment. Thus, this increased risk of SA in RA may be due to not only as a consequence of the disease nature of RA but also treatment with some immunomodulatory agents. Current evidence does not support any one anti-TNF agent having a safer profile with regard to SA.

3. Risk of SSI in RA patients undergoing TJA

TJA is a major orthopaedic procedure for destructed joints. In RA, total knee arthroplasty (TKA) and total hip arthroplasty (THA) are the most common, promised surgical interventions for patients to recover from painful joints and impaired activities of daily life. However, prosthetic joint infection often requires revision of the infected prosthesis and prolonged intravenous antimicrobial therapy, and has a mortality rate of 2.7-18% [13]. Patients with RA have been identified to have a higher baseline risk of infectious diseases compared with general population. In addition, the immunosuppressive drugs used in the treatment of RA may further increase the risk of infection. Whether this increased baseline risk of infections in RA patients might influence the risk of deep infection after primary TJA is somewhat conflicting.

Wymenga et al. [14] conducted a multicenter prospective study to investigate the association between perioperative factors and SA after TKA and THA. At 1-year follow up, 9/362 patients (2.5%) after TKA and 17/2651 patients (0.64%) after THA were completed by SA. They reported that RA was a risk factor for SA for TKA (risk ratio 4.8; 95% CI 1.2-19), but they could not confirm this in THA. Schrama et al. [15] reported a retrospective study using the Norwegian Arthroplasty Register to examine the risk of revision arthroplasty due to infection in RA (6,629 procedures) compared with OA patients (102,157 procedures). The incidence of revision due to infection in TKA and THA were 0.7% (176/24,294 procedures) and 0.6% (534/84,492 procedures), respectively. The risk of revision for infection in RA patients with TKA was 1.6 (95% CI 1.06-2.38) times higher compared to OA patients, but there were no difference in THA. This discrepancy between TKA and THA were also reported by Wymenga et al. [14], and Schrama et al. mentioned that the vulnerable soft tissue envelope around the knee joint could make the TKA in RA patients more susceptible to infection, since the connective tissue disease RA and its potentially immunomodulating medication are risk factors for skin and soft tissue infections. Jansen et al. [16] analyzed primary (40,135 procedures) and revision (3,014 procedures) knee arthroplasties in a large series of knee arthroplasties from Finnish Arthroplasty Register. In total, 387 reoperations were performed for the treatment of infection (0.90%; 95% CI 0.81-0.99). The adjusted HR for reoperation due to infection in primary and revision TKA in patients with RA were 1.86 (95% CI 1.31-2.63) and 1.01 (95% CI 0.44-2.34) compared with primary OA, respectively. Robertsson et al. [17] also reported using another large series of knee arthroplasties, the Swedish Knee Arthroplasty Register that the risk of revision for infection was significantly higher in RA patients compared to OA patients [risk ratio (RR) 1.4; 95% CI 1.1-1.9]. The data on influences of nbDMARDs on the risk of prosthetic infection in patients with RA were absent in these studies [14-17].

Bongartz et al. [13] conducted a retrospective study using the Mayo Clinic Total Joint Registry to examine the incidence and risk factors of prosthetic joint infection in RA patients (657 procedures; THA or TKA). 23 (3.7%) joint arthroplasties were complicated by infection. The risk of prosthetic joint infections were increased in RA patients (HR 4.08, 95% CI 1.35-12.33) compared with a matched cohort of OA patients. Revision arthroplasty (HR 2.99, 95% CI 1.02-8.75), previous prosthetic joint infection of the replaced joint (HR 5.49, 95% CI

1.87-16.14), and operation time (HR 1.36 per 60-minute increase, 95% CI 1.02-1.81) were significant predictors of postoperative prosthetic joint infection. Based on the pharmacokinetic half-life and/or data on the biologic activity of each DMARD, perioperative DMARDs use was judged as either withheld or maintained. DMARDs were withheld perioperatively in 57% of procedures and stopping DMARDs therapy at the time of surgery lowered the risk of prosthesis infection (HR 0.65, 95% CI 0.09-4.95), but this was statistically not significant. There were 3 prosthesis infections in 38 patients who were treated with anti-TNF agents at the time of surgery as compared with no infection in 12 patients who stopped their anti-TNF therapy prior to surgery, but this difference was not statistically significant. Perioperative corticosteroid use was not associated with an increased risk of prosthesis infection.

Besides DMARDs, the risk of perioperative use of corticosteroids for prosthetic infection in patients with RA is controversial. Berbari et al. [18] conducted a case-control study to determine risk factors for the development of prosthetic joint infection. 462 episodes of prosthetic joint infection in 460 patients were used for analysis. Univariate analysis identified that RA, steroid therapy as risk factors for joint prosthetic infection with odds ratio (OR) of 2.0 (95% CI 1.3-3.0) and 2.0 (95% CI 1.3-3.1) respectively. Wilson et al. [19] reported that 67 (1.6%) out of the 4,171 TKA were complicated by infection. The incidence of infection in RA patients (2.2%; 45/2076) was significantly higher than in OA (1%; 16/1857) ($P < 0.0001$). Despite the fact that a higher percentage of patients who had RA and infection had used steroids than had those who did not have an infection (75% compared with 46%), a history of oral use of steroids was not a significant risk factor.

While most of papers agreed with increased risk of prosthetic infection in RA patients, da Cunha et al. [20] conducted a retrospective study to compare the incidence of infections between RA and OA patients in THA and TKA, and reported that no significant difference was observed between the RA and OA groups regarding the rates of prosthesis infections (TKA 7.1% vs. 0% and THA 2.1% vs. 0%, respectively, both with $P > 0.1$), incisional infections (TKA 14.3% vs. 3.3% and THA 4.3% vs. 1.3%, respectively, both with $P > 0.1$), and systematic infections (TKA 7.1% vs. 3.6%, $P = 0.92$ and THA 4.3% vs. 10.7%, $P > 0.1$, respectively). They concluded that RA was not identified as a risk factor for perioperative infections in THA and TKA in their case series. The low incidence of infections in both groups may explain their findings. Although the data on usage and mean dose of DMARDs, biologics and corticosteroids were reported, the association between prosthesis infection and these drugs were not analyzed in this study.

Whether the use of nbDMARDs constitutes an independent risk factor for SSI remains unclear. Among nbDMARDs, only MTX had been investigated in a prospective and randomized study. Grennan et al. [3] reported that signs of infection or surgical complications occurred in two of 88 procedures (2%) in the group of MTX continuation, 11 of 72 procedures (15%) in the group of MTX discontinuation, and 24 of 228 procedures (10.5%) in the MTX naïve group. Furthermore, accumulated data support the perioperative use of MTX, and international 3E Initiative stated in the recommendation that MTX can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery [21].

In summary of this section, most of studies support the increased prevalence of TJA infection in RA patients. Among nbDMARDs, only MTX had been intensively investigated the influences of the perioperative use on the risk of SSI, and accumulated data support the safety of perioperative continuation of MTX undergoing elective orthopaedic surgery. We should be aware that TJA in RA patients is high-risk in infection and sufficient antibiotic prophylaxis should be taken with a careful follow-up.

4. Risk of SSI in RA patients treated with anti-TNF- α agents undergoing orthopaedic surgery

The information about the risk of SSI in RA patients treated with anti-TNF- α agents undergoing orthopedic surgery is very limited, and to date, there are only 14 studies on this matter.

We at first take up 4 studies those analyzed whether continuation of TNF blockers in perioperative period increases the risk of SSI in patients on anti-TNF therapy.

Talwalker et al. [22] performed a small retrospective study. 16 procedures in 11 patients (RA; n=10, psoriatic arthritis; n=1) on anti-TNF undergoing elective joint surgery were reviewed. TNF blockers were continued in group A (4 procedures), while in group B (12 procedures), they were withheld before surgery and restarted after the procedure. In group A, IFX was used in one operation, the patient receiving the injection 3 days before surgery while ETN was used in three patients. In group B, IFX was stopped nearly 4 weeks before surgery, whereas ADA and ETN was stopped at 2 weeks. The timings for restarting the drug were variable. Postoperatively, none of the patients in either group developed serious wound and systematic infections, but one flare up occurred in a patient receiving ETN in group B.

Wendling et al. [23] conducted a retrospective study with a sample size of 50 surgical procedures (foot and ankle; 13, hand and wrist; 11, TJA; 12, others; 14) in 30 patients with RA treated with TNF blockers. TNF blockers at the time of surgery was IFX (n=26), ETN (n=13), ADA (n=11), with a mean exposure of 12.1 months (range 1-42). TNF blockers were withheld before surgery in 18/50 patients, and for the rest, surgery was performed between two TNF blocker injections. Postoperatively, no infections occurred in either group whether TNF blocker was discontinued or not, but RA flares were observed in 6 cases (12%) and significantly associated with anti-TNF interruption before surgery (5 interruptions/6 cases of flare vs. 13 interruption/44 surgical procedures without flare; Fisher's exact value=0.02).

Den Broeder et al. [24] performed a large retrospective study. Two parallel cohorts were defined: cohort 1 did not use anti-TNF, cohort 2 used anti-TNF but had either stopped (2A) or continued anti-TNF preoperatively (2B), the cutoff point being set at 4 times the half-life time of the drug. In total, 1,219 procedures were performed (wrist/hand; 317, ankle/foot; 280, knee; 195, hip; 172, shoulder; 114, elbow; 102, other; 39). Crude infection risk in cohorts 1, 2A, and 2B were 4.0% (41/1023), 5.8% (6/104), and 8.7% (8/92), respectively. History of prior SSI or skin infection was found to be the strongest predictor for SSI (OR 13.8, 95% CI 5.2-36.7, $P<0.0001$), but perioperative use of anti-TNF was not significantly associated with

an increase in SSI rates (OR 1.5, 95% CI 0.43-5.2, $P=0.43$). However, wound dehiscence occurred more frequently in patients that continued anti-TNF compared to patients that temporarily discontinued anti-TNF treatment (OR 11.2, 95% CI 1.4-90).

Bongartz et al. [13] conducted a retrospective, single-center, double cohort study that included all patients with RA who underwent THA or TKA at the Mayo Clinic Rochester between January 1996 and June 2004. 657 surgeries in 462 patients with RA were identified. There were 3 prosthesis infections in 38 patients who were treated with anti-TNF agents at the time of surgery as compared with no infection in 12 patients who stopped their anti-TNF therapy prior to surgery. However, the result did not reach statistical significance.

Secondary, we take up 7 studies which compare the perioperative risk of infection between patients on TNF blockers and those on nbDMARDs.

Bibbo et al. [25] reported a 12-month prospective study that compared foot and ankle surgery in 16 RA patients (mean age 50 years) on TNF blockers (group 1) (IFX; 5, ETN; 11) compared with 15 controls (mean age 60 years) on nbDMARDs (group 2). Patients on TNF blockers discontinued treatment prior to surgery (ETN; mean 2.6 days, IFX; mean 20.2 days) and resumed treatment postoperatively. Infectious complications occurred in two patients: one case of a superficial infection in a group 1 patient and one case of a deep infection (osteomyelitis) in a group 2 patient. Delayed wound healing occurred in three patients, all occurred in group 2. Bone healing complications occurred in three patients, all in group 2, comprised of two nonunions and one delayed union. When considered individually, the occurrence of an infectious or healing complication proved to be statistically similar between groups 1 and 2. However, when complications summed (infectious and healing complications), group 2 demonstrated a statistically higher overall complication rate ($P=0.033$, Fisher's exact test). They concluded that the use of TNF blockers may be safely undertaken in the perioperative period without increasing the risk of infectious or healing complications in the patients with RA undergoing elective foot and ankle surgery.

Hirano et al. [26] performed retrospective cohort study where adverse events of surgical wounds were compared between patients treated with TNF blockers ($n=39$) (IFX; 24, ETN; 15) and those on nbDMARDs ($n=74$). TKA is the commonest surgery followed by THA. Administration of TNF blockers was stopped prior to surgeries (IFX; mean 29.8 days, ETN; mean 9.6 days) and restarted after surgical wounds were completely healed. Adverse events of surgical wounds occurred after two operations in the TNF group (5.1%) and five operations in the nbDMARDs group (6.8%), which was not statistically significant difference by Fisher's exact test ($P=1.0000$). OR was 0.7459 (95% CI 0.1380-4.0336). Although most of adverse events of surgical wounds were wound dehiscence and continuation of discharge, postoperative infection occurred in one TKA in the TNF group. They concluded that the use of anti-TNF agents dose not cause specific adverse events on surgical wounds after elective orthopedic surgeries in RA patients.

Kawakami et al. [27] performed a retrospective case-control study to identify perioperative complications associated the use of TNF blockers. RA patients on anti-TNF (64 procedures/49 patients) were compared to those on nbDMARDs (64 procedures/63 patients).

TKA is the commonest surgery followed by THA. TNF blockers (IFX; 35 and ETN; 29) were withheld 2-4 weeks prior to surgery according to the British Society for Rheumatology and the Japan College of Rheumatology guidelines (2-4 weeks for ETN, 4 weeks for IFX). Multivariate logistic regression analysis identified the use of TNF blockers (OR 21.80, 95% CI 1.231-386.1, $P=0.036$), prednisone dosage (OR 1.433, 95% CI 1.007-2.040, $P=0.046$), and disease duration (OR 1.169, 95% CI 1.030-1.326, $P=0.015$) as risk factors for SSI. SSIs were developed 12.5% (8/64) in the anti-TNF group, whereas 2% (1/64) in the nbDMARDs group ($P=0.016$), but there was no delayed wound healing occurred in either groups. RA flare-ups during the perioperative periods were found in 17.2% (11/64) of anti-TNF group. These flare-ups were significantly increased in ETN group (31.0%, 9/29) compared with the IFX group (5.7%, 2/35) ($P=0.009$). Multivariate logistic regression analysis also revealed that the use of TNF blockers was the only risk factors for DVT (OR=2.83, 95% CI 1.10-7.25, $P=0.03$) in their study. DVT were developed 51% (23/45) in the anti-TNF group, whereas 26% (12/45) in the nbDMARDs group ($P=0.015$). They concluded that TNF blockers were likely cause SSI and DVT in RA patients undergoing elective orthopaedic surgery.

Momohara et al. [28] performed a retrospective study to identify risk factors for acute SSI after TJA (THA; 81, TKA; 339) in RA patients treated with biologics (48 patients, THA; 11, TKA; 37) and nbDMARDs (372 patients). In the biologics group, 19 (4.5%) received IFX, 23 (5.5%) received ETN, two (0.5%) received ADA, and four (1.0%) received tocilizumab (TCZ). Of the patients undergoing THA or TKA, 24 cases (5.7%) developed a superficial incisional SSI requiring the use of antibiotics and the three cases (0.7%) developed an organ/space SSI necessitating surgical treatment to remove the artificial joint prosthesis. Multivariate logistic regression analysis revealed that the use of biologics (OR=5.69; 95% CI 2.07-15.61, $P=0.0007$) and longer RA duration (OR=1.09; 95% CI 1.04-1.14, $P=0.0003$) were the only significant risk factors for acute SSI. Furthermore, multivariate logistic regression analysis of individual medication (nbDMARDs and biologics) adjusted for disease duration indicated that TNF blockers increased the risk of SSI (IFX OR=9.80; 95% CI 2.41-39.82, $P=0.001$; ETN OR=9.16; 95% CI 2.77-30.25, $P=0.0003$). They found that the use of biologics (IFX or ETN) and longer disease duration were associated with an increased risk of acute SSI in RA patients.

The Committee on Arthritis of the Japanese Orthopedic Association [29] investigated the prevalence of postoperative complications in patients with RA in teaching hospitals in Japan. The number of surgical procedures under treatment with biologic agent was 3,468 (IFX; 1,616, ETN; 1686, ADA; 41, TCZ; 102, abatacept; 23) and the prevalence of infection was 1.3% (46 procedures). For IFX, ETN, and TCZ, the mean times of withdrawal before surgery were 26.4, 14.1, and 19.8 days, respectively. The prevalence of infection was 1.0% (567 procedures) in 56,339 procedures under treatment with nbDMARDs. There were no significant differences between biologics and nbDMARDs groups with respect to the prevalence of infections (OR 1.32, 95% CI 0.98-1.79, $P=0.07$). In the joint arthroplasty group, the prevalence of infection was 2.1% (34/1,626 procedures) in biologics group and 1.0% (298/29,903 procedures) in nbDMARDs group. There was a significant difference between biologics and nbDMARDs groups (OR 2.12, 95% CI 1.48-3.03, $P<0.0001$). They concluded that the infection risk of joint

arthroplasty in RA patients on anti-TNF therapy was more than twofold greater compared with those treated with nbDMARDs.

Kubota et al. [30] performed a retrospective study to analyze the influence of biological agents on delayed wound healing and the postoperative SSI in RA patients. The patients were divided into two groups, those treated with biologics (bio group; 276 joints) and not treated with biologic agents (non-bio group; 278 joints). Biologics administered in the bio group were IFX (n=14), ETN (n=236), ADA (n=8), and TCZ (n=18), and these agents were withheld 2-4 weeks before surgery. TKA is the commonest surgery followed by THA. In the bio group, postoperative superficial and deep infection developed in one and two joints, respectively. In the non-bio group, superficial infection developed in one joint, and deep infection was not observed. The incidence of SSIs did not differ significantly between the two groups (Mann-Whitney *U*-test, $P=0.31251$). Delayed wound healing occurred in 15 joints (5.4%) in the bio group (all the patients were treated with ETN), and 12 joints (4.3%) in the non-bio group, but the difference was not statistically significant (Mann-Whitney *U*-test, $P=0.522$). They concluded that the use of biologics may not affect the incidence of postoperative adverse events related to SSI and wound healing.

Hayata et al. [31] performed a retrospective study to investigate the complications of orthopedic surgery for RA patients treated with IFX (52 patients). Commonest surgery was arthroscopic synovectomy (n=30), followed by TJA (n=16). The mean timing of surgery after infusion of IFX was 4 weeks. There were two cases (3.8%) of superficial wound infection (one case was foot arthroplasty and the other was spine surgery), but there was no deep wound infection. Furthermore, there is no correlation between infection and clinical factors including age, disease duration, preoperative CRP, MMP-3, rheumatoid arthritis particle-agglutination (RAPA) and the period until surgery after IFX infusion. They concluded that IFX did not increase the risk of either infection or surgical complications occurring in patients with RA within 1 year of orthopedic surgery.

Thirdly, we take up 3 studies which compare the patients with postoperative infection and those without, to identify the association between anti-TNF therapy and the risk of infection.

Gilson et al. [32] carried out a retrospective case-control study using French RATIO registry to analyze the risk factors for TJA infections in patients receiving TNF blockers. 20 patients (18 with RA) treated with TNF blockers (IFX; 7, ETN; 5, ADA; 8) and presented with TJA infections were compared to controls (40 patients) without TJA infections on TNF blockers. TJA infections concerned principally the knee (n=12, 60%) and the hip (n=5, 25%). 8 cases (40%) versus 5 controls (13%) had undergone primary or revision TJA for the joint subsequently infected during the previous year ($P=0.03$). Of these procedures, TNF blockers were continued in 5 cases compared to 1 in the control group ($P=0.08$). Multivariate analysis demonstrated that the predictors of infection were primary TJA or TJA revision for the joint subsequently infected within the last year (OR 88.3, 95% CI 1.1-7071.6, $P=0.04$) and increased daily steroid intake (OR 5.0 per 5 mg/day increase, 95% CI 1.1-21.6, $P=0.03$). They concluded that TJA infection was rare but potentially severe in patients receiving TNF blockers. Important risk factors were primary TJA or TJA revision for the joint subsequently infected within

the last year, particularly when TNF blockers were not interrupted before surgery, and the daily steroid intake.

Giles et al. [33] performed a retrospective study to investigate the association between anti-TNF therapy and the development of serious postoperative infection in RA patients undergoing orthopaedic surgery. 91 patients were identified as having at least one orthopedic procedure, and 10 of the 91 patients (11%) developed serious postoperative infection. The demographic features and RA therapies between infection group (n=10) and no infection group (n=81) were comparable. But infection group (7/10 patients; 70%) were significantly more likely treated with TNF- α blocker at the time of surgery compared with no infection group (28/81 patients; 35%) ($P=0.041$). Univariate analysis revealed that anti-TNF was significantly associated with the development of postoperative infections (OR 4.4, 95% CI 1.10-18.41). This association remained statistically significant after adjustment for age, sex, and disease duration (OR 4.6, 95% CI 1.1-20.0); prednisone use, diabetes, and serum rheumatoid factor status (OR 5.0, 95% CI 1.1-21.9); and all these 6 variables simultaneously (OR 5.3, 95% CI 1.1-24.9). They concluded that treatment with TNF blockers associated with increased risk of early infectious complications following orthopaedic surgery in patients with RA. They suggest that TNF blockers should be withheld prior to orthopaedic surgery.

Ruyssen-Witrand et al. [34] performed a systematic retrospective study to assess the complication rates after surgery in rheumatic patients treated with TNF blockers. 127 surgical procedures (107 orthopaedic procedures, 84.3%) performed in 92 rheumatic patients (71 RA patients, 77.2%) receiving TNF blockers. Orthopaedic procedures had a postoperative complication rate of 12% (n=13) with 5.6% (n=6) of infections, whereas 'clean' orthopedic procedures such as joint replacement or vertebral surgery had a complication rate of around 10% (n=4) with 7% (n=3) infections. Among the procedures where TNF blockers were discontinued more than 5 half-lives before surgery (36 procedures), there were 19.4% (7/36) complications compared to 18.4% (12/65) for procedures where anti-TNF therapy was interrupted less than 5 half-lives before or was not interrupted at all ($P=0.48$). If therapy was discontinued for more than 2 half-lives the complication rate was 17.6%, versus 30.0% if therapy was discontinued less than 2 half-lives before or was not discontinued ($P=0.24$). Thus, interrupting TNF blockers did not decrease the postoperative complications. No risk factors, either demographic or for severity, were statistically significant in predicting post-surgical complications. Analysis of treatments showed more complications with ADA (28.6%) than ETN (11.5%), but this was not statistically significant ($P=0.18$). The cumulative corticosteroid dose was higher in the group with postoperative complications, but this was not also statistically significant. The authors concluded that the postoperative complication rate is high in patients treated with TNF blockers, thus discontinuing TNF therapy before surgery should be considered.

In summary of this section, it is difficult to make definite conclusion on the association between anti-TNF therapy and SSI in RA patients undergoing orthopedic surgery due to the retrospective nature and small sample size of most of reported studies. In 4 studies [13, 22-24], perioperative continuation of anti-TNF therapy did not increase the risk of SSI, whereas in 3 studies [27-29], the risk of SSI was increased in anti-TNF therapy group, regardless of discontinuation of the therapy perioperatively. Another point of view, preopera-

tive discontinuation of TNF blockers causes the reduction of effects of the agents at the operation date, thus the results of these studies may not show the accurate influences of TNF blockers on the risk of SSI. However, in the other four studies [25, 26, 30, 31], appropriate preoperative discontinuation of TNF blockers did not increase the risk of SSI compared with group on nbDMARDs. The risk factors for SSI, which most of RA patients undergoing TJA are considered to have, reported in 17 studies were the use of TNF blockers (OR 21.80 [27], OR 5.69 [28], and OR 4.4 [33]), prednisone dosage (OR 1.433 [27], increased daily steroid intake (OR 5.0 per 5mg/day increase) [32], longer disease duration (OR 1.169 [27] and OR 1.09 [28]), history of prior SSI or skin infection (OR 13.8) [24], primary or revision TJA for the joint subsequently infected within the last year (OR 88.3) [32], and “clean” surgical procedure such as TJA (OR 2.12) [29]. Thus, it may be preferable to perform TJA, if needed, before the induction of TNF blockers [32]. In cases of prosthetic surgery after induction of TNF blockers, their withdrawal during the perioperative period is highly recommended and steroid intake should be reduced as low as possible before surgery [32].

Further larger prospective studies are clearly needed to make clear the association between perioperative use of TNF blockers and SSI, and in clinical practice until these studies are done, we should discontinue TNF blockers and take a sufficient antibiotic prophylaxis with a careful follow-up.

5. Risk of wound healing complications in RA patients treated with anti-TNF- α agents

Patients with RA are already predisposed to impaired wound healing as a result of reduction in skin thickness [2, 35]. Thus, many orthopaedic surgeons consider the risk of wound healing complication to be high in RA patients, especially treated with TNF blockers [36]. Wound healing is a complex process and TNF- α is required for normal wound healing. An “acute” wound healing process generally includes haemostasis/inflammation, proliferation and tissue remodeling stages [37]. On the other hand, in a “chronic” wound, wound healing is impaired and is characterized by excessive inflammation, enhanced proteolysis, and reduced matrix deposition. Tarnuzzer et al. [38] demonstrated that the levels of TNF- α in fluid from “chronic” wounds were approximately 100-fold higher than those in fluid from an “acute” wound (mastectomy incision). However, the experimental data on the role of TNF- α in wound healing is still controversial. Mooney et al. [2] reported that local application of TNF- α increased wound disruption strength and eventually promoted wound healing, whereas Rapala et al. [39] and Salomon et al. [40] reported that local application of TNF- α down-regulated the synthesis of collagen and was detrimental to wound healing. Some studies analyzed the effect of blockade of TNF- α on wound healing. Mori et al. [41] reported that in TNF receptor p55-deficient mice, angiogenesis, collagen accumulation, and reepithelialization were up-regulated, and wound healing was accelerated eventually. Iglesias et al. [42] analyzed wound healing in SWISS-OF1 mice and reported that surgical wounds showed a higher degree of collagenization in ETN-treated versus untreated mice, with no difference in the time course of wound healing. They concluded that anti-TNF therapy did

not affect wound healing. Streit et al. [37] reported a case series of patients with “chronic”, therapy-resistant leg ulcers responded well to topical application of IFX. Ashcroft et al. [43] also reported that inhibiting TNF- α is a critical event in reversing the severely impaired wound healing.

Surgical wound in elective orthopaedic surgery is basically considered as “acute” wound. In the 9 of 17 studies taken up in section 4, the association between anti-TNF therapy and “acute” wound healing complications in RA patients were reported as follows. Den Broeder et al. [24] reported that wound dehiscence occurred more frequently in patients who continued anti-TNF therapy (9/92 cases, 9.8%) compared to those temporarily discontinued anti-TNF therapy (1/104 cases, 0.9%) (OR 11.2, 95% CI 1.4-90). Wendling et al. [23] reported that three cases (6%) of delayed wound healing were recorded in patients on TNF blockers (50 surgical procedures). Ruysse-Witrand et al. [34] reported that postoperative wound healing complications occurred in 6 cases (4.7%) in patients treated with TNF blockers (127 surgical procedures). Kubota et al. [30] reported that delayed wound healing occurred in 15 joints (5.4%) in bio group and 12 joints (4.3%) in non-bio group, but the difference between two groups was not statistically significant. Hirano et al. [26] reported that adverse events of surgical wounds occurred after two operations (5.1%) in the TNF group (n=39) and five operations (6.8%) in the nbDMARDs group (n=74), but the difference between two groups was not statistically significant. Suzuki et al. [29] reported that delayed wound healing occurred in 14 cases (IFX; 2, ETN; 9, TCZ; 3) (0.4%) in biologics group (n=3,468). In the remaining 3 of 9 studies by Kawakami et al. [27], Momohara et al. [28], and Bibbo et al. [25], there was no delayed wound healing in patients with anti-TNF therapy.

In summary of this section, the role of TNF- α in wound healing is still controversial. Anti-TNF therapy seems to be preferable for improvement in healing of “chronic” wounds where the level of TNF- α is excessive compared with “acute” wounds. Thus, perioperative discontinuation of anti-TNF therapy is preferable to decrease the risk of wound healing complications, but reported data are controversial and insufficient to make clear conclusion about this matter.

6. Perioperative discontinuation of anti-TNF- α agents and risk of RA flare

For orthopaedic surgeons, one of the major concerns is whether perioperative discontinuation of TNF blockers results in flare up of the disease activity. Because RA flare may compromise postoperative rehabilitation, which strongly affect the result of orthopaedic surgery. However, the information about perioperative RA flare after discontinuation of anti-TNF therapy in perioperative period is very limited. Only some comments about the flare were reported in 3 of 17 studies taken up section 4. Talwalker et al. [22] reported that one flare up occurred postoperatively in a patient receiving ETN, but the flare up was well controlled once the drug was restarted. Wendling et al. [23] reported that postoperative RA flares were observed in 6 cases (12%) and significantly associated with anti-TNF interrup-

tion before surgery (5 interruptions/6 cases of flare vs. 13 interruption/44 cases without flare; Fisher's exact value=0.02). Kawakami et al. [27] reported that RA flares during the perioperative periods were found in 17.2% (11/64) of anti-TNF group. These flares were significantly increased in ETN group (31.0%, 9/29) compared with the IFX group (5.7%, 2/35) ($P=0.009$). The reason for increased risk of postoperative RA flare in ETN compared with IFX is unclear, but considered as follows. The half-life of IFX is longer than that of ETN, and in the IFX group, the surgery was usually performed in the middle of the 8-week treatment of period, and there was actually no withholding of anti-TNF therapy. Moreover, the function of IFX is based on an antigen-antibody reaction, whereas the function of ETN is a reversible connection response of ETN of TNF [27, 44].

On the other hand, intensive treatment with TNF blockers and MTX leads to clinical remission in approximately 20-50% of RA patients. This excellent clinical result raised a new problem, whether the patients with RA on TNF therapy can discontinue their therapy after acquisition of low disease activity (LDA). In the BeST study [45], 67% of RA patients treated early with combination of IFX and MTX were able to stop anti-TNF treatment. Brocq et al. [46] performed a small prospective cohort study to determine the time to relapse after cessation of TNF antagonist therapy. The mean disease duration was 11.3 years. Amongst the 20 patients, three quarter (75%) relapsed within the first 12 months with the mean time to relapse of 15 weeks. Saleem et al. [47] reported comparative data for patients treated early ($n=27$) versus late ($n=20$) with combination therapy of MTX and anti-TNF. All patients fulfilled the criteria of clinical remission for at least 6 months. Anti-TNF therapy was then discontinued, while remaining on MTX for 24 months. The primary outcome measure was a flare of the disease determined by an increase in Disease Activity Score (DAS). At 24 months, there were significantly more patients in the initial treatment group that had sustained remission compared with the delayed treatment group (59% vs. 15%, $P=0.003$). Shorter disease duration was found for be a predictor of sustained remission following cessation of TNF blockers. Tanaka et al. [48] conducted a multicenter study (remission induction by Remicade in RA; RRR study) to determine whether IFX might be discontinued after achievement of LDA in patient with RA and to evaluate progression of articular destruction during the discontinuation. 114 RA patients with RA who had received IFX treatment, and discontinued the drug after achieving DAS 28<3.2 (LDA) for >24 weeks, were studied. The mean disease duration of the 114 patients was 5.9 years, mean DAS28 5.5 and modified total Sharp score (mTSS) 63.3. 12 patients withdrew from the study. Out of the 102 patients, 56 patients (55%) remained to have DAS 28<3.2 (RRR-achieved group) and 44 patients (43%) reached DAS 28<2.6 at 1 year after discontinuing IFX. On the other hand, 29 patients flared within 1 year (mean duration 6.4 months) after the discontinuation and in 17 patients DAS28 was >3.2 at 1 year. Thus, the remission induction by IFX was failed in 46 patients (45%) at 1 year after the discontinuation (RRR-failed group). Yearly progression of mTSS (Δ TSS) remained <0.5 (structural remission) in 67% and 44% of the RRR-achieved and RRR-failed group, respectively. Patients for whom RRR was achieved were younger (49.5 vs. 56.1 years), their disease duration was shorter (4.8 vs. 7.8 years) and mTSS was lower (46.9 vs. 97.2) than for those whom RRR failed. DAS28 at RRR-study entry had the most marked correlation with the maintenance of LDA for 1 year after the discontinuation. They concluded that after attaining LDA by IFX, 55% of the patients with RA able to discontinue IFX for >1 year without progression of radiological articular

progression. Klarenbeek et al. [49] conducted a study using five-year data of the BeSt study to determine the relapse rate after discontinuing treatment in patients with RA in sustained clinical remission, to identify predictors of relapse and evaluate treatment response after restarting treatment. 508 patients with recent-onset RA were randomized into four dynamic treatment strategies, aiming at $\text{DAS} \leq 2.4$. When DAS was < 1.6 for ≥ 6 months, the last DMARD was tapered and discontinued. If DAS increased ≥ 1.6 , the last DMARD was immediately reintroduced. 115/508 patients (23%) achieved drug-free remission during a five-year period. Of these 53/115 patients (46%) restarted treatment because the $\text{DAS} \geq 1.6$ after a median of 5 months, 59/115 patients (51%) remained drug-free remission for median duration of 23 months. To focus the group of initial combination with IFX ($n=128$), 36/128 patients (28%) achieved drug-free remission during a five-year period. Of these 15/36 patients (42%) restarted treatment, 21/36 patients (58%) remained drug-free remission. Of the 53 patients who restarted treatment, 39 (74%) again achieved remission 3-6 months after the restart without showing radiological progression during the relapse.

As mentioned above, after maintaining LDA by intensive treatment with TNF blockers, discontinuation of TNF blockers without disease flare, joint damage progression, and functional impairment is possible in some RA patients. Patients with shorter disease duration are more likely to remain in remission after discontinuing TNF blockers compared to their counterparts with established disease [45-48]. Furthermore, patients with longstanding disease are more likely to have orthopaedic surgical intervention, especially prosthetic surgery, compared to those with early disease. However, the significance of discontinuation of anti-TNF therapy in perioperative periods is different from the cessation after achievement of LDA. Because perioperative discontinuation of anti-TNF therapy is basically temporary, and the therapy is restarted promptly after confirmation of good wound healing and no evidence of infection. Therefore, if TNF blockers are withheld prior to surgery, those with longer disease duration need to be monitored carefully for features of relapse [36].

In summary of this section, perioperative discontinuation of anti-TNF therapy in elective orthopaedic surgery likely caused postoperative RA flare. The risk of postoperative flare was increased in ETN which had a shorter half-life compared with IFX, and also increased in the patients with long disease duration. Shortening the period of withholding anti-TNF therapy is desirable to prevent the postoperative flare, but shortening the duration of discontinuation may cause an increase in SSI and wound healing complications. This is the clinical dilemma for orthopaedic surgeons. Data on this matter also insufficient to make definite conclusion, thus further studies are clearly needed.

7. Recommended perioperative discontinuation period of anti-TNF- α agents in national guidelines

Although the conclusions about the influences of continuation of anti-TNF therapy in perioperative period on SSI, wound healing and RA flare are somewhat conflicting, but there are few studies which recommend the perioperative continuation of anti-TNF therapy positive-

ly. The national guidelines on each society recommend preoperative discontinuation of TNF blockers and show the preoperative off-period based on the half-life of each agents (Table 1).

	mean half-life	2 half-lives	3 half-lives	5 half-lives
	(days)	(days)	(days)	(days)
Infliximab (IFX)	8-10	16-20	24-30	40-50
Etanercept (ETN)	4.3	8.6	12.9	21.5
Adalimumab (ADA)	14	28	42	70
Golimumab (GOL)	12	24	36	60
Certolizumab (CTZ)	14	28	42	70

Table 1. Mean half-lives of TNF blockers

The current American Society of Rheumatology (ACR) guidelines (2008) state that anti-TNF should not be used during the preoperative period, for at least 1 week prior to and 1 week after surgery. It was recommended this decision should be further tempered by the pharmacokinetic properties of a given biologic agent (e.g., longer periods of time off therapy may be appropriate when using agents with longer half-lives.), and the type of surgery [50].

The recently updated British Society of Rheumatology (BSR) guidelines (2010) propose as follows. In RA patients on anti-TNF, the potential benefit of preventing postoperative infections by stopping treatment (different surgical procedures pose different risks of infection and wound healing) should be balanced against the risk of a perioperative flare in RA activity. If anti-TNF is to be stopped before surgery, consideration should be given TNF blockers three to five times the half-life of the relevant drug prior to surgery and should not be restarted after surgery until there is good wound healing and no evidence of infection [51].

The Club Rhumatismes et Inflammation (CRI) (French Society of Rheumatology) provides guidelines that based on drug half-lives and clinical settings. For minor surgery, in a sterile setting with minor risk infection, IFX, ADA and ETN should be withheld, respectively, at least 1 month, 3-4 weeks and 1-2 weeks. However, for surgery performed in a septic environment, the respective duration for interruption of IFX, ADA and ETN are 8, 4-6 and 2-3 weeks [52].

Recently updated the Board of Japan College of Rheumatology (JCR) guidelines (2012) caution that surgery should be delayed until a sufficient time had elapsed from the last administration of TNF- α antagonists (recommend to keep 2-4 weeks for ETN or 4 weeks for IFX with long half-life), because it is not clear whether or not TNF- α blockade interferes with the healing of wounds and prevention of postoperative infection. Treatment with TNF- α antagonists could be resumed after complete healing of the surgical wound and in the absence of any postoperative infection [53].

The Canadian Rheumatology Association (CRA) guidelines state that biologic DMARD should be held prior to surgical procedures. The timing for withholding biologic DMARD

should be based on the individual patient, the nature of the surgery, and the pharmacokinetic properties of the agent. Biologic DMARD may be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory [54].

In clinical practice, we should follow each one’s national guidelines and medical circumstance of each country. We summarized concisely the recommendations of main national guidelines in Table 2.

Recommended perioperative management of TNF blockers	
American Society of Rheumatology (ACR)	*Discontinue for at least 1week prior to and 1 week after surgery (this decision should be further tempered by the pharmacokinetic properties of a given biologic agent and the type of surgery)
British Society of Rheumatology (BSR)	*Discontinuation should be balanced against the risk of a perioperative RA flare (three to five times the half-life of the relevant drug prior to surgery) *Should not be restarted after surgery until there is good wound healing and no evidence of infection
Club Rhumatismes et Inflammation (CRI)	*Minor surgery: discontinue for at least 1 month (infliximab), 3-4 weeks (adalimumab) and 1-2 weeks (etanercept) *Surgery in a septic environment: discontinue for 8 weeks (infliximab), 4-6 weeks (adalimumab) and 2-3 weeks(etanercept)
Japan College of Rheumatology (JCR)	*Discontinue for 2-4 weeks (etanercept) or 4 weeks (infliximab) *Could be resumed after complete healing of the surgical wound and in the absence of any postoperative infection
Canadian Rheumatology Association (CRA)	*Discontinuation should be based on the individual patient, the nature of the surgery, and the pharmacokinetic properties of the agent. *Restarted postoperatively if there is no evidence of infection and wound healing is satisfactory

Table 2. Recommendations for perioperative management of TNF blockers in national guidelines

8. Conclusions

It is difficult to draw definite conclusion on the influence of perioperative use of TNF blockers on the risk of SSI, wound healing and flare of disease activity in RA patients undergoing orthopaedic surgery, due to the retrospective nature and small sample size of most of past studies. Although we have a limitation in the review of the perioperative management of TNF blockers, it is seemed for us that perioperative discontinuation of anti-TNF therapy was preferable to decrease the risk of SSI and wound healing complication, whereas it likely caused the increased risk of RA flare. At present, the national guidelines on each society recommend preoperative discontinuation of TNF blockers.

The risk factors for SSIs, which most of RA patients undergoing TJA are considered to have, are the use of TNF blockers, increased daily steroid intake, older age and longer disease duration, history of prior SSI or skin infection, and “clean” surgical procedure such as TJA, thus it may be preferable to perform TJA, if needed, before the induction of TNF blockers. When withholding the anti-TNF therapy, the potential benefit of preventing SSI (different surgical procedures pose different risks of infection and wound healing) should be balanced against the risk of RA flare, and we should also take pharmacokinetic properties of the agents into consideration. Shortening the period of withholding anti-TNF therapy is desirable to prevent the postoperative flare, but it may cause an increase in SSI and wound healing complications. This is the clinical dilemma for orthopaedic surgeons. Further larger prospective studies are clearly needed to make definite conclusion of perioperative management of TNF blockers, and in clinical practice until these studies are done, we should follow each one’s national guidelines and take a sufficient antibiotic prophylaxis with a careful follow-up.

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