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Literature Review

Influence of Medication on Flare Up and Infection After Elective Orthopedic Surgery in Rheumatoid Arthritis Patient – A Narrative Review

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ABSTRACT

Background: Orthopedic Surgery in Rheumatoid Arthritis (RA) patients is still controversial between orthopedic surgeons and rheumatologists, mainly due to infection and disease flares. The incidence of postoperative infections may be high due to the immunosuppressive effect of RA medication. Conversely, discontinuance of antirheumatic agents increases the possibility of a disease flare. The objective of our review is to assess the influence of drugs on both incidences.
Literature Review: There were 13 studies included in this review. Methotrexate (MTX) is the most common csDMARD option among the included studies. One retrospective study that the incidence of flares tends to be higher among the group of patients who received MTX therapy and stopped more than one week before surgery than the group who did not stop. The use of MTX doses of 5 to 10 mg/week did not show an association with infection or flare incidence. On the use of bDMARD, 37.0% of patients had higher surgical site infection (SSI). Specifically, Tumor Necrosis Factor-alpha (TNF-α) inhibitors significantly (OR: 9.5, 95% CI: 1.0-88.8) increase the incidence of postoperative infections in standard-dose and high-dose, but not significantly in the rate of flares.
Summary: csDMARD is recommended for continuous therapy, whereas for bDMARD, although it is recommended for withholding in the perioperative period, the results of the study did not show significant differences. The ideal dosage of medication is by the basic properties of the drug. In comparison, the incidence of flares and infections was significantly higher in biologic than csDMARD.

Keywords: Arthroplasty; DMARD; Flare-up; Infection; Rheumatoid Arthritis; Human and Medicine

INTRODUCTION

Rheumatoid Arthritis (RA) is one of the inflammatory autoimmune diseases that cause joint damage and loss of function. Therefore, orthopedic surgery, such as joint replacement, is an option to improve patient function and quality of life.[1–3] During their illness, 30-58% of patients with RA undergo an orthopedic procedure. The most common joint replacement is knee (57%).[4,5] The prevalence of RA increased by 3.0% from 2002 to 2012 among patients undergoing joint replacement.[6,7]

However, this surgical treatment is still controversial between orthopedic surgeons and rheumatologists due to the possibility of infection and disease flares related to the study, which have drawbacks closely associated with their treatment.[8,9] Guidelines developed by national rheumatic disease communities, providing recommendations for the use of

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Disease-Modifying Anti-Rheumatic Drugs (DMARDs), including conventional synthetic DMARDs (csDMARD) and biologically targeted DMARDs (bDMARD) during the perioperative period. However, these guidelines may vary and are sometimes contradictory.[10–12]

Whether DMARDs increasing the incidence of postoperative infections has been debated.[8] Immunosuppressive effects of DMARDs and immunosuppressants in RA patients treated with this drug may lead to perioperative side effects postoperative infections.[13,14] On the other hand, if the patients have inadequate therapy, the possibility of inflammatory disease in this vulnerable perioperative period would increase.[15–18]

Therefore, there is still controversy about whether to discontinue or continu**e** this treatment in patients undergoing surgery to consider the risk of infection or other complications over an increased disease flare. Our review's objective was to comprehensively assess the influence of discontinuing or continuing csDMARDs and bDMARD therapy on the incidence of disease flare and post-surgical infection in RA patients undergoing joint replacement surgery using the narrative approach. Our review will recognize areas in need of further research, including systematic reviews on specific topics. Our study will focus on the following questions:

1. What is the risk of having RA flare and infection after discontinue or continuing DMARDs in preoperative care?
2. What is the ideal dose of medication to decrease RA flare incidence and infection after RA patients' surgery?
3. Are biologics better than csDMARDs in RA flare and infection incidence after orthopedic surgical procedure?

LITERATURE REVIEW

A literature search conducted using digital databases such as Ovid-SP, PubMed, Science Direct, Springer Link, DOAJ, and US clinical trials. An investigation was done on references published from January 2000 to June 2020 in English and resulting in 532 hits. The search terms used are described in Table 1.

Table 1. Keyword and search terms

Key Word	Search terms
Rheumatoid Arthritis	Rheumatoid Arthritis
AND	DMARD
DMARD	Anti Rheumatic Drugs
AND	Arthroplasty
Arthroplasty	Surgical procedures
	Replacement
AND	Flare-up
Flare-up	Disease Activity
AND	Infection
Infection	Postoperative infection

The studies that included in this review were meet the following inclusion criteria: 1) The subject population is RA patients aged ≥18 years who have undergone any operative treatment; 2) Using DMARD intervention before surgery; 3) Patients who stop or without stopping the use of DMARD therapy in preoperative care; 4) Study outcomes in the form of flares and postoperative infections.

Journal screening was conducted by three reviewers (YR, YM, MNA) in several stages. First, a selection of the study title and abstract is conducted; studies that do not fit the criteria will be excluded. Studies that match the criteria will go into full-text filtering.

Finally, 13 studies would be reviewed in a narrative way that discusses the effect of using perioperative DMARDs therapy on the incidence of flares and postoperative infections. The evidence for each type of treatment is summarized below (Table 2).

Risk of having RA flare and infection after discontinue or continuing DMARDs

Various methods for measuring disease activity in RA have been described. Most studied groups used Disease Activity Score28 (DAS28) as a measurement tool, and other groups are using arthralgia for evaluation by subjective patient assessments.

Most patients with RA in this included-studies are being treated with Methotrexate (MTX). A retrospective study evaluating 122 RA patients showed 3.9% flares in the continued taking-MTX group perioperatively, compared to 14.3% flares in the discontinued MTX more than one week before surgery. However, this difference was not statistically significant. This study indicates that discontinuance of MTX, exceptionally high doses regimen, increases flare-up and incidence of infection, and the continuation of MTX throughout the perioperative care is not associated with an increase in infection within the first year after surgery.[19,20]

In contrast, a more extensive prospective randomized study in 338 patients reported that none of the patients who continued MTX has flares compare to 8% flares in patients who discontinue MTX and 4% flares of those who had not received MTX treatment ($p = 0.04$). This study also shows that preoperative MTX treatment does not increase the risk of infection in patients with RA within one year of elective orthopedic surgery.[21] Another retrospective study from Jain et al. found no increased risk of a flare-up with perioperative MTX treatment. The infection rate was found in 5% of patients taking MTX and 4% of patients who are not taking MTX, but no statistically significant ($p = 1.0$).[22]

In the other published study in 175 patients reported that no significant differences in postoperative disease activity in patients with versus without the use of MTX preoperatively ($P = 0.536$), or Prednisolone ($P = 0.144$). MTX or Prednisolon does not affect postoperative disease activity, whether these drugs are preoperatively administrated or not.[23]

Current guidelines developed from the American College of Rheumatology (ACR) recommends continuing csDMARDs perioperative. Multiple studies have been shown the safety of MTX treatment in preoperative care to decrease flare-ups disease and suitable with recommendations from the ACR to continue csDMARDs such as MTX for preoperative care. Hence, RA patients who

control the disease with this treatment before surgery should not stop MTX treatment.[21]

The updating guidance published by the ACR in an edition published by the American Association of Hip and Knee Surgeons (AAHK) allows for the continuation of methotrexate, sulfasalazine chloroquine hydroxy through the operation period. However, leflunomide must be sought one time two days before surgery. Leflunomide can be restarted in 1 to 2 weeks postoperatively once the wound has healed because patients treated with leflunomide have a high risk of postoperative infections by rapidly reducing parenteral leflunomide levels to prevent surgical complications, cholestyramine can be used.[24]

Another randomized study reported that the infection rate in the group who continued MTX seemed higher than the group who took steroids and combination because 2 of the three infections occurred in a single diabetic rheumatoid patient who had separate occasions. If diabetic patients are excluded from this study, the group's infection rate who use MTX medication will increase only 2.3%. The author proposes that diabetes may be correlated with this increased risk of postoperative infection.[22]

A different group of medications, known as biologic DMARDs, has a large group of medications such as Tumor Necrosis Factor-alpha (TNF-α) inhibitors (etanercept, adalimumab, infliximab), abatacept, tocilizumab, and Janus kinase (JAS) inhibitors (tofacitinib and baricitinib). The variation of mechanism initiates variation in recommendations for perioperative treatment.

American College of Rheumatologist recommends discontinuation of TNF-α inhibitors for one week before surgery. Another literature suggests etanercept for one week before surgery or four weeks before surgery for infliximab and adalimumab. These medications were restarted one week postoperative by the ACR, and variation among orthopedic literature at two weeks after surgery prevented postoperative infection.[24] While the British community recommends cutting therapy for 3-5x Half-Life drugs and the Canadian Rheumatology Association recommends cutting treatment for two and half-lives. Inconsistent use reflected inexperience at one of the centers of excellence, in which 59 patients with RA who received etanercept, with a half-life of 3-5 1/2 days, had the drug held for a range of 1-14 days before surgery.[15]

bDMARD treatment within 90 days before surgery was not associated with a statistically significant increase in infection risk. Although glucocorticoid treatment was a vital risk factor associated with a 1-year risk of infection.[8] Slight risk of infection is found in patients with RA whether TNF-α inhibitors drugs were given or not perioperatively six months after TKR surgery. Given the lack of evidence behind existing recommendations regarding the use of TNF-α inhibitors during operations, it raises the question of whether it is necessary to stop TNF-α inhibitors before surgical procedures.[25]

Table 2. Study Demographics and Characteristics

Authors (y), Study, Follow Up	Patient Number	Mean Age (Range or SD)	Gender M/F (n or %)	Disease Duration (y)	Orthopedic surgery	RA medication	Doses mg/week	Stopping or Continuing	Outcome measures
Hayasi S, 2017. [15] Retrospective cohort study 2 y after surgery	99 (Group A 94; Group B 5)	Group A 66.3±8.5; Group B 63.8±8.9	NR	Group A 18.3 ± 11.6; Group B 22.8±8.6	THA	Group A No infection (n 24 bDMARD; n 24 TNF-α inhibitors; n 8 Non-TNF-α; n 54 DMARDs except MTX, TAC; n 64 MTX; n 6 Tacrolimus n 70 PSL); Group B Infection (n 4 bDMARD; n 4 TNF-α inhibitors; n 5 PSL)	Group A (MTX 4.4±3.6mg/w; Tacrolimus 0.1±0.5 mg/day; PSL 3.6±2.7mg/day) Group B (PSL 5.8±1.3 mg/day)	NR	Late Deep Infection
Momohara S, 2011. [7] Retrospective cohort study NR	420	Mean Age: 61 y	Female (91%)	Median 14.5 y (8.9-21.0)	THA, TKA	Group A: non bDMARDs (MTX 66.4%; LFU 1%; tacrolimus 7.4%; others 47.6 Sz 22.1%; other 11.5%. Group B: biologic DMARD TNF-α inhibitors IFX 4.5%, ETN 5.5%)	NR	Group A: continued; Group B: stopped 2-4 weeks, 2-4w ETN, four weeks IFX	Surgical-site Infection (SSI)
Cordtz RL, 2017. [4] Register-based cohort study, 1 y after surgery	3913	Mean Age: 66.6 y	Female 72.8%	NR	THA, TKA	Group A bDMARD (TNF-α inhibitors 93%); Group B Non-bDMARD	NR	NR	Prosthetic joint infection, mortality

Table 2. Study Demographics and Characteristics

Authors (y), Study, Follow Up	Patient Number	Mean Age (Range or SD)	Gender M/F (n or %)	Disease Duration (y)	Orthopedic surgery	RA medication	Doses mg/week	Stopping or Continuing	Outcome measures
Johnson B, 2013. [17] Retrospective cohort study, 6m after surgery	268 (Group A 104; Group B 164)	Group A 58.7; Group B 64.4	Group A 16%/ 84 %; Group B 10%/ 90 %	Group A 21.5; Group B 19.5	TKA	Group A: iTNF-A; Group B: Non-TNF-α inhibitors	NR	Grup A *Stopped*; Grup B *NR*	SSI, Other complication
Kubota A, 2012. [19] Retrospective Cohort Study NR	554 (Group A 276; Group B 278)	Group A 59.2 ± 10.1; Group B 65.5 ± 10.1	NR	Group A 18.3 ± 12.9; Group B 16.2 ± 12.94	TKA, THA, TEA, Other.	Group A: Biological Agent (IFX, ETN, ADA, Tocilizumab); Group B: Non-bDMARD	NR	Group A stopped > 2w before surgery; Group B NR	Delayed wound healing, Surgical Site Infection
Grennan DM, 2001. [11] Prospective Randomised Study 1 y after surgery	338 (Group A 88, Group B 72, Group C 228)	Mean M/F (Group A 63/58; Group B 66/58; Group C 62/62)	NR	Group A 18; Group B 19; Group C 20	Shoulder, Elbow, Wrist, MCP, hip, knee, ankle surgery	MTX	Group A 10mg/w; Group B 7.5mg/w; Group C: not received MTX	Group A Continued; Group B: stopped 2w before surgery)	Systemic Infection, RA flares

Table 2. Study Demographics and Characteristics

Authors (y), Study, Follow Up	Patient Number	Mean Age (Range or SD)	Gender M/F (n or %)	Disease Duration (y)	Orthopedic surgery	RA medication	Doses mg/week	Stopping or Continuing	Outcome measures
Murata K, 2006. [10] Observational retrospective study NR	116 (Group A 48, Group B 12, Group C 56)	Mean M/F (Group A 66/59; Group B 51/62; Group C 65/62)	NR	Group A 15; Group B 23; Group C 19	Arthroplasty, Spine Surgery, Hand Surgery, Foot Surgery, Others	1. MTX; 2. PSL	1. MTX (Group A 4.3mg/w; Group B 4.9mg/w; Group C not received MTX); 2. PSL (Group A 5.7mg/d; Group B 8.9mg/d; Group C 4.8mg/d)	1. MTX (Group A Continued; Group B: stopped 1 - >2w before surgery); 2. NR	Wound Infection, RA flares
Jain A, 2002. [12] Observational retrospective study 4-11 m after surgery	80 (Group A 28; Group B 18; Group C 18; Group D 16)	53 (23-81)	20/60	Group A 16; Group B 14; Group C 19; Group D 20	Hand Surgery	Group A: MTX; Group B: PSL only; Group C: MTX +PSL; Group D neither MTX nor PSL	Group A: Mean dose 10mg/w); Group B: Mean dose 8.8mg/d; Group C: MTX (Mean dose 10mg/w) PSL (Mean dose 6.4mg/d)	Continued all of the group	Wound Infection, RA flares

The ideal dose of medication after surgery in RA patients

Patients with csDMARD therapy post elective orthopedic surgery; in this case, MTX takes an average dose of 5 to 10 mg/week. An observational retrospective study showed that MTX doses in the perioperative period did not associate with infection. The average dose in the infected group being 8.8 (5-12.5 mg /week). Below the average dose for the overall MTX group (10 mg/week).[22] Even in the patients who took 6–8mg/week of MTX, no infection was seen.[19]

By order of level of evidence, we also found in other prospective and retrospective cohort studies that regimen doses and treatment discontinue or continuing before surgery did not increase the risk of surgical infection complications.[21,26]

Further analysis showed no significant correlation between the incidence of flares and weekly dose levels in the group who received perioperative MTX. However, it was found that discontinuance of high-dose MTX therapy (average: 14 mg, range: 10-20 mg/week) may produce a higher incidence of flares if treatment was stopped ($p = 0.01$).[19]

In cases of early intolerance or contraindications, other csDMARD (such as leflunomide or sulfasalazine) should be considered. The basis for providing csDMARD briefly described in Table 3.[20]

Based on the recommendations, bDMARD should be added if the treatment target is not achieved with the first csDMARD strategy.[27] The dosing interval of bDMARD that used in several studies in this review was performed according to the American College of Rheumatology (ACR) 2017, British Society for Rheumatology, and Japan College of Rheumatology guideline.[12,25,28]

Table 3. Basic properties of csDMARDs

Drug	Half-life	Dosage	Route
MTX	3-15 hours	Maintain usual dose if under 20 mg/wk; consider lower dose if high-risk	SC/ PO
LFU	>14 days	If high-risk, stop two weeks before surgery	PO

MTX: Methotrexate; LFU: Leflunomide; SC: Subcutaneous; PO: Oral

Among these biologics, TNF-α inhibitors have been used successfully with standard dosing according to drug half-life.[25] For example, the basic properties of infliximab, etanercept, and adalimumab are described in Table 4.[25,29]

Table 4. Basic properties of bDMARDs

Drug	Half-life	Dosage	Route
ETN	3 - 5.5 days	25 mg twice a week	SC
IFX	7-12 days	3 mg/kg/8 week administered at weeks 0,2,6 and 8 and every eight weeks after that	IV
ADA	10-20 days	40 mg every two weeks	SC

IFX: infliximab; ADA: adalimumab; ETN: etanercept; SC: Subcutaneus; IV: Intravenous

In all included studies, the relationship of the bDMARD dose and perioperative adverse events has not been reported. This review only found that in a retrospective cohort study, in patients treated with 50 mg/week etanercept (bDMARD), wound healing was delayed in 9 joints (7.3%) compare to 6 joints (5.6%) in those treated with 25 mg/week etanercept, without a significant difference (p = 0.55) between the doses, suggesting that doses difference did not affect wound healing.[28]

Biologic or csDMARDs

The use of biologics or csDMARD in medical care and assessing postoperative RA patient's clinical outlook has been described in many studies in recent years. However, remember that flare or infection risk must choose the type of therapy to be given. In biologic or csDMARD use, both are at risk for postoperative flares. Still, a higher percentage was found in patients taking preoperative DMARD biologic therapy, especially in the TNF alpha inhibitor class of drugs. Prospective studies assessing the incidence of flares and non-flares after surgery show that the bDMARD regimen (57%) is more common in the flares group. Furthermore, MTX therapy (51%) and csDMARDs (32%) more common in the flare group, even though this difference was insignificant between the flare and non-flare.[30]

Another study reported that Patients with postoperative major joint surgery showed a significant increase in disease activity score in patients using or not using preoperative bDMARD.[23] RA flare rate is more often found in the group using TNF-α inhibitors (26%) than the non-TNF-α bDMARD group (20%), But there was no significant difference.[25] Besides, using biologics or csDMARD did not show significantly different disease activity scores before and after TKA. Still, disease activity scores were found to be higher in patients taking csDMARD before TKA, where the disease activity score is one of the predict upcoming flares in RA patients.[31]

Before undergoing surgery, the use of DMARD biologic therapy has a higher risk of postoperative flares and infections than csDMARD therapy. In retrospective study data, the risk of infection was higher for biological use than for csDMARDs. Patients taking biological drug therapy, especially TNF-α inhibitors therapy, were significantly related to the increased infection risk after joint replacement than other biological therapeutic agents (TNF-α inhibitors: OR: 11.7, 95% CI: 1.2–109.7; other biological drugs: OR: 9.5, 95% CI: 1.0-88.8), although demographic data show that non-infectious events are more common than infectious events both in biologic and csDMARDs.[26]

By stopping both types of drug use, flares and infection incidence was still higher in patients taking preoperative bDMARD. In a case-control study seeking evidence of flares in the recurrence of arthralgia that comparing patients who used csDMARDs versus TNF-α inhibitors from bDMARDs was found that in the use of TNF-α inhibitors, 2 cases in the IFX

group and 9 cases in the ETN group experienced an increased flare due to perioperative drug discontinuation in which both were significantly different (p = 0.009). This study also reported an increased risk of surgical site infection with TNF-α inhibitors (OR 21.8) in the group who had stopped TNF-α inhibitors 2-4 weeks before surgery compared to patients taking csDMARDs.[32]

Postoperative infection incidence, especially in superficial and deep surgical site infection (SSI), was higher in the bDMARD therapy group than in the non-bDMARD group, but the difference was not statistically significant.[28] The risk of prosthetic joint infection with Crude incidence rate per 1000 py in the bDMARD group was 28.3 (14.7-53.3) with a rate ratio of 1.50 (0.71-3.19), whereas, in the non-bDMARD group, the incidence rate was 18.7 (12.9-27.1).[8]

Another study also revealed group bDMARDs experiencing SSI (37.0%) higher than non-SSI and significantly increase the risk of infection associated THA and TKA (OR: 5.69, 95% CI: 2:07 -1 5.61). in addition, the main agent of bDMARD, in this case, the use of TNF-α inhibitors has the risk of increasing the incidence of SSI (IFX P = 0.001, OR = 9.80, 95% CI 2.41-39.82; ETNP=0,0003, OR=9,16, 95% CI 2,77–30,25). Although non-biologic DMARD was more frequent in the non-SSI group in this study, there were no statistically significant differences.[12] Specifically in the use of bDMARD, a study comparing the use of TNF-α inhibitors and non- TNF-α inhibitors found that local infection sites were more frequent in the TNF-α inhibitors therapy group (3.26%) than the non- TNF-α inhibitors group (2.10%), but were not seen a significant difference between the two.[25]

Biologic DMARDs Standard and high doses combined with or without csDMARDs increase the risk of severe infection in RA compared to csDMARDs only, but low-dose biological drugs did not increase the risk of severe infection, but this fact was statistically insignificant.[33] The use of TNF-α inhibitors therapy has increased the risk of infection, while the initial innate immune response initiated by Chemokines includes Il-6 and TNF-α.[15]

Bone and joint infection in RA patients, mostly due to *Staphylococcus aureus*. Patients treated with TNF-α inhibitors therapy compared to patients who were not exposed to TNF-α inhibitors therapy were more likely to experience persistent colonization by *Staphylococcus aureus*.[15]

Current evidence has clarified that continuing csDMARDs such as methotrexate, sulfasalazine, hydroxychloroquine, and azathioprine are safe treatment options in RA patients without comorbidities because they have a low postoperative infection risk.[33]

MTX was very well tolerated in some patients with RA; around 40% of patients have never had side effects. These findings have been published in studies with a long history of RA and long-used MTX therapy. Subcutaneous

therapy is more effective than oral therapy. It can be used successfully in patients with ineffective oral combination therapy or in patients who are intolerant to oral therapy and can reduce biological agents' need. To note, because of the positive effect on liver enzymes and the potential to reduce side effects, the use of folic acid is approved for patients taking MTX therapy.[34]

CONCLUSION

csDMARD is recommended for continuous therapy, with low doses do not increase the risk of infection and prevent flares. Whereas for bDMARD, although it is recommended for withholding in the perioperative period, the results of the study did not show significant differences. The medication's ideal dosage to decrease RA flare incidence and infection after surgery in RA patients is by the drug's basic properties. The higher the dose, the higher the infection risk was. In comparison, the incidence of flares and infections was significantly higher in biologic than csDMARD. Therefore, clinicians should carefully calculate the balance between benefits and harms before starting biological treatments for RA, especially for patients who will undergo surgical therapy. Future studies are needed to compare the incidence of infections and flares directly.

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