The use of biologic disease-modifying anti-rheumatic drugs (bDMARDs) with short perioperative discontinuation does not associate with surgical site infection (SSI) and delayed wound healing (DWH) after orthopaedic surgeries for rheumatoid arthritis (RA)

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INTRODUCTION: Several reports have shown that perioperative continuation of bDMARDs in RA patients increased the risk for SSI and DWH due to their immunosuppressive effects. Decisions of bDMARDs discontinuation for preventing SSI and DWH should be balanced against the risk of disease flares. It is reasonable to discontinue bDAMRDs during the perioperative period of orthopaedic surgeries as several guidelines recommend. However, there is concern that long withdrawal leads to the flare of systemic inflammation. In our institutions, based on the biological half-time, the preoperative discontinuation period of bDAMRDs has been set relatively short (Table 1). This study aimed to examine whether our protocol for perioperative discontinuation of bDMARDs increases the incidence of SSI and DWH after orthopaedic surgery for RA.

METHODS: In this retrospective, cross-sectional study, we investigated the incidence of SSI and DWH from medical records of 965 elective orthopaedic procedures for RA between 2013 and 2019 in our institutions. The mean age and disease duration were 64.7±11.5 years old and 22.3±11.7 years, respectively (Table 2). The procedures for infection were excluded due to the object of this study. The bDMARDs were withheld as described above, and restarted after healing of the surgical wound and removal of stitches. Patients' background factors are age, sex, disease duration, preoperative laboratory data, disease activity score (DAS)28-CRP, body mass index, diabetes mellitus (DM), glucocorticoid use, smoking, methotrexate (MTX) use, bDMARDs use, surgical procedure. Histories of surgery in the same area, bacterial infection requiring hospitalization, and musculoskeletal infection were also included. The incidence of SSI and DWH was compared between the bDMARDs user group and the non-user group. The propensity score (PS) matchingwas performed to reduce covariate bias between the two groups. Then the possible risk factors for SSI and DWH were identified by univariate and multivariate logistic regression analysis. In this study, the definition of flare-up is arthritis symptoms outside the surgical site and requiring therapeutic intervention.

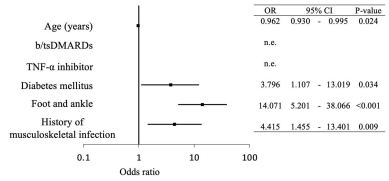
RESULTS: In all cases, SSI and DWH occurred in 12 cases (1.2%) and 28 cases (3.0%), respectively. Four hundred fourteen cases were treated with bDAMRDs at the time of surgery. Three cases (0.7%) and 9 cases (1.6 %) of SSI, and 17cases (4.1%) and 11 cases (2.0%) of DWH were observed in the bDMARDs user and non-user groups, respectively (SSI; p=0.252, DWH; p=0.079). Propensity score (PS) matching yielded 315 patients in each group. After PS matching, SSI and DWH occurred in 9 cases (1.4%) and 19 cases (3.0%), respectively. Two cases (0.6%) and 7 cases (2.2 %) of SSI, and 12 cases (3.8%) and 7 cases (2.2%) of DWH were observed in the bDMARDs user and non-user groups respectively (SSI; p=0.125, DWH; p=0.359).Perioperative disease flare of RA occurred in 19 cases (4.6%) of bDMARD users. Age (odds ratio (OR), 0.962; 95% confidence interval (CI), 0.930–0.995; p=0.024), DM(OR, 3.796; 95% CI, 1.107–13.019; p=0.034), foot and ankle surgery(OR, 14.071; 95% CI, 5.201–38.066; p<0.001), and history of musculoskeletal infections(OR, 4.415; 95% CI, 1.455–13.401; p=0.009) were associated with an increased risk of DWH (Figure 1). No risk factors for SSI were identified.

DISCUSSION AND CONCLUSION:

Avoiding periprosthetic joint infection is significantly more important to patients than flare-up. Therefore, ACR/AAHKS guidelines recommend preoperative discontinuation according to the dosing interval of bDAMRDs for total hip and knee replacement. However, If the withdrawal period can be shortened without increasing infectious complications, a shorter discontinuation period is preferred to prevent the disease flare.

We have utilized shorter discontinuation protocol based on the biological half-time of these agents. The results of the current study showed that bDMARDs use was not a risk factor for SSI and DWH with this protocol. The strength of this study is the use of PS matching for the analysis. The limitations are the retrospective nature of the design and small numbers of SSI and DWH for statistical analysis. In conclusion, even in the bDAMRDs era, with a minimum period of perioperative discontinuation, orthopaedic surgeries can be performed without increased risk of SSI and DWH.

Figure1. Univariate and multivariate logistic regression analysis of risk factors for DWH



bDMARDs: biological disease-modifying antirheumatic drugs , TNF: tumor necrosis factor , n.e.: not entered (the factors is not significant)

Table 1 . Preoperative discontinuation period of bDMARDs

	Current dosing inteval	ACR/AAHKS guidelines based on the dosing interval	Our protocol based on the biological half-time
Infliximab	Every 4, 6, or 8 weeks	5, 7, or 9 weeks	2, 3, or 4 weeks
Golimumab Abatacept i.v. Tocilizumab i.v.	Every 4 weeks	5 weeks	2 weeks
Certolizumab	Every 2, or 4 weeks	3, or 5 weeks	2 weeks
Adalimumab	Every 2 weeks	3 weeks	2 weeks
Tocilizumab s.c. Etanercept Abatacept s.c.	weekly	2 weeks	1 weeks

i.v. : Intravenous Injection, s.c. : subcutaneous injection

Table 2 . Patient's background at the time of surgical procedures

cases, n	965
Gender (male/female), n	74/891
Age, years	64.7 ± 11.5 (23-88)
Disease duration, years	22.3 ± 11.7 (0.2-64.7)
pre-operative DAS28-CRP	2.7 ± 0.9 (1.0-6.1)
bDMARDs use, n (%)	414 (42.9)
Methotrexate use, n (%)	594 (61.6)
Glucocorticoid use, n (%)	510 (52.8)
Surgical procedure	
Hand and wrist, n (%)	292 (30.2)
Foot and ankle, n (%)	275 (28.5)
TKA, n (%)	95 (9.8)
THA, n (%)	41 (4.2)
TEA, n (%)	100 (10.3)
TSA, n (%)	21 (2.2)
Synovectomy, n (%)	28 (2.9)
Spine, n (%)	40 (4.1)
Others, n (%)	73 (7.6)

Mean ± standard deviation (SD)
CRP: C-reactive protein, DAS: disease activity score, bDMARDs: biological disease-modifying antirheumatic drugs, TKA: total knee arthroplasty, THA: total hip arthroplasty, TEA: total elbow arthroplasty, TSA: total shoulder arthroplasty, Others: open reduction and internal fixation, neurolysis, tumor excision, hemiarthroplasty for femoral neck fractures, intraosseous foreign body removal, open manipulation, tenosynovectomy.