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Original Article

The use of biologic disease-modifying antirheumatic drugs does not increase surgical site infection or delayed wound healing after orthopaedic surgeries for rheumatoid arthritis

Yohei Kiso[a], Keiichiro Nishida[b,*], Ryozo Harada[c], Yoshihisa Nasu[d], Ryuichi Nakahara[d], Yoshifumi Hotta[a], Shuichi Naniwa[a] and Toshifumi Ozaki[a]

[a]Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[b]Locomotive Pain Center, Okayama University Hospital, Okayama, Japan
[c]Department of Orthopaedic Surgery, Kurashiki Sweet Hospital, Okayama, Japan
[d]Department of Orthopaedic Surgery, Okayama University Hospital, Okayama, Japan

*Correspondence: Keiichiro Nishida; knishida@md.okayama-u.ac.jp; Locomotive Pain Center, Okayama University Hospital, 2-5-1, Shikata-Cho, Kitaku, Okayama, Japan.

ABSTRACT

Objective: To investigate the effect of the use of biologic disease-modifying antirheumatic drugs (bDMARDs) on surgical site infection (SSI) and delayed wound healing (DWH) in rheumatoid arthritis (RA) patients undergoing orthopaedic surgery.

Methods: We retrospectively reviewed the records of 965 elective orthopaedic procedures undertaken in RA patients. The incidences of SSI and DWH were compared between the bDMARDs user and nonuser groups. Subsequently, univariate and multivariate logistic regression analyses were performed to evaluate risk factors for SSI and DWH after propensity score matching. The incidence of postoperative flare-up was also examined.

Results: In 965 procedures, SSI and DWH were identified in 12 and 28 cases, respectively. SSI and DWH were identified in 3 and 17 of 414 procedures treated with bDMARDs, respectively. Flare-up occurred in 21 cases. Propensity score matching identified 315 cases in both groups, with no significant difference in incidence between the two groups. No risk factors for SSI were identified, whereas age, diabetes mellitus, foot and ankle surgery, and a history of musculoskeletal-related infection were identified as risk factors for DWH.

Conclusion: The use of bDMARDs was not associated with an increased incidence of SSI or DWH, with the incidence of flare-up being relatively low.

KEYWORDS: Biologic DMARDs; delayed wound healing; orthopaedic surgery; rheumatoid arthritis; surgical site infection

Introduction

Pharmacotherapy of rheumatoid arthritis (RA) has advanced significantly with the introduction of biologic disease-modifying anti-rheumatic drugs (bDMARDs) during the last two decades [1, 2]. They have substantially improved disease activity and reduced disability among patients with RA compared to previous treatments [3, 4], allowing them to undergo orthopaedic procedures under better conditions. Recently, the proportion of RA patients undergoing orthopaedic procedures while on bDMARDs has increased, and ∼40% of RA patients undergoing arthroplasty reported using bDMARDs at the time of surgery [5–8].

Numerous studies have investigated the risk of surgical site infection (SSI) and delayed wound healing (DWH) associated with perioperative bDMARDs use in RA patients undergoing orthopaedic surgery. Some reports described that perioperative bDMARDs use increases the risk of SSI or DWH [9–16], while others, including our previous study [17], indicated no association between bDMARDs use and these complications [8, 18–30]. On the basis of the evidence from these studies, many guidelines recommend discontinuing bDMARDs during the perioperative period. The recommended duration of perioperative discontinuation of bDMARDs is based on the dosing interval or half-life of each agent. For determining the perioperative discontinuation of bDMARDs, the British Society for Rheumatology (BSR) recommends adhering to the preoperative dosing intervals of each agent [31]. Additionally, the American College of Rheumatology (ACR) and the American Association for Hip and Knee Surgery recommend 1 week of withdrawal in addition to the preoperative dosing intervals of each agent for patients with RA undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) [32, 33]. The German Society for Rheumatology changed the withdrawal period for bDMARDs to one half-life in its 2023 guidelines from the two half-lives recommended in 2014 [34, 35]. Therefore, the duration of perioperative discontinuation

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varies among the guidelines of different societies due to a lack of prospective studies and the low frequencies of SSI and DWH [31–35]. In addition, the BSR [31] and van Duren *et al.* [5] reported that the potential benefits of perioperative discontinuation of bDMARDs in preventing postoperative SSI and DWH need to be balanced against the risk of perioperative relapse in disease activity associated with bDMARDs discontinuation.

We have previously reported a retrospective study in which surgeries were performed with relatively short discontinuation periods based on the dosing intervals of each bDMARDs formulation during the period from 2004 to 2012 [17]. The percentage of bDMARDs use in surgery was 18.9% during this period and has since increased to ∼40%. In the present study, we reviewed the incidences of SSI and DWH in orthopaedic surgery for RA patients at our institution from 2013 to 2019. The aim was to investigate whether bDMARDs are a risk factor for SSI and DWH under our discontinuation protocol and to determine the incidence of perioperative flare-up of the disease activity after discontinuation of bDMARDs.

Patients and methods

We retrospectively reviewed the medical records of 1099 procedures of orthopaedic surgery in RA patients at Okayama University Hospital and Kurashiki Sweet Hospital (Okayama prefecture, Japan) from 2013 to 2019. In this study, 965 procedures were included, excluding cases of surgeries for infection ($n = 61$), cases under disease control by Janus kinase inhibitors ($n = 27$), and cases with incomplete data ($n = 46$)

All patients fulfilled the 1987 revised ACR criteria for RA [36]. The study was approved by our institution's Ethics Committee, and all subjects provided written informed consent (approval number 1901–002).

The patient background at the time of the procedure is presented in Table 1. The perioperative discontinuation protocol of bDMARDs was based on the dosing period of each agent [17] with consideration of the individual treatment schedule, as shown in Table 2. Infliximab was restarted 4 weeks postoperatively, and the other agents were restarted after achieving healing of a surgical wound and suture removal. Perioperative antibiotics followed the Japanese Orthopaedic Association Clinical Practice Guideline on the Prevention of Surgical Site Infections in Bone and Joint, with first-generation cephem antibiotics administered according to guidelines [37]. Clindamycin was used for patients with β-lactam allergy. A flare-up was defined as the postoperative increase of pain or appearance of tenderness and/or swelling of the joint unrelated to the surgical site, requiring therapeutic intervention, and its incidence was examined. We also investigated the possible clinical risk factors for SSI and DWH, including a history of same-site surgery and previous infection (bacterial infection requiring hospitalisation and musculoskeletal-related infection). SSI was defined according to the 2013 US Center for Disease Control and Prevention guidelines for the prevention of SSI [38]. Cases in which suture removal was later than 2 week after surgery or which required re-suturing were regarded as DWH [17].

The incidences of SSI and DWH were reviewed and compared between the bDMARDs user and nonuser groups. Owing to differences in clinical characteristics between these groups, propensity score (PS) matching was performed to reduce or eliminate the baseline differences [39]. The PS was estimated by a logistic regression model for both the user and nonuser groups, with previously reported and potential clinical risk factors as predictive factors: age, sex, disease duration, preoperative haemoglobin, albumin (Alb), C-reactive protein

Table 1. Patients' background at the time of surgical procedures.

Cases, *n*	965
Sex (male/female), n	74/891
Age, years	64.7 ± 11.5 (23–88)
Disease duration, years	22.3 ± 11.7 (0.2–64.7)
Preoperative Hb, g/dl	12.3 ± 1.4 (7.2–16.5)
Preoperative Alb, mg/dl	4.0 ± 0.4 (2.3–5.8)
Preoperative CRP, mg/dl	0.6 ± 0.9 (0.0–8.7)
Preoperative DAS28-CRP	2.7 ± 0.9 (1.0–6.1)
bDMARDs use, *n* (%)	414 (42.9)
Methotrexate use, *n* (%)	594 (61.6)
Methotrexate, mg/week	4.2 ± 4.0 (0.0–16.0)
Glucocorticoid use, *n* (%)	510 (52.8)
Glucocorticoid, mg/day	2.1 ± 2.5 (0.0–10.0)
Body mass index, kg/m^2	21.8 ± 3.5 (12.9–36.7)
Diabetes mellitus, *n* (%)	68 (7.0)
Smoking, *n* (%)	76 (7.9)
Same-site surgery, *n* (%)	197 (20.4)
Past infection	158 (16.4)
Medical infection, *n* (%)	109 (11.3)
Musculoskeletal-related infection, *n* (%)	54 (5.6)
Surgical procedure	
Hand and wrist, *n* (%)	292 (30.3)
Foot and ankle, *n* (%)	275 (28.5)
TKA, *n* (%)	95 (9.8)
THA, *n* (%)	41 (4.2)
TEA, *n* (%)	100 (10.4)
TSA, *n* (%)	21 (2.2)
Synovectomy, *n* (%)	28 (2.9)
Spine, *n* (%)	40 (4.1)
Others, *n* (%)	73 (7.6)

Mean ± standard deviation (SD).
Abbreviations: Hb: hemoglobin; Alb: albumin; 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.

Table 2. Discontinuation periods of bDMARDs.

bDMARDs	Number of procedures (%)	Discontinuation periods	
		Preoperative (days, range)	Postoperative (days, range)
Etanercept	122 (29.5)	9.2 (2–21)	14.9 (6–48)
Golimumab	53 (12.8)	19.5 (8–43)	18.2 (6–57)
Infliximab	39 (9.4)	30.3 (12–80)	29.8 (13–106)
Adalimumab	31 (7.5)	15.1 (8–32)	16.6 (5–56)
Certolizumab pegol	7 (1.7)	15.7 (15–18)	16.0 (10–32)
Tocilizumab i.v.	43 (10.4)	21.6 (9–40)	17.0 (6–34)
Tocilizumab s.c.	40 (9.7)	14.6 (5–31)	16.4 (7–65)
Sarilumab	4 (1.0)	20.5 (10–39)	9.0 (7–11)
Abatacept s.c.	38 (9.2)	9.1 (6–19)	14.7 (6–21)
Abatacept i.v.	37 (8.9)	20.2 (12–57)	21.9 (12–103)

Abbreviations: bDMARDs: biological disease-modifying antirheumatic drugs; s.c.: subcutaneous injection; i.v.: intravenous Injection.

(CRP) and disease activity score 28-CRP, methotrexate and glucocorticoid (GC) use, body mass index, diabetes mellitus (DM), smoking, surgical procedure, and a history of same-site surgery and previous infection (bacterial infections requiring hospitalisation and musculoskeletal-related infections) [17, 20]. Risk factors for SSI and DWH were assessed using univariate and multivariate logistic regression analyses, with the factors used in PS matching serving as explanatory variables.

Statistical analysis

Discrimination of PS models was evaluated using the receiver operating characteristic area under the curve value. PS matching was performed using the nearest neighbour and one-to-one pair matching algorithm with a ± 0.1 calliper and no replacement. The absolute standardised difference (ASD) was used to measure covariate balance, with covariates having an ASD of <0.1 considered to be balanced. Chi-squared tests were applied to compare the bDMARDs user and nonuser groups. The Mc-Nemar test was performed to compare the incidences of SSI and DWH between the two groups in the matched cohort.

Risk factors for SSI and DWH were assessed using univariate and multivariate logistic regression analyses with the factors used in PS matching as explanatory variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the statistics. First, we performed univariate logistic regression analysis on the factors and selected those with $P < .20$ for further analysis. Subsequently, multivariate logistic regression analysis with the method of increasing variables of likelihood ratio was performed for the selected factors. P-values < .05 were considered as statistically significant. Statistical analysis was performed using SPSS 24.0 (IBM Japan, Ltd., Tokyo, Japan) and statistical software Easy R.

Results

Patient demographics and bDMARDs usage

From a total of 965 procedures, 414 (42.9%) involved procedures under disease control by bDMARDs. The bDMARDs user group comprised: 122 procedures (29.5%) treated with etanercept; 53 (12.8%) with golimumab; 39 (9.4%) with infliximab; 31 (7.5%) with adalimumab; 7 (1.7%) with certolizumab pegol; 83 (20.0%) with tocilizumab; 4 (1.0%) with sarilumab; and 75 (18.1%) with abatacept. The preoperative and postoperative discontinuation period of each bDMARDs is shown in Table 2.

Surgical procedures

Surgical procedures (number, %) were: hand and wrist surgeries (292, 30.3%), foot and ankle surgeries (275, 28.5%), TKA (95, 9.8%), THA (41, 4.2%), total elbow arthroplasty (100, 10.4%), total shoulder arthroplasty (21, 2.2%), synovectomy (28, 2.9%), spine surgeries (40, 4.1%), and others (73, 7.6%).

Surgical history and previous infections

Same-site surgery was observed in 197 cases (20.4%), including 51 revision resection arthroplasty of toe procedures, 35 revisions of artificial joint, 16 removals of hardware, 14 ulnar nerve releases, and 3 peri-prosthetic fractures. Regarding the history of previous infection, 109 cases (11.3%) had a history of bacterial infection requiring hospitalisation and 54 (5.6%) had a history of musculoskeletal-related infection. Bacterial infection requiring hospitalisation (number) were: bacterial pneumonia (44), appendicitis (41), pyelonephritis (7), cholecystitis (7), bacterial pneumonia and appendicitis (6), haemorrhoidal fistula (3), and Streptococcal infection (1). Musculoskeletal-related infections (number) were: lower extremity soft tissue infections (25), wound infection in other parts of the body (14), pyogenic arthritis (7), osteomyelitis (6), pyogenic tendonitis (1), and pyogenic bursitis (1).

Incidence of SSI and DWH

In 965 procedures, SSI and DWH were identified in 12 (1.2%) and 28 cases (2.9%), respectively (Supplementary Tables S1 and S2). Among patients with SSI, superficial and deep infections were identified in 7 and 5 cases, respectively. In the bDMARDs user group, there were 3 (0.7%) of SSI and 17 cases (4.1%) of DWH, while in the bDMARDs nonuser group, there were 9 (1.6%) of SSI and 11 cases (2.0%) of DWH, with no significant difference in incidence between the two groups. There was no significant difference in the incidence of SSI or DWH between bDMARDs (Supplementary Table S3).

Additionally, PS matching identified 315 patients in both groups (Table 3). Following matching, the incidence of SSI and DWH in the bDMARDs user group was 2 (0.6%) and 12 cases (3.8%), respectively, while the incidence of SSI and DWH in the bDMARDs nonuser group was 7 (2.2%) and 7 (2.2%) cases, with no significant difference between two groups.

Risk factor analysis

Univariate logistic regression analysis revealed no risk factors for SSI (Figure 1), and the incidence of SSI was low at 1.2%. Therefore, multivariate logistic regression analysis was not conducted for SSI. In contrast, univariate and multivariate logistic regression analyses revealed that age (OR, 0.962; 95% CI, 0.930–0.995; $P = .024$), DM (OR, 3.796; 95% CI, 1.107–13.019; $P = .034$), foot and ankle surgery (OR, 14.071; 95% CI, 5.201–38.066; $P < .001$), and a history of musculoskeletal-related infection (OR, 4.415; 95% CI, 1.455–13.401; $P = 0.009$) were associated with an increased risk of DWH (Figures 2 and 3). Preoperative use of bDMARDs was not an independent risk factor for SSI (OR, 0.440; 95% CI, 0.118–1.634; $P = .220$) or DWH (OR, 2.102; 95% CI, 0.974–4.537; $P = .058$).

Perioperative flare-up

A perioperative flare-up occurred in 21 patients (5.1%), including 8 with etanercept, 7 with tocilizumab, 3 with abatacept, 2 with infliximab, and 1 with certolizumab pegol (Supplementary Table S4). A flare-up of disease occurred in 11 cases before suture removal and 10 cases after suture removal. Among the 11 cases with a flare-up before suture removal, 6 cases restarted bDMARDs after achieving wound healing and prompt suture removal, while 4 cases were treated with increased oral GCs and 1 case with non-steroidal anti-inflammatory drugs (NSAIDs), and bDMARDs were subsequently restarted after suture removal. Among the 10 cases with a flare-up after suture removal, 6 cases only restarted bDMARDs, 2 cases were treated with NSAIDs,

Table 3. Patients' background before/after propensity score matching.

	Before PS matching			After PS matching			
	bDMARDs (+)	bDMARDs (−)	*P*-value	bDMARDs (+)	bDMARDs (−)	*P*-value	ASD
Cases, *n*	414	551		315	315		
Sex (male/female), *n*	28/386	46/505	0.360	24/291	23/292	0.879	0.012
Age, years	62.8 ± 12.2	66.2 ± 10.8	<0.001[a]	64.6 ± 10.8	64.0 ± 11.4	0.449	0.060
Disease duration, years	22.9 ± 10.2	21.9 ± 12.7	0.223	22.6 ± 9.8	22.0 ± 13.3	0.538	0.049
Preoperative Hb, g/dl	12.5 ± 1.4	12.2 ± 1.4	0.003[a]	12.4 ± 1.3	12.3 ± 1.5	0.597	0.042
Preoperative Alb, mg/dl	4.1 ± 0.4	3.9 ± 0.4	<0.001[a]	4.0 ± 0.4	4.0 ± 0.4	0.800	0.020
Preoperative CRP, mg/dl	0.4 ± 0.9	0.6 ± 0.9	<0.001[a]	0.5 ± 1.0	0.5 ± 0.7	0.582	0.044
Preoperative DAS28-CRP	2.6 ± 0.9	2.8 ± 0.9	<0.001[a]	2.6 ± 0.9	2.7± 0.9	0.578	0.044
Methotrexate use, *n* (%)	238 (57.5)	356 (64.6)	0.024[b]	195 (61.9)	194 (61.6)	0.935	0.007
Methotrexate, mg/week	3.9 ± 4.0	4.5 ± 3.9	0.013[a]	4.3 ± 4.1	4.3 ± 3.9	0.853	0.015
Glucocorticoid use, *n* (%)	199 (48.1)	311 (56.4)	0.010[b]	161 (51.1)	154 (48.9)	0.577	0.044
Glucocorticoid, mg/day	1.9 ± 2.5	2.3 ± 2.4	0.018[a]	2.0 ± 2.4	1.9 ± 2.3	0.476	0.057
Body mass index, kg/m^2	22.2 ± 3.3	21.5 ± 3.7	0.002[a]	21.8 ± 3.0	21.8 ± 3.8	0.887	0.011
Diabetes mellitus, *n* (%)	23 (5.6)	45 (8.2)	0.117	20 (6.3)	17 (5.4)	0.611	0.041
Smoking, *n* (%)	34 (8.2)	42 (7.6)	0.736	25 (7.9)	32 (10.2)	0.331	0.078
Same-site surgery, *n* (%)	89 (21.5)	108 (19.6)	0.469	63 (20.0)	58 (18.4)	0.613	0.040
Past infection							
Medical infection, *n* (%)	48 (11.6)	61 (11.1)	0.799	37 (11.7)	37 (11.7)	0.999	0.000
Musculoskeletal-related infection, *n* (%)	32 (7.7)	22 (4.0)	0.012	17 (5.4)	13 (4.1)	0.454	0.060
Surgical procedure							
Hand and wrist, *n* (%)	128 (30.9)	164 (29.8)	0.699	99 (31.4)	96 (30.5)	0.796	0.021
Foot and ankle, *n* (%)	124 (30.0)	151 (27.4)	0.386	86 (27.3)	89 (28.3)	0.790	0.021
TKA, *n* (%)	37 (8.9)	58 (10.5)	0.412	31 (9.8)	33 (10.5)	0.792	0.021
THA, *n* (%)	13 (3.1)	28 (5.1)	0.139	13 (4.1)	10 (3.2)	0.524	0.051
TEA, *n* (%)	42 (10.1)	58 (10.5)	0.847	33 (10.5)	35 (11.1)	0.797	0.020
TSA, *n* (%)	14 (3.4)	7 (1.3)	0.026	5 (1.6)	6 (1.9)	0.761	0.024
Synovectomy, *n* (%)	9 (2.2)	19 (3.4)	0.243	7 (2.2)	7 (2.2)	0.999	0.000
Spine, *n* (%)	14 (3.4)	26 (4.7)	0.302	12 (3.8)	11 (3.5)	0.832	0.017
Others, *n* (%)	33 (8.0)	40 (7.3)	0.679	29 (9.2)	28 (8.9)	0.890	0.011

Mean ± standard deviation (SD). Abbreviations: bDMARDs: biological disease-modifying antirheumatic drugs; Hb: hemoglobin; Alb: albumin; CRP: C-reactive protein; DAS: disease activity score; TKA: total knee arthroplasty; THA: total hip arthroplasty; TEA: total elbow arthroplasty; TSA: total shoulder arthroplasty.
[a]Unpaired *t*-test.
[b]Chi-squared test.

and 1 case had an injection of steroids in the knee joint. In these cases, symptoms resolved rapidly after treatment intervention. In one case, switching to a different bDMARDs was required after achieving wound healing with increased doses of GCs.

Discussion

The current retrospective study of 965 orthopaedic procedures in RA patients identified no risk factors for SSI, including the use of bDMARDs with perioperative discontinuation. Age, DM, foot and ankle surgery, and a history of musculoskeletal-related infections were risk factors for DWH. Even after matching patients' backgrounds, perioperative bDMARDs use was not different in the incidence of SSI or DWH.

In the present study, the present study used the 2013 CDC guidelines for the definition of SSI. The overall incidence of SSI was low, with 12 patients (1.2%) among all patients and 3 patients (0.7%) in the bDMARDs user group. No significant risk factors for SSI were identified, including bDMARDs use. A systematic review reported a prevalence of SSI with perioperative bDMARDs use ranging from 0 to 20.8% [40]. It has also been reported that the low frequency of SSIs in actual clinical practice leads to different opinions on infection risk with bDMARDs regardless of the presence or absence of a single case of SSI [27]. Therefore, the low incidence of SSI seen in the current study may be one reason why bDMARDs use and other factors were not risk factors for SSI.

Several reports have identified foot and ankle surgery as a potential risk for SSI in RA patients [8, 17, 20]. We have previously investigated the risk factors of SSI and DWH after 1036 elective orthopaedic procedures undertaken in RA patients, and reported foot and ankle surgery was significantly associated with an increased risk of SSI [17]. In the present study, we did not find it to be an independent risk factor. In foot and ankle surgery, the incidences of SSI decreased from 8 cases (5.1%) to 5 cases (1.8%), while the incidences of DWH increased from 3 cases (1.9%) to 23 cases (8.3%). The reasons why foot and ankle surgery were not a risk factor for SSI in the present study were considered to be that the incidence of SSI decreased and that the incidence of DWH occurred but was treated early enough to prevent the transition to SSI.

In the present study, a history of musculoskeletal-related infections among previous infections was identified as a risk factor for DWH. DWH was mainly associated with foot and ankle surgery, with three patients having a history of lower extremity soft tissue infection. A history of skin infection was reported as a state of enhanced susceptibility to SSI at baseline that is independent of traditional SSI risk factors and

adherence to current infection control practices [41]. A previous skin or SSI history was also reported as being particularly important as a risk factor for SSIs in elective procedures for patients with RA [20]. DWH can lead to prolonged treatment in some cases and can cause superficial SSI, refractory osteomyelitis, and deep infection of implants, particularly in foot and ankle surgery [40]. Therefore, early intervention is necessary to prevent progression from DWH to SSI. When restricted to foot and ankle surgeries, a possible synergistic effect on DWH may exist with a history of musculoskeletal-related infections and body mass index (Supplementary Table S5). The operative time did not affect the DWH in this study. No relationships were found between the identified risk factors, including age, diabetes, and a history of musculoskeletal-related infection for DWH and the use of bDMARDs in patients who underwent foot and ankle surgeries (data not shown).

The risk of DWH on perioperative bDMARDs use is also strongly debated. In the present study, DWH was identified in 28 cases (2.9%), including 17 cases (4.1%) in the use of bDMARDs. A systematic review reported that the DWH incidence ranges from 0% to 5.4% with perioperative bDMARDs use [40]. Our study and several previous studies [17, 26–29] have reported that bDMARDs use did not increase the risk of DWH, whereas tocilizumab use increased the risk factor for DWH [16]. Although bDMARDs did not result in a significant risk of DWH in the present study, they still occur with each agent and require caution in perioperative bDMARDs use. Conversely, another study reported that continued bDMARDs use in the perioperative period did not increase the risk of developing DWH [5]. Therefore, the impact of bDMARDs continuation or discontinuation in the perioperative period on DWH remains uncertain, requiring further research.

A perioperative flare-up occurred in 21 of 414 procedures (5.1%). van Duren *et al.* reported that disease flare-up occurred in 7.3% (3/41) of patients who continued bDMARDs in the perioperative period and in 25.7% (9/35) of those who discontinued them, with significantly decreased flare-up occurring when bDMARDs were continued (OR, 0.22; CI, 0.5–10.95; $P = .04$) [5]. Our institution has been using the protocol of discontinuing bDMARDs in the perioperative period [17], and our findings were comparable to those in the report of continuing bDMARDs [5].

There are several limitations in this study. First, our data were collected retrospectively using medical records of patients who had undergone procedures, which may have introduced selection and information bias in the selection of risk factors. Second, although the present study determined the definition of a flare-up, the definition varied between studies [5]. Third, the population of surgeries in our institution may be different from those in other institutions, which may be a bias in the analysis. Fourth, although there was no significant difference in the incidence of SSI or DWH among bDMARDs, the number of each bDMARDs differed within the study period, and the period of bDMARDs use has not

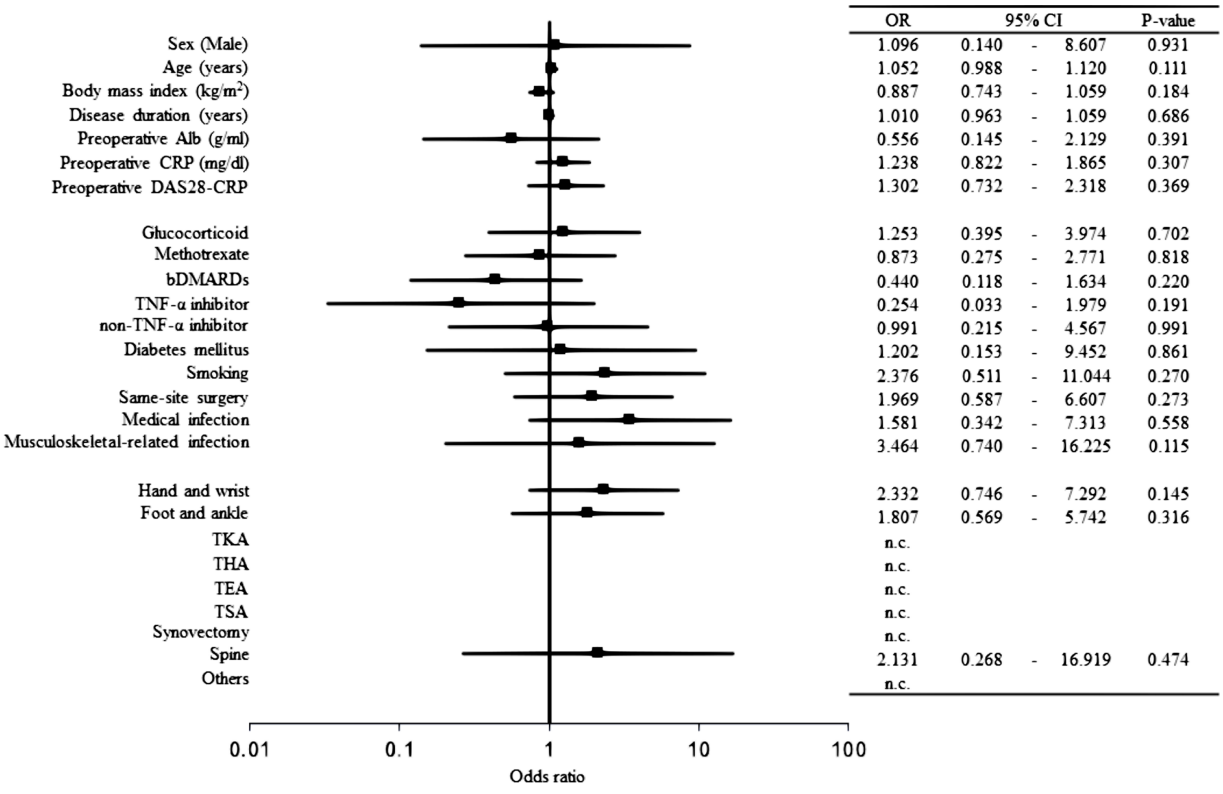

Figure 1. Results of univariate logistic regression analysis showing risk factors for SSI. Univariate logistic regression analysis revealed no risk factors for SSI. Abbreviations: Alb: albumin; CRP: C-reactive protein; DAS: disease activity score; bDMARDs: biological disease-modifying antirheumatic drugs; TNF: tumour necrosis factor; TKA: total knee arthroplasty; THA: total hip arthroplasty; TEA: total elbow arthroplasty; TSA: total shoulder arthroplasty; n.c.: not countable (No SSI case).

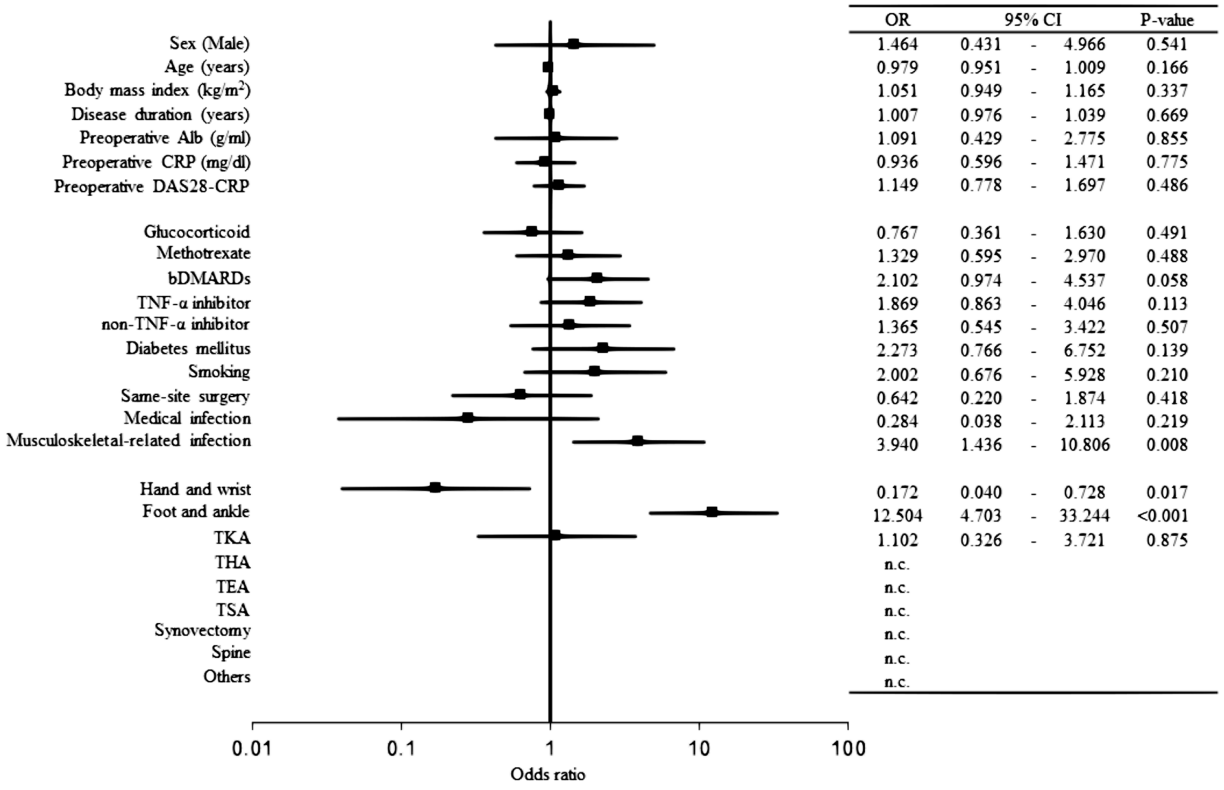

Figure 2. Results of univariate logistic regression analysis showing risk factors for DWH. Factors with $P < .20$ (age, bDMARDs, TNF-α inhibitors, Diabetes mellitus, Musculoskeletal-related infection, Hand and wrist, Foot and ankle) were selected for further analysis. n.c.: not countable (no DWH case). Abbreviations: Alb: albumin; CRP: C-reactive protein; DAS: disease activity score; bDMARDs: biological disease-modifying antirheumatic drugs; TNF: tumour necrosis factor; TKA: total knee arthroplasty; THA: total hip arthroplasty; TEA: total elbow arthroplasty; TSA: total shoulder arthroplasty; n.c.: not countable (No DWH case).

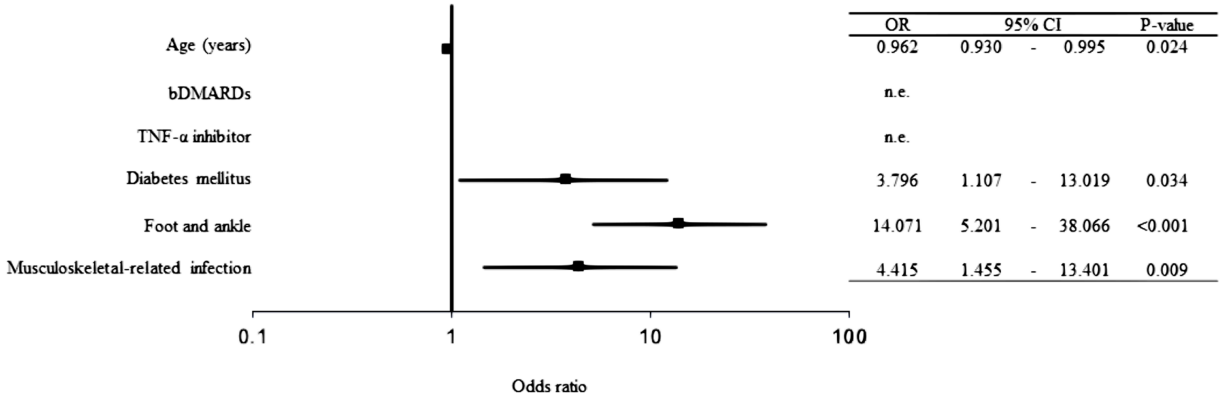

Figure 3. Results of multivariate logistic regression analysis using the variable increasing method of likelihood ratios showing for the selected factors. Univariate and multivariate logistic regression analyses revealed that age, diabetes mellitus, foot and ankle surgery, and a history of musculoskeletal-related infection were associated with an increased risk of DWH. Abbreviations: bDMARDs: biological disease-modifying antirheumatic drugs; TNF: tumour necrosis factor; n.e.: not entered (the factors is not significant).

been examined. Finally, we applied PS matching to investigate the impact of bDMARDs use on SSI and DWH occurrence. The population of bDMARDs users among patients who underwent orthopaedic surgeries increased during these 10 years in our institute, allowing PS matching. Given the challenge of detecting relatively rare perioperative complications such as SSI and DWH owing to limited case numbers, we believe that the PS matching method was appropriate for balancing patients' backgrounds. However, it should be noted that the matching process excluded ∼35% of cases and that some of the excluded cases may have influenced the results. Therefore, a large multicentre study adhering to the same bDMARDs discontinuation protocol and definitions of complications such as SSI and DWH could provide valuable insights.

In conclusion, the use of bDMARDs under our institution's discontinuation protocol was not a risk factor for postoperative SSI or DWH in RA patients, even with PS

matching backgrounds, and the prevalence of flare-up was relatively low. Regarding DWH, our results suggested that more attention should be paid to soft tissue manipulation when operating on patients with a history of musculoskeletal-related infections, including soft tissue infections of the lower extremities.

Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

Conflict of interest

K.N. has received scholarship grant from Chugai, and speaking fees or other remuneration from Eisai, Chugai, Asahi-Kasei, Daiichi-Sankyo, and Ayumi Pharmaceutical Corporation. All other authors have declared no conflicts of interest.

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References

[1] Smolen JS, Aletaha D, Barton A *et al*. Rheumatoid arthritis. *Nat Rev Dis Primers* 2018;**4**:18001.
[2] Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. *JAMA* 2018;**320**:1360–72.
[3] Izawa N, Hirose J, Fujii T *et al*. The utility of 25-question geriatric locomotive function scale for evaluating functional ability and disease activity in Japanese rheumatoid arthritis patients: a cross-sectional study using NinJa database. *Mod Rheumatol* 2019;**29**:328–34.
[4] Yamanaka H, Tanaka E, Nakajima A *et al*. A large observational cohort study of rheumatoid arthritis, IORRA: providing context for today's treatment options. *Mod Rheumatol* 2020;**30**:1–6.
[5] van Duren BH, Wignall A, Goodman S *et al*. The effect of perioperative biologic disease-modifying anti-rheumatic drugs on the risk of postoperative complications: surgical site infection, delayed wound healing, and disease flares following orthopaedic surgical procedures. *J Bone Joint Surg Am* 2022;**104**:1116–26.
[6] Goodman SM, Menon I, Christos PJ *et al*. Management of perioperative tumour necrosis factor α inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis. *Rheumatology* 2016;**55**:573–82.
[7] Goodman SM, Johnson B, Zhang M *et al*. Patients with rheumatoid arthritis have similar excellent outcomes after total knee replacement compared with patients with osteoarthritis. *J Rheumatol* 2016;**43**:46–53.
[8] Kubota A, Sekiguchi M, Nakamura T *et al*. Does use of a biologic agent increase the incidence of postoperative infection in surgery for rheumatoid arthritis after total joint arthroplasty? *Mod Rheumatol* 2014;**24**:430–3.
[9] Mabille C, Degboe Y, Constantin A *et al*. Infectious risk associated to orthopaedic surgery for rheumatoid arthritis patients treated by anti-TNF alpha. *Joint Bone Spine* 2017;**84**:441–5.
[10] Scherrer CB, Mannion AF, Kyburz D *et al*. Infection risk after orthopedic surgery in patients with inflammatory rheumatic diseases treated with immunosuppressive drugs. *Arthritis Care Res* 2013;**65**:2032–40.
[11] Giles JT, Bartlett SJ, Gelber AC *et al*. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. *Arthritis Rheum* 2006;**55**:333–7.
[12] Kawakami K, Ikari K, Kawamura K *et al*. Complications and features after joint surgery in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: perioperative interruption of tumor necrosis factor-alpha blockers decreases complications? *Rheumatology* 2010;**49**:341–7.
[13] Momohara S, Kawakami K, Iwamoto T *et al*. Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. *Mod Rheumatol* 2011;**21**:469–75.
[14] Suzuki M, Nishida K, Soen S *et al*. Risk of postoperative complications in rheumatoid arthritis relevant to treatment with biologic agents: a report from the Committee on Arthritis of the Japanese Orthopaedic Association. *J Orthop Sci* 2011;**16**:778–84.
[15] Ito H, Murata K, Sobue Y *et al*. Comprehensive risk analysis of postoperative complications in patients with rheumatoid arthritis for the 2020 update of the Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis. *Mod Rheumatol* 2022;**32**:296–306.
[16] Okita S, Ishikawa H, Abe A *et al*. Risk factors of postoperative delayed wound healing in patients with rheumatoid arthritis treated with a biological agent. *Mod Rheumatol* 2021;**31**:587–92.
[17] Kadota Y, Nishida K, Hashizume K *et al*. Risk factors for surgical site infection and delayed wound healing after orthopedic surgery in rheumatoid arthritis patients. *Mod Rheumatol* 2016;**26**:68–74.
[18] Clay M, Mazouyes A, Gilson M *et al*. Risk of postoperative infections and the discontinuation of TNF inhibitors in patients with rheumatoid arthritis: a meta-analysis. *Joint Bone Spine* 2016;**83**:701–5.
[19] Berthold E, Geborek P, Gülfe A. Continuation of TNF blockade in patients with inflammatory rheumatic disease. An observational study on surgical site infections in 1,596 elective orthopedic and hand surgery procedures. *Acta Orthop* 2013;**84**:495–501.
[20] den Broeder AA, Creemers MC, Fransen J *et al*. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. *J Rheumatol* 2007;**34**:689–95.
[21] Ruyssen-Witrand A, Gossec L, Salliot C *et al*. Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers. *Clin Exp Rheumatol* 2007;**25**:430–6.
[22] Bongartz T, Halligan CS, Osmon DR *et al*. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. *Arthritis Rheum* 2008;**59**:1713–20.
[23] Talwalkar SC, Grennan DM, Gray J *et al*. Tumour necrosis factor alpha antagonists and early postoperative complications in patients with inflammatory joint disease undergoing elective orthopaedic surgery. *Ann Rheum Dis* 2005;**64**:650–1.
[24] Wendling D, Balblanc JC, Brousse A *et al*. Surgery in patients receiving anti-tumour necrosis factor alpha treatment in rheumatoid arthritis: an observational study on 50 surgical procedures. *Ann Rheum Dis* 2005;**64**:1378–9.
[25] Somayaji R, Barnabe C, Martin L. Risk factors for infection following total joint arthroplasty in rheumatoid arthritis. *Open Rheumatol J* 2013;**29**:119–24.
[26] Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. *Foot Ankle Int* 2004;**25**:331–5.
[27] Tada M, Inui K, Sugioka Y *et al*. Delayed wound healing and postoperative surgical site infections in patients with rheumatoid arthritis treated with or without biological disease-modifying antirheumatic drugs. *Clin Rheumatol* 2016;**35**:1475–81.

[28] Ito H, Tsuji S, Nakayama M *et al*. Does abatacept increase postoperative adverse events in rheumatoid arthritis compared with conventional synthetic disease-modifying drugs? *J Rheumatol* 2020;**47**:502–9.
[29] Hirano Y, Kojima T, Kanayama Y *et al*. Influences of anti-tumour necrosis factor agents on postoperative recovery in patients with rheumatoid arthritis. *Clin Rheumatol* 2010;**29**:495–500.
[30] Gilson M, Gossec L, Mariette X *et al*. Risk factors for total joint arthroplasty infection in patients receiving tumor necrosis factor α-blockers: a case-control study. *Arthritis Res Ther* 2010;**12**: R145.
[31] Holroyd CR, Seth R, Bukhari M *et al*. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. *Rheumatology* 2019;**58**:e3–42.
[32] Goodman SM, Springer B, Guyatt G *et al*. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. *Arthritis Rheumatol* 2017;**69**:1538–51.
[33] Goodman SM, Springer BD, Chen AF *et al*. 2022 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. *Arthritis Care Res* 2022;**74**:1399–408.
[34] Krüger K, Albrecht K, Rehart S *et al*. Recommendations of the German Society for Rheumatology on the perioperative approach under therapy with DMARDs and biologicals in inflammatory rheumatic diseases. *Z Rheumatol* 2014;**73**:77–84.
[35] Albrecht K, Poddubnyy D, Leipe J *et al*. Perioperative management of patients with inflammatory rheumatic diseases: updated recommendations of the German Society for Rheumatology. *Z Rheumatol* 2023;**82**:1–11.
[36] Arnett FC, Edworthy SM, Bloch DA *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
[37] Committee on Clinical Practice Guideline on the Prevention of Surgical Site Infections in Bone and Joint. *The Japanese Orthopaedic Association (JOA) Clinical Practice Guideline on the Prevention of Surgical Site Infections in Bone and Joint*. Japan: Nankodo, 2015.
[38] National Healthcare Safety Network. *Surgical Site Infection Surveillance (SSI)*. Center for Disease Control and Prevention, 2013. https://apic.org/Resource_/TinyMceFileManager/Academy/ASC_101_resources/Surveillance_NHSN/ASCA_NHSN_SSI_Surveillance_2013.pdf. accessed on May 6, 2024.
[39] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res* 2011;**46**:399–424.
[40] Ito H, Kojima M, Nishida K *et al*. Postoperative complications in patients with rheumatoid arthritis using a biological agent - a systematic review and meta-analysis. *Mod Rheumatol* 2015;**25**:672–8.
[41] Faraday N, Rock P, Lin EE *et al*. Past history of skin infection and risk of surgical site infection after elective surgery. *Ann Surg* 2013;**257**:150–4.

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