# Does Abatacept Increase Postoperative Adverse Events in Rheumatoid Arthritis Compared with Conventional Synthetic Disease-modifying Drugs?

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***ABSTRACT.*** ***Objective.*** To investigate whether abatacept (ABA) causes more adverse events (AE) than conventional synthetic disease-modifying antirheumatic drugs (csDMARD) after orthopedic surgery in patients with rheumatoid arthritis (RA).

***Methods.*** A retrospective multicenter nested case–control study was performed in 18 institutions. Patients receiving ABA (ABA group) were matched individually with patients receiving csDMARD and/or steroids (control group). Postoperative AE included surgical site infection, delayed wound healing, deep vein thrombosis or pulmonary embolism, flare, and death. The incidence rates of the AE in both groups were compared with the Mantel-Haenszel test. Risk factors for AE were analyzed by logistic regression model.

***Results.*** A total of 3358 cases were collected. After inclusion and exclusion, 2651 patients were selected for matching, and 194 patients in 97 pairs were chosen for subsequent comparative analyses between the ABA and control groups. No between-group differences were detected in the incidence rates of each AE or in the incidence rates of total AE (control vs ABA: 15.5% vs 20.7% in total, 5.2% vs 3.1% in death).

***Conclusion.*** Compared with csDMARD and/or steroids without ABA, adding ABA to the treatment does not appear to increase the incidence rates of postoperative AE in patients with RA undergoing orthopedic surgery. Large cohort studies should be performed to add evidence for the perioperative safety profile of ABA. (J Rheumatol First Release November 1 2019; doi:10.3899/jrheum.181100)

*Key Indexing Terms:*

| | | |
|---|---|---|
| RHEUMATOID ARTHRITIS | ORTHOPEDIC SURGERY | INFECTIONS |
| ABATACEPT | PERIOPERATIVE COMPLICATIONS | DEATH |

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Advances in molecular biology and basic and clinical research in recent years have produced several new classes of drugs, in particular, biological disease-modifying antirheumatic drugs (bDMARD) and targeted synthetic DMARD (tsDMARD), which can reduce disease activity, joint destruction, functional impairment, and even mortality in patients with rheumatoid arthritis (RA)[1,2,3,4,5,6,7]. One desirable result of these new drugs is the probable trend toward decreasing use of surgery for patients with RA, especially joint replacement[8,9,10,11,12]. However, some patients must still undergo orthopedic surgical interventions to alleviate joint discomfort and to recover functional ability[13,14,15].

The perioperative AE with bDMARD have been surgical site infection (SSI), delayed wound healing, disease activity flare, and deep venous thrombosis/pulmonary embolism (DVT/PE)[16,17,18,19,20]. SSI is the most common AE in association with bDMARD. However, given the relative rarity of SSI, it is difficult to obtain a sufficient number of cases to achieve statistical significance. Goodman, *et al* reported in a systematic review that patients treated with a tumor necrosis factor-α (anti-TNF-α) inhibitor tended to have a higher risk of developing SSI compared with those not treated with one, although the trend was not statistically significant[17]. There is far less data on the perioperative safety of the other 3 types of bDMARD available [antiinterleukin 6 (IL-6) agents and B cell and T cell function modifiers] than the anti-TNF-α inhibitors, although these non-TNF agents are used increasingly in clinical practice[21,22]. Further, postoperative AE other than SSI have not been examined sufficiently. In a systematic review and metaanalysis, we reported that bDMARD, including tocilizumab (TCZ), slightly but significantly increased the risk of SSI compared with conventional synthetic DMARD (csDMARD), but not the risk of delayed wound healing[16]. However, fewer patients were taking TCZ than TNF-α inhibitors.

Abatacept (ABA) was developed as a fusion protein of T-lymphocyte–associated antigen 4 and immunoglobulin and suppresses T cell activation by binding to CD80/86 costimulatory antigens, thereby blocking interaction with CD28. ABA is clinically used as the only T cell modifier available for RA treatment and has shown efficacy similar to TNF inhibitors and a safer profile, especially a lower infection ratio in registry data[23,24]. We previously reported that, in orthopedic operations, ABA has a similar safety profile to TNF-α inhibitors, but the study included only 8 patients without any comparison arm[25]. Using registry data, Latourte, *et al* published the results of perioperative complications of orthopedic and other types of surgery in patients treated with ABA[26]. However, they did not compare the complication rates with those in patients who received csDMARD. Therefore, it remains unknown whether ABA is associated with more postoperative complications than csDMARD. Moreover, guidelines by the American College of Rheumatology (ACR)/American Association of Hip and Knee Surgeons regarding rheumatic disease management at the time of hip or knee arthroplasty recommend withholding all current biologic agents including ABA prior to surgery, but the recommendation is only for patients undergoing elective total hip and knee arthroplasty, with limited body of evidence[27].

The aims of our study were to investigate whether ABA is associated with more AE after orthopedic surgery compared with csDMARD, and if so, to identify significant risk factors for those events. Because a prospective randomized controlled study would not be allowed from an ethical and practical viewpoint, we conducted a retrospective multicenter nested case–control study to allow for direct comparison between ABA and csDMARD. We collected only cases involving orthopedic surgery because this is different from other operations such as abdominal surgery regarding the seriousness of SSI and higher rate of DVT/PE, as shown in previous studies[20,26].

## MATERIALS AND METHODS

*Study design and setting*. Our retrospective multicenter nested case–control study was designed in accordance with the Helsinki Declaration and was approved by the ethics committee of Kyoto University Graduate School and Faculty of Medicine (No. R0053) and by that of each participating institution.

*Patients*. The inclusion criteria were the (1) fulfillment of the ACR/European League Against Rheumatism classification criteria of 1987 or 2010 for RA, and (2) undergoing an orthopedic operation between April 2011 and March 2014. The exclusion criteria were (1) age < 18 years, and (2) < 1 year of followup after the operation. Fulfillment of the criteria for RA was confirmed by registered rheumatologists in each institution. Patients who met the inclusion criteria and did not fulfill the exclusion criteria were selected in 18 medical institutions, all of which were authorized and registered as training institutions by the Japan College of Rheumatology (JCR). The bDMARD were infliximab, etanercept, adalimumab, TCZ, and ABA, and

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all were clinically available during the study period. Rituximab and anakinra were not approved for RA in Japan at the time of our study.

*Matching criteria*. The matching criteria had been decided before the start of the study based on reported risk factors[18,19,28,29,30,31] and included the following: sex, disease activity categorized by the rheumatologist (remission, low, moderate, or high activity), use or non-use of oral steroids, operation site (5 sites: spine, shoulder or elbow, hand or wrist, hip or knee, or ankle or foot), type of operation (spinal, synovectomy, arthroplasty with implants, arthroplasty without implants, arthrodesis, soft tissue procedures including tendon surgeries, and others), and the institution where the operation was performed. Among the patients included, those who had been treated with ABA for > 3 months with the last injection within 3 months before the surgery, and without other types of bDMARD or tsDMARD > 6 months before the surgery, were enrolled in the ABA group, irrespective of the concomitant use of csDMARD and/or steroids. Each of these patients was matched individually using the computer software R with a patient who received the same type of operation on the same body part in the same institution and who was treated with csDMARD and/or steroids without the use of any bDMARD or tsDMARD within 6 months before the operation as a control group.

*Clinical information and evaluation*. Evaluators were registered before the start of the study, and the evaluation methods were confirmed through face-to-face meetings before the start of the study. All evaluators were rheumatologists approved by the JCR. The clinical information included those for matching criteria, type of medical treatment (use of steroids, csDMARD, ABA, and/or other types of bDMARD or tsDMARD at the time of surgery), and treatment history (starting, switching, and/or stopping bDMARD or tsDMARD within 6 mos before the operation). This information was collected at each institution and then sent to the study center at Kyoto University. After checking the appropriateness of the collected data, all information was sent to an external analytical department (SIP Corp.). Statistical analysis was performed by the analytical department independent of the study researchers.

In the 2 patient groups, information on each patient was sent back to each institution, and the following information was collected as known risk factors for postoperative AE and sent again to the study center: age; sex; duration of RA; followup period after the operation; history of smoking; presence of diabetes mellitus and/or chronic lung disease; history of serious infection in any body part; plasma C-reactive protein (CRP) and serum matrix metalloprotease-3 concentrations at the time of the operation; positivity for rheumatoid factor and anticitrullinated protein antibodies; disease activity using the 28-joint Disease Activity Score-CRP at the time of the operation; treatment type and history for RA as described above; use, dose, and administration route (subcutaneous injection or intravenous infusion) of ABA at the time of surgery; discontinuation of ABA use before the operation; operation site (5 body parts); and type of operation (7 categories). We specifically collected data about the occurrence of SSI, delayed wound healing, DVT or PE, flare of disease activity, other serious complications directly related to the operation such as postoperative nosocomical infection, and death, whether related or not to the operation.

*Verification of AE*. SSI was diagnosed by the surgeon according to the Centers for Disease Control and Prevention definition[32]. Delayed wound healing was judged by the surgeon as an insufficiently healed wound beyond 3 weeks after the operation[19,33]. Flare of disease activity was judged by an attending rheumatologist who agreed with the patient's report of worsening of the disease status associated with apparent aggravation of joint symptoms and CRP[19,34]. DVT/PE was diagnosed by a cardiologist within 1 month after the operation in the respective institute[34]. Other serious AE (SAE) directly related to the operation were judged by an attending rheumatologist. Death, whether related or not to the operation, was judged by an attending rheumatologist and the surgeon.

*Statistical analyses*. P values of 0.05 or less were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Japan), a graphical user interface for R (The R Foundation for Statistical Computing)[35]. Categorical variables are expressed as n (%) and are compared with the Mantel-Haenszel test. Continuous variables are expressed as mean ± SD and are compared with paired t test. To compare the percentages for AE for within-group analyses, we used Fisher's exact test. The OR with 95% CI for SAE are calculated by logistic regression models in total subjects or in ABA subjects, respectively.

The sample size was calculated before the start of the study by an independent contributor (Moritoshi Furu). Briefly, the required number of patients for each arm was calculated as 95 and 104 using Fisher's exact probability test with an $\alpha$ error of 0.08, an effect size of interest of 0.8, and significance level of 5% based on 2 previous similar reports of SSI[34,36]. During the study period from April 2011 to March 2014, data were collected for 11 patients who met the inclusion criteria and did not meet the exclusion criteria in the ABA group at the study center (Kyoto University Hospital). Matching of these 11 patients produced 9 nine ABA–control pairs. Assuming that orthopedic surgery was performed on an average of 10 patients in the ABA group in each participating institution, we calculated that the ABA group would consist of 180 patients, and that 80% of matched pairs would be possible with 20% of patients who would lack sufficient data. Therefore, we decided to include 100 pairs for comparative analyses.

If a patient had undergone more than 1 operation, each operation was planned to be counted separately. However, we found that no patients underwent more than 1 operation.

## RESULTS

A total of 3358 operations were included, and 2651 met the inclusion criteria and did not meet the exclusion criteria (Figure 1). In total, 147 of the patients who underwent orthopedic surgery had received ABA within 3 months before the operation. The analytical department selected 102 pairs (204 patients), matched using a statistical program. Additional detailed information was then collected from each institution. Five pairs were excluded because of insufficient data for either the ABA or the control patient, and 97 pairs (194 patients) were included in the statistical analyses.

Demographic data did not differ between the 2651 patients who met the inclusion criteria and did not meet the exclusion criteria and the 194 patients included in the comparative analyses (data not shown). Detailed demographic data did not significantly differ between the ABA and control groups (Table 1, Table 2). The incidence rates for each AE did not differ significantly between the ABA and control groups (Table 3). A late deep infection occurred in a patient who received arthroplasty with an implant in the control group. Within the ABA group, the incidence rates did not differ significantly between shorter and longer preoperative discontinuation periods of ABA (< 6 or ≥ 7 days, or < 14 or ≥ 14 days) or administration route (intravenous infusion or subcutaneous injection; data not shown). Further, a subgroup analysis with matched cases only with hip and knee arthroplasties showed that the incidence rates did not differ significantly between ABA and control groups, either (Appendix 2).

As Table 3 shows, the number of cases of postoperative death within a year was unexpectedly high. Therefore, we next analyzed whether any background data were associated with an increased OR of this particular serious complication in each group and found that no significant risk factor was

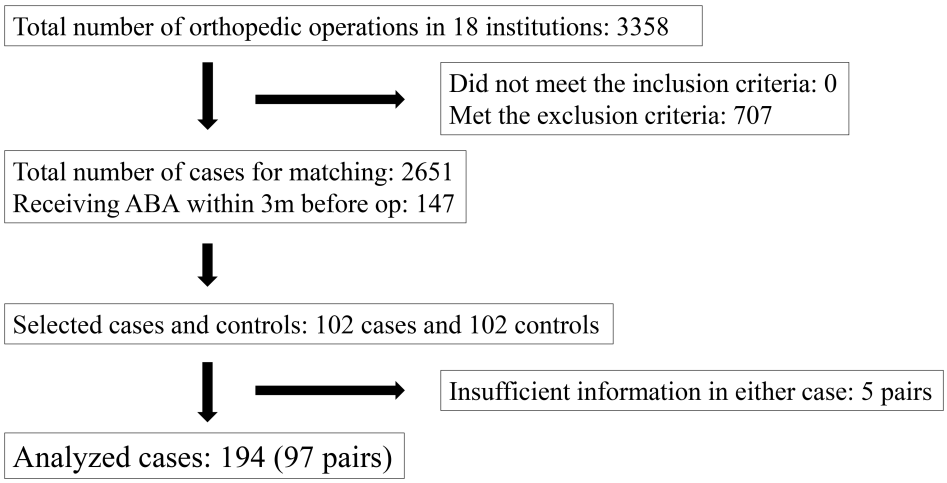


*Figure 1*. Patient selection for analysis. ABA: abatacept.

associated with this complication in this cohort (data not shown). We further analyzed whether corticosteroid dosage affected any risk of postoperative death within a year, but univariate analysis shows the dosage did not affect the rate of postoperative death in our study (OR 1.0, 95% CI 0.82–1.13).

*Table 1*. Demographic data of matching criteria of control and ABA groups.

| Characteristics | Control, n = 97 | ABA, n = 97 | p |
|---|---|---|---|
| Female | 85 (87.6) | 83 (85.6) | 0.48 |
| Disease activity | | | 0.056 |
| Remission | 1 (1.0) | 1 (1.0) | |
| Low | 24 (24.7) | 22 (22.7) | |
| Moderate | 58 (59.8) | 55 (56.7) | |
| High | 14 (14.4) | 19 (19.6) | |
| Oral steroid use | 67/96 (69.8) | 71/96 (74.0) | 0.42 |
| Operation site and method | | | 0.33 |
| Spine | | | |
| Spinal surgery | 1 (1.0) | 2 (2.1) | |
| Hip and knee | | | |
| Arthroplasty with implant | 43 (44.3) | 37 (38.1) | |
| Synovectomy | 3 (3.1) | 2 (2.1) | |
| Others | 0 (0) | 2 (2.1) | |
| Foot and ankle | | | |
| Arthroplasty with implant | 4 (4.1) | 4 (4.1) | |
| Arthrodesis | 1 (1.0) | 0 (0) | |
| Arthroplasty without implant | 4 (4.1) | 5 (5.2) | |
| Synovectomy | 0 (0) | 1 (1.0) | |
| Soft tissue procedure | 0 (0) | 1 (1.0) | |
| Others | 6 (6.2) | 3 (3.1) | |
| Shoulder and elbow | | | |
| Arthroplasty with implant | 5 (5.2) | 7 (7.2) | |
| Arthroplasty without implant | 0 (0) | 2 (2.1) | |
| Synovectomy | 0 (0) | 4 (4.1) | |
| Others | 3 (3.1) | 0 (0) | |
| Wrist and fingers | | | |
| Arthroplasty with implant | 5 (5.2) | 7 (7.2) | |
| Arthrodesis | 5 (5.2) | 8 (8.2) | |
| Arthroplasty without implant | 10 (10.3) | 3 (3.1) | |
| Synovectomy | 2 (2.1) | 3 (3.1) | |
| Soft tissue procedure | 3 (3.1) | 2 (2.1) | |
| Others | 2 (2.1) | 2 (2.1) | |

Data are expressed as n (%) and are compared with Mantel-Haenszel test. ABA: abatacept.

*Table 2*. Demographic data of control and ABA groups.

| Variables | Control, n = 97 | ABA, n = 97 | p |
|---|---|---|---|
| Age, yrs | 64.9 ± 9.7 | 64.1 ± 10.8 | 0.55 |
| Disease duration, yrs | 17.0 ± 10.1 | 17.9 ± 10.6 | 0.48 |
| RF positivity | 70/84 (83.3) | 71/84 (84.5) | 1.00 |
| ACPA positivity | 41/45 (91.1) | 41/45 (91.1) | 1.00 |
| MTX use | 64 (66.0) | 54 (55.7) | 0.19 |
| MTX dose, mg/week | 7.4 ± 3.9 | 6.5 ± 3.9 | 0.45 |
| Other csDMARD use | 40/96 (41.7) | 43/96 (44.8) | 0.74 |
| Steroid dose of steroid user, mg/day | 4.2 ± 2.8 | 4.4 ± 2.7 | 0.54 |
| ABA dose, mg | 0 | 502.8 ± 133.8 | 0.54 |
| CRP, mg/l | 13 ± 20 | 18 ± 67 | 0.40 |
| MMP-3, ng/ml | 158.7 ± 121.5 | 146.4 ± 122.3 | 0.59 |
| DAS28-CRP | 3.4 ± 0.9 | 3.4 ± 1.0 | 0.22 |
| Past history of smoking | | | 0.64 |
| Past smoker | 6/92 (6.5) | 6/92 (6.5) | |
| Current smoker | 9/92 (9.8) | 13/92 (14.1) | |
| DM | 8 (8.2) | 11 (11.3) | 0.55 |
| Chronic lung disease | 10/94 (10.6) | 15/94 (16.0) | 0.36 |
| Past history of severe infection | 11/95 (11.6) | 7/95 (7.4) | 0.34 |

Categorical variables are expressed as n (%) and are compared with Mantel-Haenszel test. Continuous variables are expressed as mean ± SD and are compared with paired t test. ABA: abatacept; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; MTX: methotrexate; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; CRP: C-reactive protein; MMP-3: matrix metalloprotease-3; DAS28-CRP: 28-joint count Disease Activity Score-CRP; DM: diabetes mellitus.

*Table 3*. Postoperative complication rates of control and ABA groups.

| Variables | Control, n = 97 | ABA, n = 97 | OR (95% CI) | p |
|---|---|---|---|---|
| SSI | 1 (1.0) | 0 (0) | 0.33 (0.01–8.20) | 1.00 |
| Delayed wound healing | 2 (2.1) | 3 (3.1) | 1.52 (0.25–9.28) | 1.00 |
| DVT/PE | 4/88 (4.5) | 7/88 (8.0) | 1.81 (0.51–6.44) | 0.55 |
| Flare | 2/67 (3.0) | 4/67 (6.0) | 2.06 (0.36–11.67) | 0.68 |
| Death | 5 (5.2) | 3 (3.1) | 0.59 (0.14–2.53) | 0.72 |
| Other serious adverse events | 0 (0) | 0 (0) | — | 1.00 |

Data are n (%) and are compared with Mantel-Haenzel test. ABA: abatacept; SSI: surgical site infection; DVT/PE: deep venous thrombosis/pulmonary embolism.

## DISCUSSION

Compared with other bDMARD used in clinical treatment of RA, the T cell modulator, ABA, is associated with a slightly lower rate of AE such as infections compared with other bDMARD[23,24]. We found no differences in the incidence rates of the AE after the orthopedic surgeries, including SSI, between the patients treated with ABA or csDMARD for RA, even though they were matched on background characteristics.

Our study is the first, to our knowledge, to report on the incidences of AE after orthopedic surgeries, including SSI, delayed wound healing, DVT/PE, flare, and death, in patients treated with ABA and csDMARD and/or steroids matched according to background characteristics. The risk ratios of each SAE did not differ significantly between 2 groups. These data suggest that, compared with csDMARD, adding ABA to the medications may not increase the incidence rates of postoperative AE in patients with RA who undergo orthopedic surgery, even though the sample size may not be sufficient. Further, within the ABA group, the risk ratios did not differ between any 2 groups based on discontinuation period before the operation or according to the administration route.

To determine whether ABA increases the risk of postoperative AE compared with csDMARD, a randomized controlled study would be desirable. However, there are numerous hurdles to conducting such a study. For example, operative interventions for RA are characteristically diverse regarding the operation site and procedure, and patients' characteristics such as age and sex, duration of symptoms, disease activity, and history of medication. The incidence rates of AE can be affected by the patient's status and the type of institution; for example, the volume of operations in the institution and the surgeon's experience performing the operation can affect the risk of AE. In addition, a randomized controlled study would take a long time, and the medical situation would inevitably change over time. Another possibility is to conduct an extremely large cohort study for the

purpose of excluding potential bias, but it would be impractical because the surgical complications such as SSI are relatively rare, and one would not find a sufficient number of cases during the study period. To overcome this, a nested case–control study like ours is one possible and potent solution. We selected the term of 2011 to 2014 because 3 types of bDMARD were already available. Although golimumab and certolizumab pegol had become available during this period, these are classified as TNF-α inhibitors and would not have substantially affected the clinical practice in terms of operative intervention for RA. Another potent DMARD, tsDMARD, had also become available during this period, but we experienced very few operations in patients with RA who received this medication in this period.

SSI is one of the common and serious AE after an orthopedic operation. Most of the studies on the effects of DMARD on postoperative AE focused on SSI. The results differ between studies, probably because of the numbers of patients, study period duration, and medical situations at the time of the study. However, large studies and metaanalyses have shown that steroid and TNF-α inhibitors increase the risk of SSI[16,17,18,27,28,29,30,31,33,34,37]. By contrast, to our knowledge, our study shows for the first time that adding ABA does not increase the risk of SSI compared with csDMARD alone in patients matched according to demographics. The number of patients and operations in our study may not be sufficient to draw a definite conclusion, but the matched nested case–control design applied in our study is a reliable enough and practically oriented study design. Although the data in our study show very few occurrences of this complication compared with previous reports with unknown reasons[34,36], our data suggest that ABA may not increase the rate of SSI even for immunocompromised patients who are prone to infection. However, this notion remains to be investigated in future.

Other postoperative AE such as delayed wound healing, DVT/PE, RA flare, and death have not been fully investigated despite the seriousness of such events. For example, delayed wound healing can easily lead to SSI. Even if it does not cause SSI, it is more likely to cause joint contracture and/or residual pain. Flare of disease activity can also contribute to further joint destruction and functional impairment. Goodman, *et al* very recently reported that flares are frequent in patients with RA undergoing arthroplasty[38]. DVT/PE is one of the most serious postoperative AE, and anticoagulant therapy has become a frequently used countermeasure for patients undergoing orthopedic surgery as well as other procedures. Although death is the most serious postoperative AE, the ratio has scarcely been reported after orthopedic surgery until recently. Our study presents accurate ratios of these events in patients with RA who took current medications and underwent orthopedic surgery. The data may provide a useful reference for studying operative AE in the future.

An unexpected finding of our study was the high ratio of postoperative death within a year after orthopedic operation. Although the surgeons and attending rheumatologist reported all of the deaths as unrelated to the operation itself, the ratio should be carefully considered. Unfortunately, what directly induced the deaths was unknown because of the lack of detailed information on each patient in our study. The reasons may be the seriousness of the patient's medical condition in this particular group or the matching process unexpectedly selecting serious patients. Further, RA itself has been reported to be associated with a higher rate of mortality after orthopedic operations. Cordtz, *et al* recently reported that patients with RA following total hip or knee arthroplasty had an increased risk of death compared with patients with osteoarthritis[18]. Exact ratios and causes of death remain uncertain, so this issue should be continuously investigated in the future.

Our study has several limitations. First, it was a retrospective, non-blinded study that fundamentally contains scientific bias in the comparison of the 2 groups. Moreover, the design was a nested case-control study, and the precision and power might be lower than in a cohort study. Also, our study design inevitably contains several limitations such as selection bias and observation bias. However, the control subjects receiving csDMARD and/or steroids were matched based on reported risk factors before the start of the study, and were selected automatically using the R. Second, the sample number limits the ability to draw firm conclusions because of a lack of statistical power, although we included as many patients as possible from major orthopedic institutes nationwide. To overcome this, a worldwide, multicenter study might have to be scheduled, but it might not be feasible because of many practical hurdles. Every center does things differently, such as performing of the operation, stopping medication, and collecting data. Third, evaluation of patients and AE may have varied between evaluators at the institutions, which may have introduced bias into the incidence ratios and risk factors for AE, although the evaluators were registered before the study, and we tried to keep the evaluation methods consistent through several face-to-face meetings during the study period. Fourth, our study is not a comparative study between ABA and csDMARD and/or steroids. We did not compare ABA alone with csDMARD and/or steroids. The patients in the ABA group received csDMARD and/or steroids. Last, what caused the deaths reported here was not fully investigated, although each evaluator reported that the cause was not directly related to the operation. Further analyses are required on this matter.

Compared with csDMARD and/or steroids without ABA, adding ABA may not increase the incidence rates of postoperative AE in patients with RA who undergo orthopedic surgery. Large cohort studies should be performed to add evidence for the perioperative safety profile of ABA.

## APPENDIX 1.

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**APPENDIX 2.** Postoperative complication rates of control and ABA groups in matched hip and knee arthroplasty cases.

| Variables | Control, n = 51 | ABA, n = 51 | p |
|---|---|---|---|
| SSI | 1 (2.0) | 0 (0) | 1.00 |
| Delayed wound healing | 1 (2.0) | 2 (3.9) | 1.00 |
| DVT/PE | 2 (3.9) | 3 (5.9) | 1.00 |
| Flare | 4/50 (8.0) | 7/50 (14.0) | 0.55 |
| Death | 2 (3.9) | 1 (2.0) | 1.00 |
| Other serious adverse events | 0 (0) | 0 (0) | 1.00 |

Data are expressed as n (%) and compared with Mantel-Haenszel test. ABA: abatacept; SSI: surgical site infection; DVT/PE: deep venous thrombosis/pulmonary embolism.