Full length manuscript

Does abatacept increase postoperative adverse events in rheumatoid arthritis compared with conventional synthetic disease-modifying drugs?

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Funding
This work was supported by a research grant from Bristol-Myers Squibb and ONO Pharmaceutical Co., Ltd. (No.IM101-552).

Competing interests
H.I. has received a research grant and/or speaker fee from Bristol-Myers Squibb, Astellas, Asahi-Kasei and Eli Lilly. K.N. has received scholarship donation from Eisai, Chugai, Ono and Mitsubishi-Tanabe, and speaking fees or other remuneration from Pfizer, Mitsubishi-Tanabe, Chugai and Astellas. T.K. has received a research grant from Chugai, scholarship donation from Eisai, Daiichi-Sankyo, Novartis, Nihobkayaku and speaking fees from Takeda, Chugai, Diichi-Sankyo and Astellas. T.Mo. has received a research grant and/or speaker fee from Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly and Janssen. I. M. has received speaking fees from Bristol-Myers, Mitsubishi-Tanabe,
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AbbVie, Eisai, Astellas and Ono. T.Ma. has received speaker honoraria from Pfizer, Nichi-Iko, Astellas, Meiji Seika, Ltd., Bristol-Myers Squibb, AbbVie, Janssen, Chugai, Eisai, and Ayumi. The sponsors were not involved in the study design; in the collection, analysis, interpretation of data; in the writing of this manuscript; or in the decision to submit the article for publication. The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

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Short running head: abatacept and surgical complications

Keywords: rheumatoid arthritis, orthopedic surgery, infections, abatacept, perioperative complications, death
ABSTRACT

Objectives The aim of this study was to investigate whether abatacept (ABT) causes more adverse events than conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) after orthopedic surgery in patients with rheumatoid arthritis (RA).

Methods A retrospective multicenter nested case–control study was performed in 18 institutions. Patients receiving ABT (ABT group) were matched individually with patients receiving csDMARDs and/or steroids (control group). Postoperative adverse events included surgical site infection, delayed wound healing, deep vein thrombosis or pulmonary embolism, flare-up and death. The incidence rates of the adverse events in both groups were compared with Mantel-Haenzel test. Risk factors for adverse events 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 ABT and control groups. No between-group differences were detected in the incidence rates of each adverse event or in the incidence rates of total adverse events (control vs ABT: 15.5% vs 20.7% in total, 5.2% vs 3.1% in death).

Conclusions Compared with csDMARDs and/or steroids without ABT, adding ABT to the treatment does not appear to increase the incidence rates of postoperative adverse events in RA patients undergoing orthopedic surgery. Large cohort studies should be performed to add evidence for the perioperative safety profile of ABT.
INTRODUCTION
Advances in molecular biology and basic and clinical research in recent years have produced several new classes of drugs, in particular, biological disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), which can decrease disease activity, joint destruction, functional involvement and even mortality in patients with rheumatoid arthritis (RA) (1-7). One desirable result of these new drugs is the probable trend toward decreasing use of surgery for RA patients, especially joint replacement (8-12). However, some patients must still undergo orthopedic surgical interventions to alleviate joint discomfort and to recover functional ability (13-15).

The perioperative adverse events with bDMARDs have been reported to be surgical site infection (SSI), delayed wound healing, disease activity flare-up, and deep venous thrombosis/pulmonary embolism (DVT/PE) (16-20). SSI is the most common adverse event to be studies in association with bDMARDs. However, given the relative rarity of SSI, it is difficult to obtain a sufficient number of cases to achieve statistical significance. Goodman et al. recently reported in a systematic review that patients treated with an anti-tumour necrosis factor α (anti-TNFα) 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 three types of bDMARDs available, anti-interleukin 6 (IL-6) agents and B-cell and T-cell function modifiers, than the anti-TNFα inhibitors, although these non-TNF agents are used increasingly in clinical practice (21, 22). Furthermore, postoperative adverse events other than SSI have not been examined sufficiently. In a recent systematic review and meta-analysis, we reported that bDMARDs including tocilizumab slightly but significantly increased the risk of SSI compared with that with conventional synthetic DMARDs (csDMARDs), but not that of delayed wound healing (16). However, fewer patients were taking tocilizumab than TNFα inhibitors.

Abatacept (ABT) has been developed as a fusion protein of T-lymphocyte-associated antigen 4 and immunoglobulin and suppresses T cell activation by binding to CD80/86 co-stimulatory antigens, thereby blocking interaction with CD 28. ABT is clinically used as the only T-cell modifier available for RA treatment and has shown similar efficacy as TNF inhibitors and a safer profile, especially a lower infection ratio in registry data (23, 24). We previously published the first report that, in orthopedic
operations, ABT has a similar safety profile to TNFα inhibitors, but the study included only eight patients without any comparison arm (25). Using registry data, Latourte et al. recently published the results of perioperative complications of orthopedic and other types of surgery in patients using ABT (26). However, they did not compare the complication rates with those in patients who received csDMARDs. Therefore, it remains unknown whether ABT is associated with more postoperative complications than csDMARDs. Moreover, a recently-published guideline, 2017 American College of Rheumatology (ACR)/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, recommends withholding all current biologic agents including ABT prior to surgery, but the recommendation is for patients undergoing only elective total hip and knee arthroplasty with limited body of evidence (27).

The aims of this study were to investigate whether ABT is associated with more adverse events after orthopedic surgery compared with csDMARDs 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, a retrospective multicenter nested case–control study was scheduled to allow for direct comparison between ABT and csDMARDs. We collected only cases involving orthopedic surgery because this is different from other operations such as abdominal surgery in terms of the seriousness of SSI and higher rate of DVT/PE, as shown in previous studies (20, 26).

METHODS

Study design and setting
This 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: (1) fulfillment of the ACR/European League against Rheumatism classification 1987 or 2010 criteria for RA; and (2) undergoing an
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orthopedic operation between April 2011 and March 2014. The exclusion criteria were:
(1) age <18 years; and (2) <1 year of follow-up 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 bDMARDs were
infliximab, etanercept, adalimumab, tocilizumab, and ABT, and all were clinically
available during the study period. Rituximab and anakinra were not approved for RA in
Japan at the time of this study.

Matching criteria
The matching criteria had been decided before the start of the study based on reported
risk factors (18, 19, 28-32) and included the following: sex; disease activity categorised
by the rheumatologist (remission, low, moderate, or high activity); use or non-use of
oral steroids; operation site (five sites: spine, shoulder or elbow, hand or wrist, hip or
knee, or ankle or foot); and type of operation (seven categories: spine operation,
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 ABT for >3 months with the last injection within 3 months before the surgery, and
without other types of bDMARDs or targeted synthetic DMARDs (tsDMARDs) more
than 6 months before the surgery were enrolled in the ABT group, irrespective of the
concomitant use of csDMARDs 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
csDMARDs and/or steroids without the use of any bDMARD or tsDMARDs within 6
months before the operation, and the latter patients were enrolled in the 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 approved rheumatologists by JCR. The clinical information included
those for matching criteria, type of medical treatment (use of steroids, csDMARDs,
ABT, and/or other types of bDMARDs or tsDMARDs at the time of surgery), and
treatment history (starting, switching, and/or stopping bDMARDs or tsDMARDs within
6 months before the operation). This information was collected in 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., Machida, Japan). Statistical analysis was performed by the analytical department
independent of the study researchers.

In the two patient groups, information on each patient was sent back to each
institution, and the following information was collected as known risk factors for
postoperative adverse events and sent again to the study center: age; sex; duration of
RA; follow-up 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 (RF) and anti-citrullinated
protein antibodies; disease activity using the DAS28-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 ABT at the time of surgery;
discontinuation of ABT use before the operation; operation site (five body parts); and
type of operation (seven categories). We specifically collected data about the
occurrence of SSI, delayed wound healing, DVT or PE, flare-up 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 adverse events
SSI was diagnosed by the surgeon according to the Centers for Disease Control and
Prevention definition (33). Delayed wound healing was judged by the surgeon as an
insufficiently healed wound beyond 3 weeks after the operation (19, 34). Flare-up 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, 35). DVT/PE was diagnosed by a cardiologist within 1
month after the operation in the respective institute (35). Other serious adverse events
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, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (36). Categorical variables are expressed as n (%) and are compared with Mantel-Haenzel test. Continuous variables are expressed as mean ± standard deviation and are compared with paired T test. To compare the percentages for adverse events for within-group analyses, we used Fisher’s exact test. The odds ratio (OR) with 95% confidence interval (95%CI) for serious adverse events are calculated by logistic regression models in total subjects or in ABT 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 two previous similar reports of SSI (35, 37). 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 ABT group at the study center (Kyoto University Hospital). Matching of these 11 patients produced nine ABT–control pairs. Assuming that orthopedic surgery was performed on an average of 10 patients in the ABT group in each participating institution, we calculated that the ABT group would comprise 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 received more than one operation, each operation was planned to be counted separately. However, we found that no patients underwent more than one 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 ABT 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 ABT 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 ABT and control groups (Table 1a, b). The incidence rates for each adverse event did not differ significantly between the ABT and control groups (Table 2). A late deep infection occurred in a patient who received arthroplasty with an implant in the control group. Within the ABT group, the incidence rates did not differ significantly between shorter and longer preoperative discontinuation periods of ABT (<6 or ≥7 days, or <14 or ≥14 days) or administration route (intravenous infusion or subcutaneous injection) (data not shown). Furthermore, a subgroup analysis with matched cases only with hip and knee arthroplasties showed that the incidence rates did not differ significantly between ABT and control groups, either (suppl. Table 1).

As Table 2 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 associated with this complication in this cohort (data not shown). We further analyzed if corticosteroid dosage had any risk of postoperative death within a year, but univariate analysis shows the dosage did not affect the rate of postoperative death in this study (OR: 1.0, 95%CI: 0.82-1.13).

**DISCUSSION**

Compared with other bDMARDs used in clinical treatment of RA, the T-cell modulator, ABT, is reportedly associated with a slightly lower rate of adverse events such as infections compared with other bDMARDs (23, 24). We found no differences in the incidence rates of the adverse events after the orthopedic surgeries, including SSI, between the patients using ABT or csDMARDs for RA, even though they were matched on background characteristics.
This study is the first to report on the incidences of adverse events after the orthopedic surgeries, including SSI, delayed wound healing, DVT/PE, flare-up, and death, in patients treated with ABT and csDMARDs and/or steroids matched according to background characteristics. The risk ratios of each serious adverse event did not differ significantly between two groups. These data suggest that, compared with csDMARDs, adding ABT to the medications may not increase the incidence rates of postoperative adverse events in RA patients who undergo orthopedic surgery, even although the sample size may not be sufficient. Furthermore, within ABT group, the risk ratios did not differ between any two groups based on discontinuation period before the operation or according to the administration route.

To determine whether ABT increases the risk of postoperative adverse events compared with csDMARDs, a randomized controlled study would be desirable. However, there are numerous hurdles to conducting such a study. For example, operative interventions for RA are, by nature, diverse in terms of the operation site and procedure, patients’ characteristics such as age and sex, duration of symptoms, disease activity, and history of medication. The incidence rates of adverse events can be affected by the patient’s status and type of the institution; for example, the volume of operations in the institution and the surgeon’s experience performing the operation can affect the risk of adverse events. 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 issue, a nested case–control study, as in our study, is one possible and potent solution. We selected the term of 2011 to 2014 because three types of bDMARDs were already available. Although golimumab and certolizumab pegol had become available during this period, these are classified as TNFα inhibitors and would not have substantially affected the clinical practice in terms of operative intervention for RA. Another potent DMARDs, tsDMARDs, had also become available during this period, but we experienced very few operations in RA patients who received this medication in this period.

SSI is one of the common and serious adverse events after an orthopedic operation. Most of the studies on the effects of DMARDs on postoperative adverse
events 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 meta-analyses have shown that steroid and TNFα inhibitors increase the risk of SSI (16-18, 27-31, 34, 35, 38). By contrast, our study shows, for the first time, that adding ABT does not increase the risk of SSI compared with csDMARDs 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 study applied in this study is a reliable enough practically oriented study design. Although the data in this study shows very few occurrences of this complication compared with previous reports with unknown reasons (35, 37), our data suggest that ABT 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 adverse events such as delayed wound healing, DVT/PE, RA flare-up, and death have not fully been 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-up 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 (39). DVT/PE is one of the most serious postoperative adverse events, and anti-coagulant therapy has become a frequently used countermeasure for patients undergoing orthopedic surgery as well as other procedures. Although death is the most serious postoperative adverse event, the ratio has been scarcely reported after orthopedic surgery until recently. This 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 adverse events in future.

An unexpected result of this study was the high ratio of postoperative death within a year after orthopedic operation. Although the surgeons and attending rheumatologist reported all of the death as unrelated to the operation itself, the ratio should be paid with utmost attention. Unfortunately, what directly induced the death were unknown because of lack of detailed information of each patient in this study. The reasons may be seriousness of the patient’s medical condition in this particular group or
the matching process unexpectedly selecting serious patients. Furthermore, RA itself has been reported to be associated with higher rate of mortality after orthopedic operation. Cordtz et al. very recently reported that RA patients following total hip or knee arthroplasty had an increased risk of death compared with OA (32). Although exact ratios and causes of death remain unveiled, this issue should be continuously investigated in the future.

This study has several limitations. First, it was a retrospective, non-blinded study that fundamentally contains scientific bias in the comparison of the two groups. Moreover, the study design was a nested case control study, and the precision and power might be lower than a cohort study involving it. Also, this study design inevitably contains several limitations such as selection bias and observation bias. However, the control subjects using csDMARDs 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 doable due to many practical hurdles such that every center performs the operation, stopping medication, and collecting data differently. Third, evaluation of patients and adverse events may have varied between evaluators at the institutions, which may have introduced bias in the incidence ratios and risk factors for adverse events, 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, this study is not a comparative study between ABT and csDMARDs and/or steroids. We did not compare ABT alone with csDMARDs and/or steroids. The patients in the ABT group received csDMARDs and/or steroids. Lastly, what caused the death reported here were not fully investigated, although each evaluator reported that the cause was not directly related to the operation. Further analyses are required on this matter.

In conclusion, compared with csDMARDs and/or steroids without ABT, adding ABT may not increase the incidence rates of postoperative adverse events in RA patients who undergo orthopedic surgery. Large cohort studies should be performed to add evidence for the perioperative safety profile of ABT.
Acknowledgements

We thank professors Motomu Hashimoto, Masao Tanaka, Koichi Murata, Kohei Nishitani, Kosaku Murakami, Kyoto University, Takao Fujii, Wakayama Prefectural University, and Moritoshi Furu, Furu Clinic, for their valuable support for this study.
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FIGURE LEGENDS

Figure 1 Patient selection for analysis.
ABT; abatacept.

Table 1a. Demographic data of matching criteria of control and ABT groups
Data are expressed as n (%) and are compared with Mantel-Haenzel test. ABT: abatacept

Table 1b. Demographic data analyzed of control and ABT groups
Categorical variables are expressed as n (%) and are compared with Mantel-Haenzel test. Continuous variables are expressed as mean ± standard deviation and are compared with paired T test.

Table 2. Postoperative complication rates of control and ABT groups
Data are expressed as n (%) and are compared with Mantel-Haenzel test.
OR: odds ratio, 95%CI: 95% confidence interval, ABT: abatacept, SSI: surgical site infection, DVT/PE: deep venous thrombosis/pulmonary embolism
Figure 1 Patient selection for analysis.
ABT; abatacept.

338x190mm (54 x 54 DPI)
Table 1a. Demographic data of matching criteria of control and ABT groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 97)</th>
<th>ABT (n = 97)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>85 (87.6%)</td>
<td>83 (85.6%)</td>
<td>0.48</td>
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<tr>
<td><strong>Disease activity</strong></td>
<td></td>
<td></td>
<td>0.056</td>
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<tr>
<td>Remission</td>
<td>1 (1.0%)</td>
<td>1 (1.0%)</td>
<td></td>
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<tr>
<td>Low</td>
<td>24 (24.7%)</td>
<td>22 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>58 (59.8%)</td>
<td>55 (56.7%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>14 (14.4%)</td>
<td>19 (19.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Oral steroid use</strong></td>
<td>67/96 (69.8%)</td>
<td>71/96 (74.0%)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Operation site and method</strong></td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Spine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Spinal surgery</td>
<td>1 (1.0%)</td>
<td>2 (2.1%)</td>
<td></td>
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<tr>
<td>Hip and knee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthroplasty with implant</td>
<td>43 (44.3%)</td>
<td>37 (38.1%)</td>
<td></td>
</tr>
<tr>
<td>Synovectomy</td>
<td>3 (3.1%)</td>
<td>2 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0 (0%)</td>
<td>2 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Foot and ankle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthroplasty with implant</td>
<td>4 (4.1%)</td>
<td>4 (4.1%)</td>
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</tr>
<tr>
<td>Arthrodesis</td>
<td>1 (1.0%)</td>
<td>0 (0%)</td>
<td></td>
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<tr>
<td>Arthroplasty without implant</td>
<td>4 (4.1%)</td>
<td>5 (5.2%)</td>
<td></td>
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<tr>
<td>Synovectomy</td>
<td>0 (0%)</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue procedure</td>
<td>0 (0%)</td>
<td>1 (1.0%)</td>
<td></td>
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<tr>
<td>Others</td>
<td>6 (6.2%)</td>
<td>3 (3.1%)</td>
<td></td>
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<tr>
<td>Shoulder and elbow</td>
<td></td>
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<tr>
<td>Arthroplasty with implant</td>
<td>5 (5.2%)</td>
<td>7 (7.2%)</td>
<td></td>
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<tr>
<td>Arthroplasty without implant</td>
<td>0 (0%)</td>
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<tr>
<td>Synovectomy</td>
<td>0 (0%)</td>
<td>4 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3 (3.1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Wrist and fingers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthroplasty with implant</td>
<td>5 (5.2%)</td>
<td>7 (7.2%)</td>
<td></td>
</tr>
<tr>
<td>Arthrodesis</td>
<td>5 (5.2%)</td>
<td>8 (8.2%)</td>
<td></td>
</tr>
<tr>
<td>Arthroplasty without implant</td>
<td>10 (10.3%)</td>
<td>3 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Synovectomy</td>
<td>2 (2.1%)</td>
<td>3 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue procedure</td>
<td>3 (3.1%)</td>
<td>2 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (2.1%)</td>
<td>2 (2.1%)</td>
<td></td>
</tr>
</tbody>
</table>
Data are expressed as n (%) and are compared with Mantel-Haenzel test. ABT: abatacept
Table 1b. Demographic data analyzed of control and ABT groups

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

Categorical variables are expressed as n (%) and are compared with Mantel-Haenzel test. Continuous variables are expressed as mean ± standard deviation and are compared with paired T test.

Table 2. Postoperative complication rates of control and ABT groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 97)</th>
<th>ABT (n = 97)</th>
<th>OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSI</td>
<td>1 (1.0%)</td>
<td>0 (0%)</td>
<td>0.33 (0.01-8.20)</td>
<td>1.00</td>
</tr>
<tr>
<td>Delayed wound healing</td>
<td>2 (2.1%)</td>
<td>3 (3.1%)</td>
<td>1.52 (0.25-9.28)</td>
<td>1.00</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>4/88 (4.5%)</td>
<td>7/88 (8.0%)</td>
<td>1.81 (0.51-6.44)</td>
<td>0.55</td>
</tr>
<tr>
<td>Flare-up</td>
<td>2/67 (3.0%)</td>
<td>4/67 (6.0%)</td>
<td>2.06 (0.36-11.67)</td>
<td>0.68</td>
</tr>
<tr>
<td>Death</td>
<td>5 (5.2%)</td>
<td>3 (3.1%)</td>
<td>0.59 (0.14-2.53)</td>
<td>0.72</td>
</tr>
<tr>
<td>Other serious adverse events</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) and are compared with Mantel-Haenzel test.

OR: odds ratio, 95%CI: 95% confidence interval, ABT: abatacept, SSI: surgical site infection, DVT/PE: deep venous thrombosis/pulmonary embolism