Anti-rheumatic treatment and prosthetic joint infection: An observational study in 494 elective hip and knee arthroplasties.

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Abstract

Background Surgical site infections are more frequent among patients with rheumatic disease. To which extent this is related to immunosuppressive antirheumatic drugs is unclear, as is the value of discontinuing medication perioperatively.

Objectives To assess the rate of surgical site infections after knee and hip-replacement in patients with inflammatory joint disease, with emphasis on periprosthetic joint infection, and to investigate the importance of medical treatment in this regard.

Methods Data was collected from 494 primary elective hip- (51.4%) and knee arthroplasties along with demographic and medication data and primary outcome was surgical site infections during the first year after surgery.

Results In 78% (n=385) of the cases the patient medicated with 1 to 3 disease-modifying antirheumatic drugs perioperatively. Thirty two per cent (n=157) of patients were on a TNF-alpha inhibitor perioperatively. The rate of surgical site infections was 3.8% (n=19) The rate of periprosthetic joint infection was 1.4% (n=7), all of which were knee arthroplasties. Only in 1 case of periprosthetic joint infection the patient medicated perioperatively with a TNF-alpha inhibitor.

Conclusion Surgical site infections was not associated with ongoing medication with disease-modifying antirheumatic drugs. Due to low event rate this should be interpreted with caution. Routines at our centre, not stopping biologic disease-modifying antirheumatic drugs perioperatively, will be unchanged.

Introduction

In most affluent countries, treatment with biologic disease modifying drugs (bDMARD) such as TNF-alpha inhibitors, has during the past 20 years become part of standard of care for patients with rheumatoid arthritis (RA) as well as in other types of inflammatory joint disease, although the need for joint arthroplasty in these patients has decreased(1-7). There is still a number of patients in need of orthopedic surgery, and many of these patients are prior to the operation on treatment with conventional disease modifying drugs (cDMARDs) and/or bDMARDs.

The incidence of infections in general is higher in patients with RA than in non-RA subjects. If this is a
consequence of immunologic disturbances due to the disease itself as disease severity is a risk factor for infection, or of the immunosuppressive treatment often used, or both, is still not fully understood.

TNF-alpha inhibitors are thought to increase the general risk of infection (8, 9).

Studies vary in their findings regarding the risk of postoperative infections in patients on TNF-alpha inhibitors versus cDMARDs, such as methotrexate (Table 1). Prior studies suggest that methotrexate is not a substantial risk factor for surgical site infection (SSI) (10, 11).
| Author, year | Type of surgery | Number of operations | bDMARD | Main finding in patients not stopping bDMARDs |
|-------------|----------------|----------------------|--------|---------------------------------------------|
| Bibbo & Goldberg, 2004(45) | Foot and ankle surgery | 31 | continued treatment perioperatively | SSI\(^3\) rate decreased |
| Talwalkar, Grennan, Gray, Johnson, & Hayton, 2005(46) | Various orthopedic surgeries | 11 | TNF-inhibitors discontinued 2–4 weeks prior to surgery or continued treatment perioperatively | SSI\(^3\) rate unchanged |
| Wendling et al., 2005(47) | Various orthopedic surgeries | 50 | TNF-inhibitors discontinued 2–4 weeks prior to surgery or continued treatment perioperatively | SSI\(^3\) rate unchanged |
| Giles et al., 2006(48) | Various orthopedic surgeries | 91 | continued treatment perioperatively | SSI\(^3\) rate increased |
| Broeder et al., 2007(49) | Various orthopedic surgeries | 1 219 | TNF-inhibitors discontinued 4 t1/2 prior to surgery or continued treatment perioperatively | SSI\(^3\) rate unchanged |
| Ruyssen-Witrand et al., 2007(50) | Various surgeries | 127 | variable timing for discontinuation prior to surgery | SSI\(^3\) rate unchanged |
| Gilson et al., 2010(51) | Total joint replacement | 60 | cases treated with TNF-inhibitors included | SSI\(^3\) rate increased |
| Kawakami et al., 2010(52) | Various orthopedic surgeries | 128 | TNF-inhibitors discontinued 2–4 weeks prior to surgery and restarted if no signs of infection | SSI\(^3\) rate increased |
| Suzuki et al., 2011(53) | Arthroplasties | 1 626 | continued treatment perioperatively | SSI\(^3\) rate increased |
| Momahara et al., 2011(54) | THA\(^1\) and TKA\(^2\) | 420 | TNF-inhibitors discontinued 2–4 weeks prior to surgery, cDMARDs continued | SSI\(^3\) rate increased |
| Berthold et al., 2013(55) | Various orthopedic-and hand surgeries | 1 596 | TNF-inhibitors discontinued 2–4 weeks prior to surgery or continued treatment perioperatively | SSI\(^3\) rate increased |
| Tada et al., 2016(56) | Various orthopedic surgeries | 332 | TNF-inhibitors discontinued 2–4 weeks prior to surgery, cDMARDs continued | SSI\(^3\) rate unchanged |
| Hayashi et al., 2017(57) | THA\(^1\) | 99 | variable timing for discontinuation or not discontinuation prior to surgery | late SSI\(^3\) rate increased |
| Salt et al., 2017(58) | THA\(^1\), TKA\(^2\) and total shoulder arthroplasty | 2 212 | variable timing for discontinuation or not discontinuation prior to surgery | SSI\(^3\) rate unchanged |

1 Total hip- arthroplasty, 2 Total knee-arthroplasty, 3 Surgical site infection

SSI, and specifically periprosthetic joint infection (PJI), is one of the most serious complications of
arthroplasty and a leading cause of early revision (12,13). Risk factors for SSI include smoking, diabetes mellitus, obesity, ASA scale > 2 (“American Society of Anesthesiologists (ASA) Physical Status”), current infection and use of steroids (14-18). Rheumatic disease has been shown to be an independent risk factor for PJI (19-22).

In 2017, the American College of Rheumatology (ACR), published guidelines for the perioperative management of anti-rheumatic medication in patients with rheumatic diseases undergoing elective total hip and total knee arthroplasty. According to these recommendations, TNF-alpha inhibitors should be withheld prior to surgery and surgery planned for at the end of the dosing cycle (23).

The International Consensus Meeting (ICM) on orthopaedic infections, in Philadelphia 2018, adopted the ACR guidelines and estimated the level of evidence as moderate (24). Even the Swedish association for rheumatology has recommendations which are consistent with the ACR guidelines (25).

Guidelines on the prevention of SSI from the World Health organization, WHO, states that perioperative discontinuation of methotrexate has no effect on the risk of SSI, and perioperative discontinuation of TNF-alpha inhibitors might have a benefit in reducing the SSI rate. The evidence for this is however considered of very low quality and it is stated that "considering the scarce (or absent) evidence to support discontinuation of treatment (anti-TNF) and even potential harm it may cause (methotrexate) such as the risk of flare-up of the underlying disease(s) associated with the suspension of therapy, immunosuppressive medication should not be discontinued to prevent SSI" (26).

Since 2000 orthopedic surgery has been conducted at our departments of Orthopedics and Rheumatology Skåne University Hospital in Lund, Sweden, without interrupting methotrexate treatment. In 2006, new local guidelines were introduced and discontinuation of TNF-alpha inhibitors perioperatively in conjunction with rheumatic orthopedic surgery was abolished. Data from a study conducted at our departments from 2003 to 2009 did not indicate that the perioperative use of TNF-alpha inhibitors or methotrexate was a clinically important risk factor for PJI (27).

The aim of the present study was to answer two questions: (i) What is the one year incidence of SSI and PJI after total knee arthroplasty (TKA) and total hip arthroplasty (THA) in patients with
inflammatory joint disease; and (ii) is there an association between the use of DMARDs and infection rate?

Methods
This is an observational, non-randomized retrospective single center study, using patient data from the departments of Rheumatology and Orthopedics at Skåne University Hospital, Lund, Sweden. The study was approved by the local ethics committee in Lund (Dnr 2016/880).

All adult patients above the age of 18 with rheumatic disease operated with primary TKA or THA between 2006 and 2015 were included in the study. Some patients had undergone more than one operation; the data analysis is based on cases (operations), not patients.

Information was collected from the local operation register. We included patients with an ICD 9 code for rheumatic disease: M058 or M059 (seropositive rheumatoid arthritis), M060 (seronegative rheumatoid arthritis), M069 (other rheumatoid arthritis), M073 (psoriatic and enteropathic arthropathies) or M080 (juvenile arthritis), who had undergone TKA or THA between January 2006 and December 2015. The diagnosis was validated by crosschecking the medical records. If the patient in conjunction with other surgery had been given an ICD 9 code for inflammatory joint disease, and the diagnosis could be validated, the patient entered the study, even if he or she at the time of primary TKA or THA had been given a different diagnosis by the operating surgeon (most often osteoarthritis).

Postoperative infections are generally classified according to the US Center for Disease Control and Prevention (CDC) 1992 definition of nosocomial SSIs (28), where infections are divided into (i) superficial incisional SSI- involving the skin and subcutaneous tissue, (ii) deep incisional SSI- involving deep soft tissue of the incision and (iii) organ/space SSI- involving any part of the anatomy (e.g., organs or spaces), other than the incision, opened and manipulated during the operative procedure.

In this study we used a modified definition of SSIs, according to what is generally used in the field of orthopedics, where "deep incisional SSI" and "organ/space SSI" together are referred to as PJI and superficial incisional SSI is termed superficial SSI.

For the diagnosis of PJI at least one of the following criteria was required for the diagnosis of PJI: (i)
growth of identical microorganisms in at least two intraoperative cultures or a combination of preoperative aspiration and intraoperative cultures (ii) presence of a sinus tract communicating with the prosthetic joint, (iii) presence of purulence without another known etiology surrounding the prosthetic device (29).

By definition, superficial SSI occurs within 30 days after surgery and PJI within 1 year. Patients were followed for one year after surgery, or until death or re-operation for other reason than infection within one year. With a longer follow up time, one would expect to find a number of hematogenous infections, which was not our objective as these can not be related to medical treatment during the perioperative period. Routinely, patients were contacted by a nurse one year after the operation and asked for postoperative complications such as infections. In 8 cases, data regarding one year follow up was missing, and the patients’ medical records were scrutinized for medical contacts which could indicate a SSI.

Statistics

The association between infectious rate and medication was analyzed using chi-square test or Fisher´s exact test when appropriate, using SPSS Statistics 23 for Windows. The significance level was set at p < 0.05.

Results

A search in the local operation register provided 522 operations under the study period. Twenty-eight operations in 24 patients were excluded from further analysis. 5 patients had been diagnosed with polymyalgia rheumatica, 10 with osteoarthritis, 1 with calcium pyrophosphate arthritis, 1 with spondyloepiphyseal dysplasia, and in 7 cases data regarding rheumatic diagnosis could not be found. After exclusions, data was collected from 494 operations in 395 individual patients (Fig. 1). 92 patients had undergone more than one operation.

Patient characteristics are described in Table 2. A majority of cases were female (76%) and the mean age by time of surgery was 62 years (range 18–89). TKA comprised 51% of procedures (n = 245). A majority of cases had RA (69%) followed by juvenile idiopathic arthritis (JIA) (12%). The most used DMARD was methotrexate (55,5%), followed by a TNF-alpha inhibitor (31.8%). 18.2% of patients were
on both methotrexate and a TNF- alpha inhibitor. Details on treatment is summarized in Table 3.

### Table 2

| Patients characteristics. Values are number (percentage) unless otherwise indicated. |
|--------------------------------------|
| **All**                              | 494 |
| **Female**                           | 377 (76.3) |
| **TKA**                              | 254 (51.4) |
| **THA**                              | 240 (48.6) |
| **Age, years, by time of surgery, mean (range)** | 62.4 (18–89) |
| **ASA**, valid no 451                |     |
| ASA 1                                | 9 (2) |
| ASA 2                                | 268 (59.4) |
| ASA 3                                | 172 (38.1) |
| ASA 4                                | 2 (0.4) |
| **BMI**, kg/m^2, valid no 474, mean(range) | 26.5(14.9–44.6) |
| **Diagnosis**                        |     |
| Rheumatoid arthritis^a               | 341 (69) |
| Psoriatic arthritis                  | 35 (7) |
| Spondyloarthritis incl. ankylosing spondylitis^b | 29 (5.9) |
| Juvenile idiopathic arthritis^c      | 59 (11.9) |
| Other diagnosis^d                    | 30 (6.1) |

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^1 Total knee-arthroplasty, ^2 Total hip-arthroplasty, ^3 American Society of Anesthesiologists (ASA)

Physical Status, ^4 Body mass index

^a Seropositive rheumatoid arthritis (n = 283), seronegative rheumatoid arthritis (n = 58)

^b Ankylosing spondylitis (n = 21), other specified inflammatory spondylopathies (n = 6), inflammatory spondylopathy, unspecified (n = 2)

^c Juvenile arthritis (n = 40), juvenile arthritis with systemic onset (n = 7), juvenile polyarthritis (seronegative) (n = 6), juvenile arthritis, unspecified (n = 4), pauciarticular juvenile rheumatoid arthritis (n = 2)

^d Inflammatory polyarthropathy (n = 1), polyarthritis, unspecified (n = 4), other specified arthritis (n = 4), monoarthritis, not elsewhere classified (n = 2), systemic lupus erythematosus, unspecified (n = 5), systemic lupus erythematosus with organ or system involvement (n = 3), adult-onset Still disease (n = 2), Crohn´s disease (n = 1), ulcerative colitis (n = 1), polymyositis (n = 1), systemic sclerosis (n = 2), other overlap syndrome (n = 1), arthritis unspecified (n = 1), systemic involvement of connective tissue, unspecified (n = 2)
Table 3
Exposure. Values are number (percentage) unless otherwise indicated.

| Drug/Combination                                      | Number (Percentage) |
|-------------------------------------------------------|---------------------|
| Prednisolone                                          | 214 (43.3)          |
| Prednisolone, dose mg/d, mean (valid no 489)          | 5.5                 |
| Number of ongoing DMARDs\(^1\)                        |                     |
| 0                                                     | 109 (22.1)          |
| 1                                                     | 243 (49.2)          |
| 2                                                     | 132 (26.7)          |
| 3                                                     | 10 (2)              |
| cDMARD\(^2\)                                          | 343 (69.4)          |
| Methotrexate                                          | 274 (55.5)          |
| Methotrexate dose, mg/w, mean (valid no 488)          | 16                  |
| cDMARD\(^2\) other than methotrexate\(^a\)           | 69 (14)             |
| bDMARD\(^3\)                                          | 193 (39.1)          |
| TNF- alpha inhibitor\(^b\)                            | 157 (31.8)          |
| bDMARD\(^3\) other than TNF- alpha inhibitor\(^c\)   | 36 (7.3)            |
| Methotrexate and prednisolone                         | 124 (25.1)          |
| Methotrexate and TNF- alpha inhibitor                 | 90 (18.2)           |
| Methotrexate and prednisolone and TNF- alpha inhibitor| 40 (8.1)            |

\(^1\) Disease-modifying antirheumatic drug

\(^2\) Conventional disease-modifying antirheumatic drug

\(^3\) Biologic disease-modifying antirheumatic drug

\(^a\) azathioprine (n = 9), sulfasalazine (n = 30), hydroxychloroquine (n = 26), mycophenolate mofetil (n = 3) and leflunomide (n = 1)

\(^b\) etanercept (n = 93), golimumab (n = 5), certolizumab (n = 12), infliximab (n = 15), adalimumab (n = 32)

\(^c\) abatacept (n = 6), rituximab (n = 16), anakinra (n = 5), tocilizumab (n = 14) One patient did bilateral THA at the same session and was treated with both anakinra and rituximab

The total incidence of SSI was 3.8% (n = 19). Of these, 12 were superficial SSI; the rate of superficial SSI being 2.4%. All of these healed after wound debridement and/or antibiotic treatment.

There were seven PJI; the one-year rate of PJI being 1.4%. All PJI occurred after TKA and there was a statistically significant difference in the rate of PJI depending on operating site (p = 0.015). One of the patients suffering a PJI had a hematogenous infection 11 months after surgery, but is according to the design of the study counted as a SSI.

One patient with PJI was treated with the TNF-alpha inhibitor etanercept, and 4 patients were treated with methotrexate. There was no statistically significant difference in the rate of infection between
patients treated with a TNF-alpha inhibitor and those not, (p = 0.44) or those treated with methotrexate (p = 1.00). No association could be found between PJI and prednisolone (p = 0.25), combination of TNF-alpha inhibitor and methotrexate (p = 1.0), combination of methotrexate and prednisolone (p = 1.0), combination of TNF-alpha inhibitor, methotrexate and prednisolone (p = 1.0), BMI (p = 0.21) or ASA-score (p = 0.44) (Table 4).

Table 4
Periprosthetic joint infection(PJI) and total surgical site infections(SSI) in various subgroups.

|                | total(n) | PJI(n) | p-value | total SSI (n) | p-value |
|----------------|----------|--------|---------|--------------|---------|
| Female         | 377      | 3      |         | 14           |         |
| Male           | 117      | 4      | 0.06<sup>a</sup> | 5           | 0.78<sup>b</sup> |
| Procedure      |          |        |         |              |         |
| TKA<sup>1</sup> | 254      | 7      |         | 11           |         |
| THA<sup>2</sup> | 240      | 0      | 0.015<sup>a</sup> | 8           | 0.33<sup>b</sup> |
| BMI<sup>3</sup>, valid no 474 |          |        |         |              |         |
| < 30           | 368      | 4      |         | 12           |         |
| ≥ 30           | 106      | 3      | 0.19<sup>a</sup> | 7           | 0.16<sup>b</sup> |
| ASA<sup>4</sup>, valid no 448 |          |        |         |              |         |
| ≤ 2            | 277      | 3      |         | 10           |         |
| ≥ 3            | 174      | 4      | 0.44<sup>a</sup> | 8           | 0.60<sup>b</sup> |
| Treatment      |          |        |         |              |         |
| Methotrexate   | 274      | 4      | 1.0<sup>a</sup> | 12           | 0.49<sup>b</sup> |
| TNF-alpha inhibitor | 157     | 1      | 0.44<sup>a</sup> | 5           | 0.60<sup>b</sup> |
| Prednisolone   | 214      | 5      | 0.25<sup>a</sup> | 10           | 0.40<sup>b</sup> |
| Methotrexate and prednisolone | 124 | 2 | 1.00<sup>a</sup> | 4 | 0.79<sup>a</sup> |
| Methotrexate and TNF-inhibitor | 90 | 1 | 1.00<sup>a</sup> | 3 | 1.00<sup>a</sup> |
| Methotrexate, TNF- inhibitor and prednisolone | 39 | 0 | 1.00<sup>a</sup> | 0 | 0.39<sup>a</sup> |

<sup>1</sup> Total knee-arthroplasty, <sup>2</sup>Total hip-arthroplasty, <sup>3</sup>Body mass index <sup>4</sup>American Society of Anesthesiologists (ASA) Physical Status.

<sup>a</sup> Fisher´s exact test

<sup>b</sup> Chi-square test

No correlation could be found between the total number of SSI and medical treatment (Table 4).

Five out of 7 PJI healed after treatment with debridement and antibiotics. Details on patients suffering PJI, including outcome are described in Table 5.
Table 5: Periprosthetic joint infection (PJI), individual cases

| Diagnosis            | Age | Sex   | Type of surgery | Anti-rheumatic treatment | Infectious agents | Treatment of PJI | Outcome                  |
|----------------------|-----|-------|-----------------|--------------------------|-------------------|-----------------|--------------------------|
| RA¹, seronegative    | 65  | Female| TKA³            | Methotrexate, prednisolone | S. aureus         | Debridement and exchange of tibial insert | Healed (26 months later re-infected with the same bacteria) |
| RA¹, seropositive    | 66  | Male  | TKA³            | Etanercept, methotrexate | coagulase negative staphylococcus (CNS) | Two-stage revision | Healed                   |
| RA¹, seropositive    | 70  | Male  | TKA³            | Prednisolone, azathioprine | S. aureus         | Debridement and exchange of tibial insert | Failure (chronic infection treated with suppressive antibiotics) |
| RA¹, seropositive    | 69  | Female| TKA³            | Methotrexate, prednisolone | B. fragilis       | Antibiotics      | Failure, amputation       |
| RA¹, seropositive    | 66  | Female| TKA³            | Methotrexate, sulfasalazine, hydroxychloroquine, prednisolone | S. mitis, S. hominis | Debridement and exchange of tibial insert | Healed                   |
| RA¹, seropositive    | 67  | Male  | TKA³            | Prednisolone             | coagulase negative staphylococcus (CNS) | Debridement and exchange of tibial insert | Healed                   |
| PsA²                 | 44  | Male  | TKA³            | None                     | coagulase negative staphylococcus (CNS) | Debridement and exchange of tibial insert | Healed                   |

¹ Rheumatoid arthritis, ² Psoriatic arthritis.

- after consultation with a specialist in infectious diseases, all patients received treatment with antibiotics for a minimum of three months according to antimicrobial resistance pattern.

Four out of seven of patients with a PJI were male, although only 24% of the operations were performed on male patients. However, there was no statistically significant difference in the rate of PJI between men and women (p = 0.06) (Table 4).

Six patients died within one year of surgery. One patient died 20 days after surgery due to a gastrointestinal bleeding. Three patients died due to acute coronary syndrome, one due to a subarachnoid hemorrhage and one due to progressive dementia (Pick's disease). None of the deaths within one year of surgery could be linked directly to surgery or PJI.

Four patients underwent reoperation within one year from surgery. One patient was reoperated...
because of joint instability, two because of aseptic loosening of the prosthesis and one patient due to fracture after resurfacing hip arthroplasty.

## Discussion

The main finding in this study is that no association could be found between ongoing treatment with bDMARD and PJI, or SSI in general, amongst patients with inflammatory joint disease undergoing primary knee or hip arthroplasty.

A previous study from our center(27) showed a increased risk of PJI in patients who continued treatment with TNF-alpha inhibitors perioperatively to hand and orthopedic surgery, however the finding was caused by a very low incidence rate of PJI in foot surgery in the comparison group.

A meta analysis comparing continuation versus discontinuation of TNF- alpha inhibitors prior to orthopedic surgery favors discontinuation of bDMARD(8) although the studies included are heterogeneous with different time of treatment interruption and a variety of patients and operations included. Further, the included studies were underpowered to detect small changes in infection rate.

As shown in Table 1. other studies on the influence of TNF-alpha inhibitors on infection rates comes to different conclusions. Eight studies showed a slight increase in PJI rate(9,11,19,30–34), whereas seven(17,35–40) showed no increase or a decrease in PJI in patients treated perioperatively with TNF-alpha inhibitors. The studies included different types of surgery, some compared patients not treated with TNF-alpha inhibitors too those treated with TNF-alpha inhibitors and some compared the result after continuation versus discontinuation of TNF- alpha inhibitors prior to surgery. Also the time of treatment interruption varied which makes conclusions difficult.

The rate of PJI after TKA was 2.8% which is a higher frequency compared to data from the Swedish Knee Arthroplasty Register (SKAR). Here, the one year incidence for revision due to infection is 1.7% for TKA performed 2006–2011(41). Most patients in SKAR have osteoarthritis, and patients with RA have previously been shown to have a increased risk for PJI compared to patients with osteoarthritis(42,43). A Norwegian study with data from The Norwegian Arthroplasty Register reports a one year revision rate of 1.2% in TKA performed in RA patients(43). In a Danish cohort the one year incidence rate in a population of RA patients for PJI in TKA and THA together the was 1.6%(42).
The rate of PJI was 1.4% which is comparable to what have been found in other studies on subjects with rheumatic disease(19,42).

None of the THA performed in our study resulted in a PJI. The Swedish Hip Arthroplasty Register (SHPR) reported an re-operation rate due to infection of 1.2% in THA performed in Sweden 2005–2008(44). The fact that the incidence rate of THA was lower than expected could be coincidental or be due to low number of procedures in this study although the same pattern with higher risk of revision in RA patients undergoing a TKA than a THA has been showed previously(43).

In only one of the seven cases of PJI the patient was treated with a TNF-alpha inhibitor, in this case etanercept. In all 157 (31.8%) of patients was treated with a TNF-alpha inhibitor which means that only 0.63% of patients treated with a TNF-alpha inhibitor suffered a PJI.

In 2003–2005, before the new policy of perioperative continuation of TNF-alpha inhibitors where introduced in our departments, only 0.6% of implant operations led to a PJI (27). Compared to this very low incidence rates the present finding of 1.4% is higher, but few cases and makes interpretation difficult.

One patient with PJI suffered a hematogenous infection with streptococcus mites 11 months after surgery. The fact that the infection occurred long after surgery may suggest that the treatment at time of surgery was not a significant contributor to the infectious outcome. Leaving out this infection the rate of PJI would have been 1.2%.

Men were overrepresented in the group with PJI(p = 0.06) which s consistent with previous findings(15–17).

PJI is a serious complication of arthroplasty and potential risk factors for infection should if possible be eliminated prior to surgery. With this in mind, the risk of flares in patients with rheumatic disease when discontinuing DMARD treatment should be carefully considered when deciding whether to continue or discontinue DMARD treatment prior to surgery. Although TNF-alpha inhibitors are not discontinued perioperatively to elective arthroplasty surgery at our center we do not apply this approach as a general rule for others DMARDs such as rituximab, tocilizumab or JAK inhibitors where data are scarcer.
This was a single center study, and procedures were performed by a few experienced surgeons according to the same routines throughout the study period. One year follow-up was standardized via a telephone call and data on perioperative medications were retrieved by one investigator (YB) via medical records. There were few missing data (Table 3), mostly regarding dosing of methotrexate and prednisolone, which do not affect the result.

The limitations of this study includes that it is observational and descriptive, not including a control group. The overall rate of SSI including PJI is low, and it is thus underpowered, like all other investigations in the field. From available data, Table 1, it seems likely that treatment with TNF- alpha inhibitors per se confers a somewhat increased risk of PJI. The importance of perioperative stopping the treatment is unclear. In fact, it is not likely that a randomized, controlled trial of stopping bDMARDs perioperatively will be performed, as this would require a very large number of procedures. Furthermore, each bDMARD would require its own trial. Assuming a general PJI incidence of 2%, a clinical trial would have to include 21,108 procedures within each group (continuation versus cessation of bDMARD perioperatively) to detect a 20% increase of PJI incidence with a power of 80%.

In conclusion, in our study we found no signs of increased PJI risk despite perioperative bDMARD treatment in inflammatory joint disease patients undergoing elective TKA or THA.

The policy at our center of perioperative continuation of most bDMARDs will be unchanged. More and larger studies are needed to elucidate the role, if any, of perioperative treatment cessation in reducing PJI rates.

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**Abbreviations**

ACR- American College of Rheumatology

ASA- American Society of Anesthesiologists (ASA) Physical Status

bDMARD- biologic disease-modifying antirheumatic drug

cDMARD- conventional disease-modifying antirheumatic drug

CNS- coagulase negative staphylococcus
ICD-9- International Statistical Classification of Disease
ICM- International Consensus Meeting
PJI- Periprosthetic joint infection
PsA- psoriatic arthritis
RA- rheumatoid arthritis
SHPR- Swedish Hip Arthroplasty Register
SKAR- Swedish Knee Arthroplasty Register
SRF- Svensk reumatologisk förening
SSI- surgical site infection
THA- total hip- arthroplasty
TKA- total knee- arthroplasty
TNFα- tumor necrosis factor alpha
WHO- World Health Organisation

Declarations
There are no competing interests for any author.

Data are available upon reasonable request.

This study is approved by the Local ethics committee in Lund (Dnr 2016/880).

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Figures
After exclusions, data was collected from 494 operations in 395 individual patients (Figure 1). 92 patients had undergone more than one operation.