# Risk Factors for Surgical Site Infections and Other Complications in Elective Surgery in Patients with Rheumatoid Arthritis with Special Attention for Anti-Tumor Necrosis Factor: A Large Retrospective Study

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***ABSTRACT.*** ***Objective.*** To identify risk factors for surgical site infection (SSI) in patients with rheumatoid arthritis (RA) with special attention for anti-tumor necrosis factor (anti-TNF) treatment.

***Methods.*** All patients with RA who had undergone elective orthopedic surgery since introduction of anti-TNF were included in a retrospective parallel-cohort study with a one-year followup. Primary endpoint was a SSI according to the 1992 Centers for Disease Control and Prevention criteria and/or antibiotic use. Cohort 1 did not use anti-TNF, cohort 2 used anti-TNF but had either stopped (2A) or continued anti-TNF preoperatively (2B), the cutoff point being set at 4 times the half-life time of the drug. Infection rates were compared between cohorts, and logistic regression analysis was performed to examine risk factors.

***Results.*** In total, 1219 (768 patients) procedures were included, and crude infection risks were 4.0% (41/1023), 5.8% (6/104), and 8.7% (8/92) in cohorts 1, 2A, and 2B, respectively. Elbow surgery (OR 4.1, 95% CI 1.6–10.1), foot/ankle surgery (OR 3.2, 95% CI 1.6–6.5), and prior skin or wound infection (OR 13.8, 95% CI 5.2–36.7) were associated with increased risk of SSI, whereas duration of surgery (OR 0.42, 95% CI 0.23–0.78) and sulfasalazine use (OR 0.21, 95% CI 0.05–0.89) were associated with decreased risk. Perioperative use of anti-TNF was not significantly associated with an increase in SSI rates (OR 1.5, 95% CI 0.43–5.2).

***Conclusion.*** The most important risk factor for SSI is history of SSI or skin infection. Although our study was not powered to detect small differences in infection rates, perioperative continuation of anti-TNF does not seem to be an important risk factor for SSI. (First Release Nov 15 2006; J Rheumatol 2007;34:689–95)

*Key Indexing Terms:*

| | | |
|---|---|---|
| ANTI-TUMOR NECROSIS FACTOR | INFECTION | RHEUMATOID ARTHRITIS |
| SURGERY | BIOLOGICAL | COMPLICATION |
| ADALIMUMAB | ETANERCEPT | INFLIXIMAB |

About 25% of all patients with rheumatoid arthritis (RA) need an operation within the first 20 years of the disease, but this percentage seems to be declining[1-3]. The most important complications in elective orthopedic surgery in RA remain surgical site infections (SSI), with an incidence ranging from 2% to 15%[4-6]. SSI are almost exclusively caused by *Staphylococcus aureus*. Studies on SSI in the general population have provided insight into a large set of risk factors for SSI; however, these are not necessarily applicable to the RA population due to differences in susceptibility for infection and use of medication[7,8]. A few studies evaluating SSI after elective orthopedic surgery in RA have suggested a few risk factors, including the type of surgery (foot/knee operations), previous SSI, comorbidity (diabetes mellitus, pulmonary disease), active RA, and steroid use[4,5], although these risk factors differ substantially between studies. It is not clear whether use of classical disease modifying antirheumatic drugs (DMARD) constitutes an independent risk factor for SSI. Only methotrexate has been investigated in a prospective and randomized manner and, perhaps surprisingly, infection rates were lower in patients who perioperatively continued methotrexate[4].

The relationship between perioperative use of anti-tumor necrosis factor (anti-TNF) agents, including infliximab, etanercept, and adalimumab, and SSI risk has not been studied extensively. No increased incidence of SSI in patients using

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anti-TNF was reported in 2 small studies and a few preliminary reports[9-12], although other preliminary reports suggest high (or higher) complication rates of patients using anti-TNF[13,14]. All studies, however, were severely underpowered and of questionable design, including different types of rheumatic diseases and surgery (elective and acute, orthopedic and other localizations), and lacking properly defined control groups. More data are clearly needed, as recently recognized[15,16].

To be prudent, current guidelines include cessation of anti-TNF preoperatively. The NVR (Nederlandse Vereniging voor Reumatologie, Dutch Society for Rheumatology) guideline advises cessation of anti-TNF treatment 4 drug half-life times before an operation (for infliximab 39 days, etanercept 12 days, and adalimumab 56 days)[17]. However, there are several possible disadvantages of this approach. First, perioperative discontinuation of anti-TNF treatment may induce a flare in disease activity. The additional use of medication such as steroids may again increase the risk of infections. Indeed, some studies suggest that increased disease activity itself can give rise to a higher risk of infections[3]. An active RA would also hamper revalidation and prolong hospitalization. Second, longterm interruptions of anti-TNF therapy may induce the formation of anti-drug antibodies and subsequently cause infusion reactions and secondary ineffectiveness. Data supporting this hypothesis, however, are not yet very strong and are only present for infliximab[18].

The primary aim of our study was to assess the effect of withholding versus maintaining anti-TNF therapy on the incidence of SSI. Secondary aims include analyzing the effect of (dis)continuation of anti-TNF therapy on other complications and identifying other risk factors, and exploring descriptively the incidence and consequences of SSI in RA patients undergoing elective orthopedic surgery.

## MATERIALS AND METHODS

*Patients*. All RA patients that underwent elective orthopedic surgery between the introduction of TNF inhibitors (at Sint Maartenskliniek, January 2001; Radboud University Nijmegen Medical Centre, January 1997) and September 2004 were included in a parallel retrospective cohort study with a followup of 1 year. Patients with no known followup exceeding 1 year were excluded.

The diagnosis of RA was made according to the American College of Rheumatology (formerly American Rheumatism Association) criteria[19] by the treating rheumatologist and noted in the patient chart. Patients with another principal diagnosis were excluded. To ensure selective inclusion of all relevant patients from the source population, both the admission record of the department and the surgery planning schedule were used as source documents. Moreover, the charts of all patients receiving anti-TNF where cross-checked to assess whether they had undergone a surgical procedure.

Multiple operations performed on one patient were considered independent procedures when the second operation was not related to complications of the first and when the interval between the 2 operations exceeded 3 months. Patients with multiple operations who developed more than one SSI were censored. All infections therefore occurred in different patients, fulfilling the main assumption for the use of a regression model, which is independence of observations. Procedures where an infection was present at the start of the surgery were excluded.

The perioperative protocol in both centers required control of anticoagulant state (INR < 2.0 when using an oral anticoagulant), prophylactic lightweight molecular heparin daily, prophylactic antibiotics on the day of surgery (cefazolin 1000 mg at start of procedure; repeated after 4 h depending on duration of surgery), and when applicable a temporary increase of corticosteroid dose.

Approval by the local ethical committee was obtained where necessary, and research was carried out in compliance with the Helsinki Declaration.

*Design and data acquisition*. Two parallel cohorts were defined: cohort 1, consisting of anti-TNF-naive patients, and cohort 2, patients using anti-TNF. The latter was subdivided into patients that stopped anti-TNF treatment before surgery (cohort 2A) and patients that continued anti-TNF treatment perioperatively (cohort 2B). The allocation to cohort 2A and cohort 2B was determined by the duration of the discontinuation of anti-TNF, and the cutoff point was arbitrarily chosen to be 4 times the half-life of the anti-TNF agent used (39 days for infliximab, 12 days for etanercept, 56 days for adalimumab). Although the perioperative protocol at the Sint Maartenskliniek and the Radboud University Nijmegen Medical Centre requires cessation of anti-TNF treatment at least 2 weeks before surgery, implementation of the protocol varies depending on individual treatment schedules and adherence to the protocol. We estimated that enough variation would exist to consider this a natural experiment.

The collected data included patient characteristics, patients' history [including earlier (wound) infections], disease-specific and previous treatment related data, and characteristics of surgery and all complications. The chart review was performed by a rheumatologist and a junior research physician, and a standard case report form was used. The abstractors were masked to the primary study hypothesis. The percentage of missing values was calculated, and the presence of missing values was resolved using listwise deletion or substitution.

*Endpoints*. The combined incidence of early (< 30 days) and late (30 days to 1 year) SSI according to the modified 1992 US Centers for Disease Control and Prevention criteria for postoperative infection was chosen as the primary endpoint. These criteria are fulfilled when any of the following is present: (1) purulent discharge from a surgical site, (2) a positive culture, (3) a surgical site requires reopening, or (4) SSI is present as judged by the treating surgeon[20]. Secondary endpoints were other postoperative complications like wound dehiscence (slowed closure, leakage), bleeding and hematoma, aseptic prosthesis loosening, reoperation for any indication, and death. Although retrospective assessments of endpoints can lead to information bias, it is reasonable to assume that all important complications were documented for several reasons: RA patients are assessed by their rheumatologists every 3 months in both hospitals, followup after surgery is done according to protocols that are specified for every type of procedure, and both hospitals also document complications prospectively in a complication registry.

*Confounding by indication*. Special attention was given to possible confounding by indication — a form of allocation bias, i.e., that patients expected by the treating physician to have a higher infection risk would have a higher chance to have anti-TNF treatment stopped. First, relationships between scheduled infliximab infusions and planned procedures were checked for randomness, as a random distribution of the procedures between 2 scheduled infusions would provide a strong case against confounding by indication. In addition, remarks in the patients' charts concerning reasons for possible adaptation of the anti-TNF treatment were checked deliberately. Further, we evaluated whether prior infectious events (SSI or gram-positive skin infections like erysipelas, furunculosis) that could be interpreted by the treating physician as a risk factor for SSI were more frequent in patients that temporarily discontinued anti-TNF treatment. Finally, use of propensity scores was intended to correct for confounding by indication.

*Power calculation*. Based on a 2-sided Fisher exact test, an alpha of 0.05, an expected total number of anti-TNF users to undergo surgery of 200 (expected ratio of cohorts 2A and 2B 1:1), and expected total infection rate of 5% in the cohort that stopped anti-TNF, the study was expected to have a power of 80% to find an absolute risk of 18% (relative risk of 3.6) for infection when anti-TNF is continued.

*Analysis*. Descriptive statistics were provided for each of the cohorts. Infection risks were compared between cohort 1, 2A, and 2B. Parametric and nonparametric tests were used where applicable.

To determine predictors of SSI, univariate analyses of each determinant were performed first using cross-tables. Then a number of possible determinants, confounders, and/or effect modifiers were included in a logistic regression model using the data for cohort 1 and cohort 2 combined. The primary endpoint, occurrence of SSI, was used as the dependent variable. Candidate variables tested in univariate analyses were age, sex, body mass index, comorbid diseases including cardiovascular, diabetes, hypertension, osteoporosis, obstructive pulmonary disease, anemia and psoriasis, duration of RA and rheumatoid factor status, concomitant DMARD including methotrexate, sulfasalazine, leflunomide, hydroxychloroquine and prednisone, type (also revision) and duration of surgery, and history of SSI or skin infection.

For comparison of temporary discontinuation (cohort 2A) with continuation (cohort 2B) of TNF inhibitors, we attempted to calculate a propensity score to correct for possible confounding by indication. Stopping or continuing TNF was the main independent variable and occurrence of SSI was again the dependent variable, using cross-tables and logistic regression for analysis. Predictors for SSI were handled as potential confounders and added to the logistic model when addition changed the regression coefficient of stopping/continuing anti-TNF by 10% or more. Analyses were performed using SPSS statistical package 12.0.1 for Windows.

## RESULTS

A total of 1219 procedures were performed on 768 patients: procedures on TNF-naive patients (cohort 1), n = 1023; procedures on patients that stopped TNF treatment (cohort 2A), n = 104; and procedures on patients that continued anti-TNF treatment (cohort 2B), n = 92. Seventeen cases in cohort 2 were excluded because documentation of anti-TNF treatment was incomplete (9 infliximab, 5 etanercept, 3 adalimumab). The percentage of missing values was 3%. Due to a logistical error, data on prior SSI/skin infections were missing for cohort 1 patients from the Maartenskliniek. For cohort 2, the data were complete.

The numbers of procedures per year increased steadily, as shown in Table 1. Baseline patient characteristics are shown in Table 2, indicating a difference between cohorts 2 and 1 only in number of previous DMARD and prednisone use. No significant differences were seen between cohorts 2A and 2B. Moreover, membership of cohort 2A or 2B could not be predicted by any of the variables in multiple logistic regression with backward selection (all $p > 0.10$), thus a propensity score was neither useful nor needed to correct for prognostic differences between the groups.

Details on anti-TNF use are depicted in Table 3. Perioperative anti-TNF use increased from 7% of all procedures in 1997 to 22% in 2004. The use of etanercept and infliximab or adalimumab was not evenly distributed between cohort 2A and 2B, because of the shorter half-life of etanercept compared to infliximab and adalimumab. The distribution of the timing of the procedures between scheduled infusions of infliximab was random, with the exception of the first 2 weeks directly after the last infusion, during which procedures were seldom performed (data not shown).

Table 4 gives characteristics of the different types of surgery performed in each cohort. Hand and foot surgery were the most common procedures, followed by hip and knee surgery.

All recorded complications are described in Table 5. The numbers reported in the table refer to the number of procedures with complications; because some procedures were complicated by multiple events, total numbers are lower than the sum of the events. Twenty-two of 55 infections were backed by positive cultures, of which 14 *S. aureus*, 4 mixed culture (3 including *S. aureus*), 1 *Klebsiella pneumoniae*, and 1 *Enterobacter cloacae*.

Crude total SSI rates were 4.0%, 5.8%, and 8.7% for cohorts 1, 2A, and 2B, respectively. Bleeding and wound healing problems were the most common noninfectious complications. Procedures complicated by a SSI resulted in a longer hospitalization period (median 12 days vs 15 days; $p < 0.01$) and more frequent early and late reoperations (48/1164 vs 31/55; $p < 0.0001$).

The results of the logistic regression model to identify predictors of SSI in cohorts 1 and 2 combined (model 1) are displayed in Table 6. In the combined cohort, the only variables that were significantly associated with increased SSI risk were elbow and foot or ankle surgery and a history of SSI/skin infection. The use of sulfasalazine and a longer duration of surgery were associated with lower SSI risks. Analyses were carried out both with all missing values regarding prior SSI/skin infections set to 0 and with listwise deletion, and both approaches yielded the same results.

The results of the logistic regression to assess whether continued use of anti-TNF influences the risk of SSI (model 2) are shown in Table 6. Perioperative continuation of anti-TNF was

*Table 1*. Number of procedures per year.

| | Year of Surgery | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 1997 | 1998 | 1999 | 2000 | 2001* | 2002* | 2003* | 2004** | |
| Cohort | | | | | | | | | |
| 1 | 57 | 68 | 80 | 89 | 183 | 190 | 203 | 153 | 1023 |
| 2A | 0 | 2 | 1 | 1 | 8 | 27 | 36 | 29 | 104 |
| 2B | 2 | 4 | 3 | 3 | 13 | 22 | 20 | 25 | 92 |
| Total | 59 | 74 | 84 | 93 | 204 | 239 | 259 | 207 | 1219 |

* Including results from St. Maartenskliniek Nijmegen. ** Results from St. Maartenskliniek until September 2004.

*Table 2.* Baseline patient characteristics. Values are number (%) or mean ± SD unless stated otherwise.

| Characteristic | Total | 1 | 2A | 2B |
|---|---|---|---|---|
| Number (M/F) | 1219 (277/942) | 1023 (234/789) | 104 (26/78) | 92 (17/75) |
| Age, yrs | 60 ± 14 | 61 ± 13 | 54 ± 16 | 57 ± 13 |
| BMI, kg/m$^2$ | 26 ± 4 | 26 ± 4 | 25 ± 4 | 25 ± 4 |
| Disease duration, yrs | 17 ± 11 | 17 ± 11 | 16 ± 9 | 17 ± 8 |
| RF-positive, % | 75 | 74 | 82 | 80 |
| Comorbidity, n (%) | | | | |
| Diabetes mellitus | 73 (6) | 57 (6) | 8 (8) | 8 (9) |
| Hypertension | 242 (20) | 210 (20) | 17 (16) | 15 (16) |
| Osteoporosis | 82 (7) | 66 (7) | 8 (8) | 8 (9) |
| Psoriasis | 67 (6) | 62 (6) | 4 (4) | 1 (1) |
| Cardiovascular | 178 (15) | 148 (15) | 13 (13) | 17 (19) |
| COPD | 146 (12) | 122 (12) | 13 (13) | 11 (12) |
| Anemia | 386 (32) | 323 (32) | 32 (31) | 31 (34) |
| Prior SSI/skin infection | — | 14/448* | 5/104 | 6/92 |
| Previous DMARD | 3.3 ± 2 | 3.0 ± 2 | 5.1 ± 2 | 5.0 ± 2 |
| Concomitant MTX, n (%) | 419 (34) | 346 (34) | 38 (37) | 35 (38) |
| > 1 DMARD, n (%)** | 201 (16) | 112 (11) | 47 (54) | 42 (46) |
| Prednisone, n (%) | 388 (32) | 307 (30) | 42 (40) | 39 (42) |
| Prednisone users | 7.4 ± 7 | 7.7 ± 8 | 5.8 ± 2 | 7.0 ± 3 |
| NSAID, n (%) | 1036 (85) | 877 (86) | 83 (80) | 76 (83) |
| Anticoagulant, n (%) | 110 (9) | 91 (9) | 9 (9) | 10 (11) |

* Data from Radboud University Nijmegen Medical Centre only. ** Including anti-TNF agent. SSI: surgical site infection, BMI: body mass index, COPD: chronic obstructive pulmonary disease, DMARD: disease modifying antirheumatic drug, MTX: methotrexate, NSAID: nonsteroidal antiinflammatory drug.

*Table 3.* Characteristics of anti-TNF use. Values are number (n) or mean ± SD.

| Therapy | Total | 2A | 2B |
|---|---|---|---|
| Infliximab, n | 80 | 29 | 51 |
| Etanercept, n | 79 | 71 | 8 |
| Adalimumab, n | 37 | 4 | 33 |
| Total, n | | 104 | 92 |
| Duration of use, wks | | 62 ± 44 | 62 ± 65 |
| No. of half-lives stopped | | 5.6 ± 2.1 | 1.9 ± 1.0 |

not associated with a significant increase of the SSI risk, according to the entry model (OR 1.56, 95% CI 0.52–4.66) and when corrected for potential confounders (OR 1.50, 95% CI 0.43–5.2). The influence of the confounders was minimal. No other variables acted as confounder or effect modifier.

Analyses of the secondary endpoints showed 4 deaths, none directly related to the surgical procedure. All secondary endpoints occurred in low frequencies and were evenly distributed over all groups except for wound dehiscence, which occurred more frequently in patients that continued anti-TNF compared to patients that temporarily discontinued anti-TNF treatment (OR 11.2, 95% CI 1.4–90). The risk of wound dehiscence was, however, very low in patients that stopped anti-TNF treatment. Compared with anti-TNF-naive patients the OR for wound dehiscence was lower but still significant (RR 2.4, 95% CI 1.1–5.0).

## DISCUSSION

To our knowledge, this is the largest study to examine risk factors for surgical site infection in patients with RA and the first in the anti-TNF era. Our study shows that SSI rates in RA patients after elective orthopedic surgery are low but have important consequences. Factors associated with an increased SSI risk were similar to those seen in other studies (foot, ankle, or elbow surgery), but history of prior SSI or skin infec-

*Table 4.* Characteristics of procedures and infection rates. Values are number of procedures (%).

| Procedures | Total | 1 | 2A | 2B | Infections |
|---|---|---|---|---|---|
| Total procedures | 1219 | 1023 | 104 | 92 | |
| Wrist/hand | 317 (26) | 266 (26) | 30 (29) | 21 (23) | 8 (3) |
| Ankle/foot | 280 (23) | 226 (22) | 29 (28) | 25 (27) | 25 (9) |
| Knee | 195 (16) | 168 (16) | 12 (11) | 15 (16) | 8 (4) |
| Hip | 172 (15) | 139 (14) | 17 (16) | 16 (17) | 2 (1) |
| Shoulder | 114 (9) | 101 (10) | 7 (7) | 6 (7) | 1 (1) |
| Elbow | 102 (8) | 89 (9) | 6 (6) | 7 (8) | 9 (9) |
| Other | 39 (3) | 34 (3) | 3 (3) | 2 (2) | 2 (5) |

*Table 5*. Characteristics of all infectious and noninfectious complications. Values are number of procedures (%).

| Complication | Total | 1 | 2A | 2B |
|---|---|---|---|---|
| Total procedures | 1219 | 1023 | 104 | 92 |
| Early SSI | 32 (2.6) | 25 (2.4) | 2 (1.9) | 5 (5.4) |
| Late SSI | 36 (3.0) | 25 (2.4) | 6 (5.8) | 5 (5.4) |
| Total SSI | 55 (4.5) | 41 (4.0) | 6 (5.8) | 8 (8.7) |
| Wound dehiscence | 55 (4.5) | 45 (4.4) | 1 (0.9) | 9 (9.8) |
| Bleeding | 46 (3.8) | 40 (3.9) | 1 (0.9) | 5 (5.4) |
| Early reoperation | 22 (1.8) | 21 (2.1) | 1 (0.9) | 0 (0) |
| Loosening of prosthesis | 3 (0.2) | 0 (0) | 1 (0.9) | 2 (2.2) |
| Late reoperation | 57 (4.7) | 47 (4.6) | 5 (4.8) | 5 (5.4) |
| Death | 4 (0.3) | 4 (0.4) | 0 (0) | 0 (0) |
| Total noninfectious complications | | 115 (11.2) | 6 (5.7) | 13 (14.1) |
| Total complications | 156 (12.8) | 131 (12.8) | 8 (7.7) | 17 (18.5) |

SSI: surgical site infection.

*Table 6*. Risk factors for SSI in all patients (model 1) and the effect of anti-TNF continuation (model 2) using logistic regression.

| | ß | SE ß | OR | 95% CI | p |
|---|---|---|---|---|---|
| Model 1 (all patients) | | | | | |
| Prior SSI/skin infection | 2.62 | 0.50 | 13.8 | 5.2–36.7 | < 0.0001 |
| Elbow surgery | 1.40 | 0.46 | 4.1 | 1.6–10.1 | 0.003 |
| Foot or ankle surgery | 1.16 | 0.36 | 3.2 | 1.6–6.5 | 0.001 |
| Duration of surgery | –0.87 | 0.32 | 0.42 | 0.23–0.78 | 0.006 |
| Sulfasalazine use | –1.56 | 0.74 | 0.21 | 0.05–0.89 | 0.035 |
| Intercept | –3.0 | | | | |
| Model 2 (all anti-TNF users) | | | | | |
| Entry model | | | | | |
| Continuation of anti-TNF | 0.44 | 0.56 | 1.56 | 0.52–4.66 | 0.43 |
| Intercept | –2.79 | | | | |
| Corrected model | | | | | |
| Prior SSI/skin infection | 3.64 | 0.77 | 38.2 | 8.40–174 | < 0.0001 |
| Elbow surgery | 1.58 | 0.90 | 4.84 | 0.84–28.0 | 0.078 |
| Continuation of anti-TNF | 0.40 | 0.64 | 1.50 | 0.43–5.2 | 0.53 |
| Duration of surgery | –1.15 | 0.69 | 0.32 | 0.08–1.2 | 0.098 |
| Intercept | –2.72 | | | | |

SSI: surgical site infection.

tion was found to be the strongest predictor. Although our study was not powered to detect small differences in risks for infection, continued perioperative use of anti-TNF does not seem to be a strong risk factor for SSI.

Perioperative management is an important issue in the general care of patients with RA. Although it has been suggested that the rate of elective orthopedic surgery is declining in RA[1,2], this is not supported by our findings, as in both the university hospital and the categorical hospital the absolute number of procedures increases every year. In addition, the percentage of patients taking TNF blocking agents undergoing surgery has increased 3-fold from 1997, to 22% in 2004. In light of the important sequelae of infection (longer duration of admission, frequent reoperation), the identification of manageable risk factors for SSI warrants our attention.

The risk factors for SSI we found are compatible with risk factors described in other studies, although the associations reported previously with diabetes and prednisone use could not be confirmed in our study[4,5]. The most important risk factor was prior SSI or skin infection. Several underlying mechanisms could play a role in increased host susceptibility for gram-positive infections, including being a staphylococci carrier or having a relative immunodeficiency. Candidate immune deficiencies that affect host response to staphylococci are, for example, impaired granulocyte function and low or dysfunctional mannose binding lectin[21,22].

Two other interesting observations were made. First, the use of sulfasalazine apparently had a strong protective effect against SSI. One might speculate that this is due to the bactericidal effect of the sulfapyridine component of sulfasalazine[23]. Indeed, sulfa drugs act through competitive inhibition of the prokaryotic PABA receptor, blocking bacterial folic acid synthesis and multiplication, and are especially effective against gram-positive bacteria.

Second, a longer duration of surgery protected against infections, while in other studies duration of surgery was associated with increased risk for SSI[4,5]. We do not have a satisfactory explanation for this finding. The reverse association found in our study might be caused by the fact that procedures lasting longer than 4 hours required a per-protocol second dose of antibiotics, thus offsetting a possible increase in the infection rate. Only a small proportion of procedures, however, lasted longer than 4 hours.

The most important finding of our study is that continuation or interruption of established anti-TNF therapy does not seem to have a major influence on the risk of SSI. However, an interesting observation was that the secondary endpoints of wound dehiscence and bleeding seemed to occur significantly more frequently in patients that had continued anti-TNF. Of note, this difference was largely due to a lower incidence of wound dehiscence in the patients that interrupted anti-TNF therapy even compared with anti-TNF-naive patients. Experimental studies on the role of TNF in wound healing demonstrate different properties of this proinflammatory cytokine in different stages of wound healing. In general, both supranormal levels of TNF (e.g., sepsis) and TNF-deficient states (TNF blockade or knockout mice) are associated with decreased cell influx and impaired collagen formation, leading to decreased wound strength[24-27]. TNF blockade could therefore be expected on pathophysiological grounds to impair wound healing, although studies in humans are lacking.

Our study has a few important limitations. First, in view of the low infection rates, more patients would be necessary to detect a smaller but still clinically relevant increase in SSI rates, and this limitation affects the majority of SSI studies in selected populations. A larger number of patients would also allow separate analyses for each anti-TNF agent. Second, data on RA disease activity is lacking. Disease activity could be included as a possible risk factor for SSI, and an increase in disease activity caused by interruption of anti-TNF treatment could be monitored, thus assessing a possible drawback of this strategy. Also, data on prior SSI or skin infections were unfortunately partially missing for patients from cohort 1. Analyses using different approaches to cope with these missing values, however, yielded similar results. Finally, it can be argued that using multiple events in one patient violates the assumption of independency of observations required by regression modeling. However, patients developing an event were censored. Thus, all infections occurred in different patients. Also, most characteristics, including the stochastic moment of being inoculated with bacteria, concomitant medication, and surgery type, vary between procedures and are therefore independent. A separate analysis with only the first procedure for each patient indeed resulted in less precision (lower number of procedures and of infections) but comparable odds risks.

Another limitation of our study is the nonrandomized comparison between stopping and continuation of anti-TNF that may lead to confounding by indication. However, we found no signs for this form of bias, as there were no baseline differences between cohort 2A and 2B, and membership of cohort 2A or 2B could not be predicted by a linear combination of the baseline variables. Further, the distribution of procedures was random between 2 scheduled infliximab infusions, indicating that infusions and procedures were not postponed and indeed there were no remarks in patients' charts suggesting that this happened. Finally, the rate of prior SSI, and skin infections was higher in patients that continued anti-TNF treatment, the opposite of what would be expected when prior infections were taken into account in the decision to stop anti-TNF therapy or not.

Our results show that the most important risk factor for SSI is history of prior SSI or skin infection. Although perioperative continuation of anti-TNF does not seem to be an important independent risk factor for SSI, TNF blockade is possibly associated with impaired wound healing. We plan to extend our research in the future, but larger prospective studies are warranted to investigate this possible association.


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