Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers

A. Ruyssen-Witrand, L. Gossec, C. Salliot, M. Luc, M. Duclos, S. Guignard, M. Dougados

Paris René Descartes University, Medicine Faculty; AP-HP, Cochin Hospital, Rheumatology B Department, Paris, France.

Abstract

Objective

Tumor necrosis factor (TNF) blockers have been reported to increase the risk of infections, thrombosis, and delayed healing. However, there is little data on the risk of complications after surgery in rheumatic patients receiving TNF blockers. The aim of this study was to assess the complication rate after surgery in such patients, to assess the effect of interrupting TNF blocker therapy, and to identify other potential predictors of complications.

Methods

This was a systematic, retrospective monocenter study of all patients treated with TNF blockers and who underwent surgery. Complications were recorded and complication rates were compared based on the type of surgery and the timing of the discontinuation of TNF blockers before surgery (above 2 or 5 half-lives). The complication rates were compared with those reported in the literature (orthopaedic procedures in RA patients: 7%, abdominal surgery: 13%).

Results

Between 1997 and 2004, 770 patients were treated with TNF blockers of whom 92 underwent surgery (127 surgical procedures). The most frequent underlying disease was rheumatoid arthritis (77%). Most of the surgical procedures were orthopaedic (85%). The complication rates for orthopaedic procedures and for abdominal procedures were 13% and 43%, respectively. The infection rate after orthopaedic procedures was 6.5%. Interrupting therapy before surgery did not significantly decrease the postoperative complication risk. There were no independent factors predicting complications.

Conclusion

In daily practice the complication rate after surgery is high in patients treated with TNF blockers. Discontinuing TNF therapy before surgery should be considered, although this study did not clearly demonstrate its role.

Key words

TNF alpha blockers, surgical procedures, postoperative complications, infections, rheumatoid arthritis, spondylarthropathies.

Adeline Ruyssen-Witrand, resident; Laure Gossec*, MD; Carine Salliot, MD; Mathieu Luc, MD; Muriel Duclos, resident; Sandra Guignard, MD; Maxime Dougados, Professor of Medicine.*

**These two authors contributed equally to the conception, design, analysis and interpretation of data, and to drafting the manuscript.*

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Please address correspondence and reprint requests to: Professor M. Dougados, Hôpital Cochin, Rhumatologie B, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France.
E-mail: maxime.dougados@cch.aphp.fr

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Introduction

Tumor necrosis factor (TNF) alpha blockers are now established as an efficacious therapy for rheumatic diseases such as rheumatoid arthritis (RA) (1), ankylosing spondylitis (2) and psoriatic arthritis (3). Significant slowing of structural damage is obtained with TNF blockers (4). However, some patients still have to undergo surgery, in particular orthopaedic procedures because of previous joint destruction. Furthermore, prescription of TNF blockers has much increased since their introduction in 1997; thus, the number of surgical procedures performed in patients taking these drugs is bound to increase.

The reported infection rate after surgery in the general population is 1% to 2.5% for total joint replacement procedures, 1% to 6.5% for other types of planned orthopaedic procedures (5) and around 13% for abdominal surgery (6). In RA the infection rate after surgery could be even higher (2% to 4% for total joint replacement) though the data are conflicting (7, 8).

The safety of TNF alpha blocker intake in the weeks preceding surgery is unclear and a potential cause for concern. TNF alpha blockers are known to increase the risk of infection during treatment (9), in particular severe and unexpected infections such as tuberculosis (10) or other opportunistic infections (11). TNF alpha blockers may impair wound healing (12) and seem to play a role in thrombosis (13). Phase III efficacy studies are insufficient to prove the safety of treatments (14). Indeed, such studies cannot address the issue of the safety of TNF blockers during the peri-operative period, because they include highly selected patients and surgery during the study period is very rare.

Limited previous studies indicate that TNF alpha blockers did not increase the risk of postoperative complications in patients with Crohn's disease who underwent resective bowel surgery (15, 16). No differences in the infection or healing complication rate were observed between 16 RA patients treated with TNF alpha blockers and 15 matched RA patients who had not received these therapies while undergoing foot and ankle surgery (17). The safety of TNF blockers therapy during surgery was also suggested in two other small studies (18, 19), and in data recently presented in abstracts (20, 21). A recent concise report (22) studied serious postoperative infections in 91 RA patients and reported 7 (20%) serious postoperative infections among 35 patients treated with TNF blockers. The authors did not study the effect of interrupting therapy.

To date, data for rheumatic patients regarding infections or complications of surgery performed while taking TNF blockers is limited and to our knowledge the role of interrupting therapy before surgery has never been assessed and there is no consensus (23).

The aims of our study were to assess the complication rate (including infections, thrombosis and healing complications) for rheumatic patients being treated with TNF alpha blockers who underwent surgical procedures during this treatment, to examine the effect on the complication rate of interrupting TNF blocker therapy before surgery, and if possible to identify other risk factors predicting complications after surgery.

Patients and methods

Study design

This was a retrospective monocenter observational study which took place in a tertiary center rheumatology unit. The principles outlined in the Declaration of Helsinki were followed and all data was processed anonymously.

Patients

Files of all patients treated with TNF alpha blockers in our center were retrospectively reviewed. Patients were identified through a computerized search of the data files of outpatients and inpatients who were seen at least once between January 1, 1997 and December 15, 2004. Key words used were: anti-TNF, infliximab, REMICADE, etanercept, ENBREL, adalimumab, or HUMIRA in full text. We excluded patients who never received a TNF blocker or for whom the data files were too poor (for example, patients seen only once for the introduction of TNF ther-

apy with no follow-up afterwards). All other patient files were reviewed and we selected all patients who underwent surgery during TNF blocker treatment. Data drawn from the files were recorded on a standardised chart review tool and included information on the patient's age, sex, diagnosis, disease duration, rheumatoid factor status, comorbidities (diabetes mellitus, obesity, leucopoenia or lymphopoenia), previous cumulative intake of glucocorticoids, number of previous disease modifying antirheumatic drugs (DMARDs), and the blood cell count. A patient was considered to be rheumatoid factor positive if at any time during the follow-up rheumatoid factor was above the norm (> 20 IU/l). Similarly, lymphopoenia was defined as a lymphocyte count < 1300/mm^3 and neutropoenia as a neutrophilic polynuclear cell count < 1700/mm^3 at any time during follow-up. Surgical procedures were classified as joint replacement, arthrodesis, revision of total joint replacement or implant material revision, synovectomy, tendon surgery, septic procedure on infected lesion (e.g., abscesses), emergency orthopaedic procedures, abdominal surgery, gynaecologic procedures and other types of operations. Hip joint replacement after hip fracture was classified as an emergency orthopaedic procedure. We separated surgical procedures into 5 groups based on the risk of infectious complications: 'clean' orthopaedic procedures such as total joint replacements and vertebral surgery, orthopaedic procedures with a moderate infectious risk such as arthrodesis, synovectomy, tendon surgery and other types of orthopaedic surgery with a low risk of infection, 'high risk' orthopaedic surgery such as joint replacement and implant material revisions, septic orthopaedic surgery (e.g., for abscesses) and all emergency orthopaedic operations. The two other groups were abdominal/gynaecologic procedures and other types of procedures (e.g., ophthalmologic).

Complications were classified as infections, thrombosis, wound healing complications or other complications as reported in the medical files. Even if patients underwent surgical procedures in another center, they were examined 1 to 6 months after the surgical procedure, and complications or the lack of complications were noted clearly. Infection was characterised as the development of an infection at the surgical site, either superficial or deep, within 1 month after surgery, or within 12 months for implant material (such as prosthesis). The need for antibiotics was noted, as was recourse to surgery because of the infection (i.e., debridement or extirpation of implant materials). Other types of complications occurring within 2 months after surgery were noted. Wound healing complications included dehiscence or delayed healing as mentioned in the file.

For each surgical procedure, the time between the last infusion or injection of a TNF blocker and the date of surgery was noted from patient's files, and if a patient had discontinued TNF blocker therapy for a duration of more than 5 half-lives before surgery, it was considered that TNF blocker therapy had been interrupted (24). We also examined whether discontinuing TNF blocker only 2 half-lives before surgery changed the outcome. Recommendations in our center were to discontinue therapy before surgery for 2 weeks in the case of etanercept, one month for adalimumab, and to plan surgery between two infusions of infliximab (i.e., 4 weeks after last infusion). TNF therapy was usually re-started after complete healing.

Statistical analysis

Statistical analysis was performed using SAS version 8.0.

- Description of all surgical procedures and all complications: We performed descriptive analysis of the patients' characteristics, all surgical procedures, and all complications. Comparisons used chi-squared or T-tests, with Fisher's exact tests as appropriate.

- Effect of TNF blocker interruption on complication rates: For this analysis, septic surgical procedures were excluded since they were already infected before surgery. Complications were analysed if they were infections, thrombosis or healing complications; other types of complications were not considered to be related or potentially related to TNF blocker therapy. The chi-squared test or Fisher's exact test were used. A post-hoc power unilateral analysis was also performed.

- Other potential risk factors of complication: Other risk factors were assessed using univariate and multivariate stepwise logistic regression, where the binary dependent variable was complications (yes/no). Here also septic procedures and complications other than infections, thrombosis or healing were excluded. We analysed demographic variables (age, sex, underlying disease, disease duration, body mass index, obesity, diabetes mellitus, blood cell count) and severity variables (previous cumulative corticosteroid intake, previous DMARDs, previous orthopaedic surgery including total joint replacement or arthrodesis, positive rheumatoid factor), as well as the type of treatment (TNF blocker, concomitant methotrexate therapy, type of surgical procedure). All variables with a p value < 0.30 in univariate analysis were entered in the multivariate model.

Results

Patient selection process

Between December 2004 and March 2005 a total of 1,571 patient files were examined (Fig. 1 shows the selection process). Between January 1, 1997 and December 15, 2004, 770 patients had received at least one TNF alpha blocker in our center. Among them, 92 underwent surgical procedures during the TNF treatment course for a total of 127 surgical procedures.

Patient characteristics

Most of the patients who underwent surgery had RA (77.2%); only 20% of patients had spondylarthropathies. Sixty-nine patients (75%) underwent one surgical procedure during TNF therapy, 16 (17%) underwent 2 surgical procedures, 5 (5%) underwent 3 procedures, 1 (1%) underwent 5 procedures and 1 patient (1%) underwent 6 procedures (mean 1.4 ± 0.8 procedures per patient).

RA patients who underwent surgery were older than the other RA patients followed in our unit (mean 54.3 versus 50.6 years, $p < 0.001$), with a longer disease duration (mean 13.3 *vs* 11.4

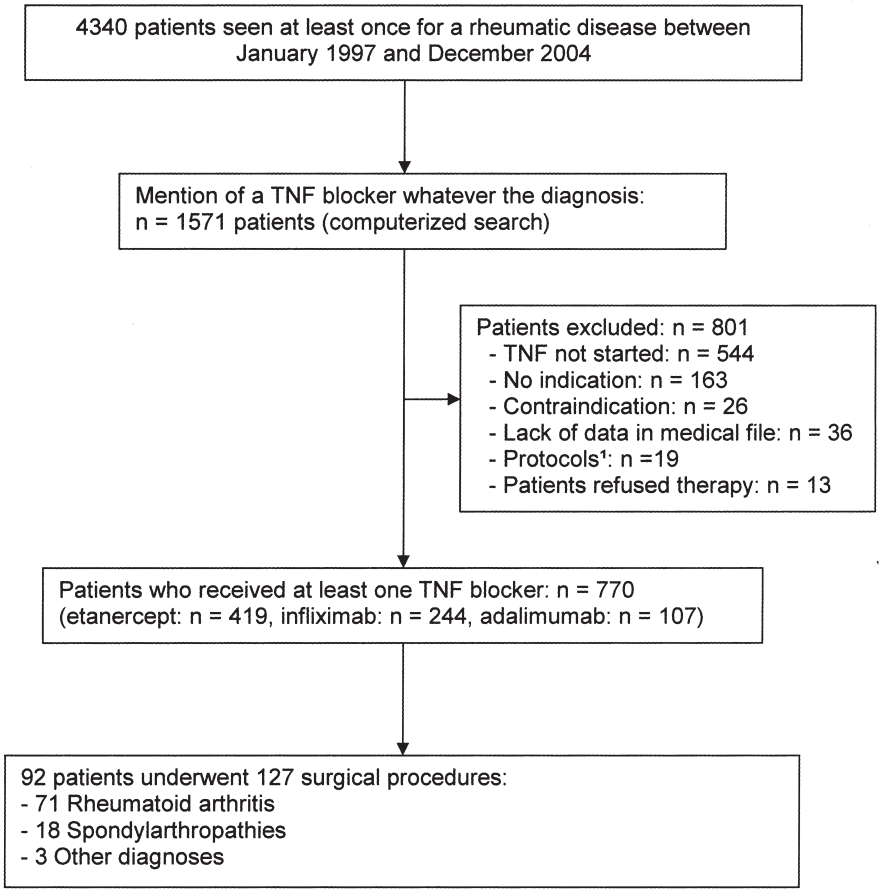

Fig. 1. Selection process of all patients files who underwent a surgical procedure during TNF blocker therapy.
[1]Protocols: these patients were excluded because they were taking placebo.

Table I. Characteristics of 127 surgical procedures.

Surgical procedures (n = 127)	Number (%)
Orthopaedic procedures	107 (84.3)
Joint replacements	38 (31.5)
Vertebral surgery	5 (3.9)
Arthrodeses (except vertebral surgery)	28 (24.4)
Synovectomy and tendon surgery	9 (7)
Others[2]	3 (2.4)
Total joint replacement and implant material revisions	8 (6.3)
Septic procedures[1]	6 (4.7)
Urgent orthopaedic procedures	10 (7.9)
Abdominal procedures[3]	6 (4.7)
Gynaecological procedures[4]	2 (1.6)
Other surgical procedures[5]	12 (9.4)

[1]Septic orthopaedic procedures: skin abscess (n = 4), phlegmon (n = 1), cellulitis (n = 1).
[2]Others: exeresis of skin lesion (n = 2), rotator cuff rupture (n = 1).
[3]Abdominal procedures: appendicectomy (n = 1), cholecystectomy (n = 1), colon abscess (n = 1), inguinal hernia (n = 2), anal abscess (n = 1).
[4]Gynaecological procedures: hysterectomy (n = 1), mastectomy (n = 1).
[5]Other surgical procedures: varix ablation (n = 2), sinusal polyposis (n = 3), thyroidectomy (n=1), adenopathy exeresis (n = 1), hydrocele ablation (n = 1), cataract (n = 3), and pace-maker replacement (n = 1).

years, $p = 0.03$), had received more corticosteroids (31.8 g *vs* 23.2 g, $p < 0.001$) and DMARDs (4.6 *vs* 3.8, $p < 0.001$) and had more often undergone previous joint replacement or arthrodesis (64.8% versus 24.1%, $p < 0.001$).

Description of surgical procedures

The surgical procedures are summarized in Table I. Most of the operations performed during TNF blocker therapy consisted of orthopaedic procedures (n = 107, 84%), including joint replacements (n = 38) and arthrodeses (n = 28). Joint replacements involved the knees (n = 13), hips (n = 16), shoulders (n = 5), ankles (n = 2), elbows (n = 1) and wrist (n = 1).

Complications

Complications according to the type of surgery are summarized in Table II. Among 127 surgical procedures, postoperative complications occurred in 24 (18.9%) cases. Postoperative complications included infections (n = 12, 9.4%), thrombosis (n = 1, 0.8%), and healing complications (n = 6, 4.7%). Other complications (n = 5, 3.9%) included ostheosynthesis breaking (n = 2), nervous lesions (n = 2), and eschar (n = 1). When we excluded those complications that could not be linked to TNF therapy, the overall complication rate was 15% (n = 19). Among patients who had a post-surgery infection, 6 (50%) were treated at home, 5 (41.7%) had to be hospitalized for treatment, and one (8.3%) went into intensive care. No patient died because of a post-surgery complication. Four of the 7 infections after orthopaedic procedures required a second operation for implant material extirpation. Other septic complications following an orthopaedic procedure involved superficial areas and could be treated with antibiotics. All abdominal and gynaecological postoperative infections were treated with antibiotics without recourse to surgery.

Ten of the 12 postoperative infections occurred within 15 days after surgery. One infection following hip total joint replacement was diagnosed 3 months after surgery and one infection of implant material was diagnosed 8 months after surgery

Orthopaedic procedures had a complication rate of 12% (n = 13) with 5.6% (n = 6) infections, whereas abdominal procedures had a complication rate of 50%, all of them infectious (n = 4). Yet patients who underwent 'clean'

Table II. Characteristics of 127 surgical procedures performed on 92 patients while they were taking TNF blockers therapy and the post-operative complications observed.

	All post operative complications	Infections	Thrombosis	Delayed healing	Others
Total surgical procedures, n = 127 (100%)	24 (18.9)	12 (9.4)	1 (0.8)	6 (4.7)	5 (3.9)
Joint replacements and vertebral surgery, n = 43 (100%)	7 (16.3)	3 (7)	0	2 (4.4)	2 (4.4)
Non-vertebral arthrodesis tendon surgery, synovectomies and others[1], n = 40 (100%)	4 (10)	1 (2.5)	0	2 (5)	1 (2.5)
Implant material revisions, septic surgery and emergency procedures, n = 25 (100%)	7 (28)	2 (8)	1 (4)	2 (8)	2 (8)
Abdominal and gynaecologic procedures, n = 8 (100%)	4 (50)	4 (50)	0	0 0	
Other type of surgeries[2], n = 12 (100%)	2 (16.7)	2 (16.7)	0	0 0	

p value analysing the entire table: p = 0.1.
[1] Exeresis of skin lesion (n = 2), rotator cuff rupture (n = 1).
[2] Other surgical procedures: varix ablation (n = 2), sinusal polyposis (n = 3), thyroidectomy (n = 1), adenopathy exeresis (n = 1), hydrocele ablation (n = 1), cataract (n = 3), and pacemaker replacement (n = 1).

Table III. Complication rate after surgery in relation to the discontinuation of TNF blocker therapy before surgery among 101 surgical procedures (6 procedures for septic lesions were excluded and for 20 procedures the date of discontinuation was unknown).

	Therapy discontinued < 2 half-lives: n = 10	Discontinuation between 2 and 5 half-lives: n = 55	Therapy discontinued > 5 half-lives: n = 36
Complications, n (%)	3 (30.0)	9 (16.3)	7 (19.4)
No complications, n (%)	7 (70.0)	46 (83.6)	29 (80.6)

p value analysing the entire table: $p = 0.56$

Table IV. Treatments that could have influenced the complication rates among 121 surgical procedures.

	Procedures with complications (n = 19)	Procedures with no complication (n = 102)	*p* value
Previous corticosteroid intake			
Current use of prednisone, n (%)	17 (89.5)	66 (64.7)	0.3
Cumulative dose (g), mean (SD)	35.6 (25.2)	26.5 (24.4)	0.18
Current prednisone dose (mg/day)	6.2 (4.2)	7 (4.1)	0.46
Methotrexate			
Prescribed at initiation of TNF therapy, n (%)	8 (42.1)	54 (52.9)	0.38
TNF therapy			
Infliximab (n = 39), n (%)	6 (15.4)	33 (84.6)	0.17
Etanercept (n = 61), n (%)	7 (11.5)	54 (88.5)	
Adalimumab (n = 21), n (%)	6 (28.6)	15 (71.4)	
Type of surgical procedure			
Revision of total joint replacement or implant material versus other orthopaedic procedures	3 (21.4)	5 (5.7)	0.077

orthopaedic procedures such as joint replacement or vertebral surgery had a complication rate of around 10% (n = 4) with 7% (n = 3) infections.
Complication rates among patients who underwent emergency orthopaedic procedures was 20% (n = 2).
Four patients underwent surgery for orthopaedic or abdominal infected lesions (6 procedures) and were excluded from the following analyses.

Interruption of TNF blockers and complications
Table III shows the complication rate based on the timing of TNF blocker discontinuation. Among the procedures where TNF blockers were discontinued more than 5 half-lives before surgery (36 surgical procedures), there were 19.4% complications compared to 18.4% (12 complications for 65 surgical procedures) for procedures where TNF blocker therapy was interrupted less than 5 half-lives before or was not interrupted at all ($p = 0.48$). If therapy was discontinued for more than two half-lives the complication rate was 17.6%, *vs* 30.0% if therapy was discontinued less than 2 half-lives before or was not discontinued ($p = 0.24$). The power of the test was 78.5%.

Risk factors of complications
No risk factors, either demographic or for severity, were statistically significant in predicting post-surgical complications (Table V). Joint replacement or implant material revisions were more often associated with postoperative complications (15.8 *vs* 4.9), but this did not reach statistical significance ($p = 0.077$) even in multivariate analysis. Analysis of treatments (Table IV) showed more complications with adalimumab than etanercept (28.6% *vs* 11.5%), but this difference was not statistically significant ($p = 0.18$). The cumulative corticosteroid dose was higher in the group with postoperative complications, but this also was not statistically significant. Multivariate analysis also did not show any risk factor that influenced the complication rates (data not shown).

Discussion

This study indicates a very high post-surgery complication rate (15% com-

Table V. Logistic regression analysis of the risk factors that could have influenced the rate of postoperative complications among 88 patients.

	Patients with complications	Patients with no complication	*p* value
Patients, n = 88, number (%)	19 (21.6)	69 (78.4)	NA
Age, years, mean (DS)	54.5 (9.2)	51.3 (12.2)	0.24
Females, n (%)	7 (36.8)	17 (24.6)	0.38
Disease duration, years mean (DS)	13.9 (9.3)	13.8 (8.4)	0.95
Rheumatoid arthritis, n (%)	16 (84.2)	54 (78.3)	0.75
Rheumatoid arthritis with RF+, n (%)	13 (68.4)	36 (52.2)	0.29
Orthopaedic procedures before TNF therapy, n (%)	11 (57.9)	44 (63.8)	0.64
Diabetes mellitus, n (%)	2 (10.5)	2 (2.9)	0.20
Obesity, n (%)	4 (21.1)	6 (8.7)	0.21
Number of previous DMARDs, mean (DS)	4.1 (2.1)	4.1 (2.2)	0.97

plications with 9.4% infections) for patients undergoing surgery while taking TNF blockers. Orthopaedic procedures had a complication rate of around 12% with 5.6% of infections, whereas abdominal procedures had a complication rate of 50%, all infectious. This complication rate was very high whatever the surgical procedure. Interrupting TNF blockers for more than 5 half-lives before surgery did not seem to decrease that rate. Interrupting treatment before surgery for at least 2 half-lives did not significantly decrease the postoperative complication rate (17.6% *vs* 30.0%, $p = 0.24$). No other risk factors influenced the complication rates in this study.

The effect of interrupting TNF blocker therapy before a surgical procedure is a matter of debate. The importance of TNF alpha in the host defence against intracellular organisms has been known for some time and it would be expected that the neutralization of TNF alpha could lead to a higher infection rate, especially if the period between the last infusion or injection and the surgical procedure is short. There is little data about the role of interrupting therapy before the surgical procedure, or other risk factors of complications. The French Rheumatology Society recommends interrupting TNF therapy for two half-lives (16-19 days for infliximab, 20-40 days for adalimumab, 7 days for etanercept) before surgery in a sterile setting such as cataract surgery, and for five half-lives (40-47.5 days for infliximab, 50-100 days for adalimumab, 14.5 days for etanecept) for septic surgery or surgery with a risk of infection such as colorectal surgery or total joint replacement (25).

To evaluate the effect of interrupting TNF blockers, we chose a period of 5 half-lives because of pharmacokinetic data suggesting that after this period it can be considered that the drug has been eliminated (24). There were relatively few patients in the group whose treatment had been interrupted for more than 5 half-lives. This can be explained because of the length of the half-lives of these therapies, especially infliximab and adalimumab; thus respecting an interruption period of five half-lives could create an inflammatory flare of the underlying disease. Furthermore, some patients had to undergo emergency surgery and did not have time to interrupt treatment for five half-lives.

We did not find a significant effect on the complication rates of interrupting TNF blockers; however, there was a trend for more infections when the TNF blocker was not interrupted. A potential confounding factor was that most of the surgical procedures performed in patients who did not interrupt therapy or did so for less than 2 half-lives were emergency surgical procedures, which could also explain the higher complication rate. Therefore this study does not support the need to interrupt TNF blockers systematically. Post-hoc power analysis was performed and the power of our test analysing the fact of interrupting TNF therapy before surgery was 78.5%, i.e. it is possible but not probable that a larger study would demonstrate an effect of interrupting therapy.

In previous studies several potential risk factors of postoperative complications were detected such as obesity, diabetes mellitus, age, and a diagnosis of RA (26). In our study no risk factor in logistic regression appeared to increase the rate of complication after surgery. However, the sample size was not sufficiently large to exclude a potential risk factor increasing the complication rate due to the under-powering of the study. Adalimumab compared to etanercept seemed to be a potential risk factor for complications (28.6% *vs* 11.5%). This may be because adalimumab was given last (because marketed later) to patients for whom other drugs were not efficacious and who perhaps had more active or more resistant disease. We also observed that patients with post-surgery complications had often received a higher cumulative dose of corticosteroids before the beginning of TNF blocker therapy, even if this difference was not statistically significant.

Our study has some limits: because it was retrospective, some data were missing and the lack of a control group of patients not treated with TNF alpha blockers during the same period precludes any comparison of the rates of complications. All patients treated with TNF blockers were systematically reviewed; therefore the diagnosis of the underlying disease was variable. Nevertheless, most of our patients presented with RA, so the results observed in this study should not be extrapolated to other diagnoses. Concerning missing data, some patients underwent surgery in other centers; therefore, some minor postoperative complications may be underreported in our files. However, rheumatologists are particularly attentive with patients being treated with TNF blockers, and we believe that all infectious complications were reported in the files. Because this study was retrospective, we did not assess RA characteristics such as the HAQ score or joint count in the risk of post-surgical complications. These characteristics were not recorded in all of the files in the months before surgery and do depend on disease duration. Some other risk factors for poor healing such as smoking status, nutritional status and peripheral vascular diseases were not assessed because of too many missing data in the files.

Nevertheless, the present study has great assets: because it was a systematic retrospective study, all files for all rheumatic patients receiving TNF alpha in daily practice were analysed with no selection bias. Altogether, 770 data files with 92 patients undergoing surgery (127 surgical procedures) were analysed. Hence this represents the largest published study to date, and the results are in accordance with the most recent paper on the subject (22), although Giles *et al*. reported a much higher infection rate (20%) for RA patients undergoing orthopaedic surgery. Furthermore, since the use of TNF blockers has become more widespread, the question of its long-term safety (27) is becoming more and more important. Phase III efficacy trials cannot examine the effect of these treatments during the peri-operative period and only retrospective studies can assess the risk (14).

The results observed in this study have potential clinical implications. Since these data suggest that TNF blockers increase the complication risk during surgery compared to other data in the literature, such patients should be very carefully monitored for complications. Further large prospective studies are needed to confirm the role of discontinuing TNF therapy before undergoing surgical procedures.

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