Safety of surgery in patients with rheumatoid arthritis treated with tocilizumab: data from the French (REGistry – RoAcTEmra) Regate registry

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Abstract

Objective

To investigate the frequency and risk factors of postoperative complications in RA patients treated with tocilizumab (TCZ).

Methods

The French registry REGATE recruited 1496 RA patients receiving TCZ in routine care. Data from patients treated with TCZ who underwent surgery were reviewed. Frequency of post-surgery complications was collected and compared in patients with and without complications in order to identify factors associated with complications. Similar analysis was performed in patients with postoperative infection.

Results

We identified 167 patients who underwent 175 surgical procedures including 103 orthopaedic surgeries (58.9%). The patients were mainly women (84%) with a mean disease duration of 14.96±11.29 years. The mean delay between surgery and the last TCZ infusion was 4.94±1.74 weeks. Fifteen patients experienced 15 complications (8.6%) with 10 severe infections including 5 surgical site infections (33.3%). There was no significant difference between patients with and without complications. In multivariate analysis, previous treatment with rituximab in the previous year tended to be associated with postoperative complications (OR: 3.27, IC95% 0.92–11.49, p=0.06). Concerning postoperative infections, diabetes mellitus tended to be associated with this complication (OR: 3.73, IC95% 0.88–15.79, p=0.06) in multivariate analysis.

Conclusion

In RA patients treated with TCZ in perfusion, the rate of surgical complications was low: 8.6%. The median time between surgery and last infusion was relatively short according to half-life of TCZ but did not influence the rate of postoperative complications.

Key words

tocilizumab, rheumatoid arthritis, surgery, safety, biologics

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Introduction

A high number of patients with inflammatory rheumatic disease are submitted to surgical procedures, in particular orthopaedic surgeries (1). Rheumatoid arthritis (RA) patients have a higher baseline risk of infectious diseases compared to the general population (2), which in turn may result in the higher infection rate after surgery compared to the general population (3). Treatments, especially targeted disease modifying anti rheumatic drugs (tDMARDs) used to control RA, increase this risk of infection. It is therefore recommended to stop tDMARDs before surgery procedures. But dropping active treatment prior to surgery in patients with RA can result in a disease flare, which in turn can require steroids, also known to increase infection risk, and can also impact on postoperative rehabilitation (4, 5). It remains unclear whether the use of biological DMARDs, including tocilizumab (TCZ), constitutes an independent risk factor for postoperative complications (3). To date, few data are available concerning surgical procedures in TCZ treated patients, and none of these studies was powered to look at the global postoperative risk (6-8). French, British and American health authorities recommend withholding tDMARDs in patients with RA undergoing elective joint replacement surgery (9-11). Unfortunately, in non-orthopaedic procedures, data are lacking, and similar recommendations should be followed. Data from registries reflect daily clinical practice in unselected patients, and therefore allow estimating the risk of surgery in patients treated with biologic DMARDs. In this study, we used data from the REGistry-RoAcTEmra (REGATE) to evaluate the safety and predictive factors of complications after surgery in rheumatoid arthritis patients receiving TCZ in routine care.

Patients and methods

The REGATE registry is a nationwide cohort study investigating the long-term safety and efficiency of intravenous TCZ for treating RA. The French Society of Rheumatology is the promoter of this registry. Trained technicians collected standardised data prospectively in every centre at baseline, and every 6 months for 5 years. Characteristics of these patients have been described elsewhere (12). Serious adverse event, such as "hospitalisation in a surgical department" were collected in the electronic case report form, and validated by the coordinator of the registry (J. Morel). We retrieved preoperative data from the last follow-up visit scheduled in the REGATE registry preceding the surgery. When TCZ was interrupted more than 12 weeks prior to surgery, patients were excluded from this analysis. Missing data for factors such as associated treatment at the time of surgery, and details of postoperative complications were requested in each centre by e-mail.

Postoperative complications were collected and imputed to the procedure if complication occurred within the 12 weeks following surgery. A surgery followed by a postoperative complication was defined as a "surgery with complication". We distinguished different types of surgery between orthopaedic surgery (with or without arthroplasty or foot surgery), abdominal surgery and other surgery. First, we described the frequency of post-surgical complications after any surgery. Then, we compared the baseline data of patients with and without complications, and preoperative data for surgeries, in order to determine whether some baseline parameters, or concomitant treatments were associated with subsequent postoperative side effects. Finally, we separately analysed and compared patients with or without infectious complications. We separated infectious complications (surgical site infection and general infection), and other complications such as deep venous thromboembolism haemorrhagic complication, bowel obstruction or RA flare. A venous thromboembolism was defined as a pulmonary embolism or a deep vein thrombosis. Haemorrhagic complication was defined as bleeding that required surgical reexploration to achieve haemostasis. Bowel obstruction was defined as a partial or complete block of the small or large intestine. RA flare was defined as an episode of increased RA disease activity according to the rheumatolo-

gist. A delayed wound healing was defined as an abnormal healing process as judged by the surgeon or the rheumatologist at 4 weeks following surgery, in the absence of surgical site infection. In accordance with the 1992 Centers for Disease Control definitions, surgical site infection (SSI) were defined as infections occurring within the first 30 days after any surgery or the first year in case of arthroplasty, and as superficial or deep if involving tissue above or below the aponeurosis, respectively (13). General infections were defined as infection not fulfilling criteria for SSI. Serious infections in the registry were defined as an infection requiring hospitalisation, intravenous antibiotics or resulting in death.

Statistical analysis

Data for surgeries with and without complications were compared. We analysed the number (percentage) of patients or the median and extreme values (minimal / maximal). Each surgery was considered individually, even if one patient experienced multiple surgery procedures during the follow-up. The following variables were considered potential risk factors of postoperative complications: age; sex; weight; disease duration at the time of surgery; smoking; diabetes mellitus; chronic lung disease; chronic cardiac disease; recurrent infection; presence and level of rheumatoid factor or anti-cyclic citrullinated peptide antibodies; number of previous TCZ infusions at the time of surgery; previous use of biologic DMARDs in the year before the surgery; rituximab treatment in the year before the surgery; time since the last TCZ infusion before surgery; concomitant use of DMARDs (methotrexate (MTX), leflunomide, sulfasalazine or hydroxychloroquine), MTX and steroids dose at the time of surgery; type of surgery; blood neutrophil count; Disease Activity Score in 28 joints (DAS28) before surgery. Qualitative variables were compared by Fisher's exact test and the Mann-Whitney U-test was used to compare the quantitative variables. All variables showing a potential association with $p<0.25$ on univariate analysis were entered into a stepwise forward multivariate model. Statistical analysis involved use of SPSS v. 15.0, $p<0.05$ was considered significant.

Table I. Characteristics of RA patients at last visit preceding 175 surgery procedures.

	Data available	n (%) or Mean ± SD
Women (%)	175	147 (84%)
Mean age (years)	175	58.11 ± 12.8
Mean weight (kg)	171	71.1 ± 15.8
Mean disease duration (years)	167	14.96 ± 11.3
Smoker (%)	166	38 (22.9%)
Diabetes mellitus (%)	175	20 (11.4)
Chronic respiratory disease (%)	175	32 (18.3%)
Recurrent infection (%)	175	9 (5.1%)
Chronic cardiac disease (%)	175	7 (4%)
Mean DAS28	137	3.43 ± 1.74
Positive rheumatoid factor (%)	149	111 (74.5%)
Positive ACPA (%)	132	98 (74.2%)
Concomitant sDMARDs (%)	175	106 (60.57%)
Concomitant MTX (%)	175	82 (46.9%)
Mean dose (mg/week)		15.06 ± 4.81
Concomitant Leflunomide (%)	175	20 (11.4%)
Concomitant Hydroxychloroquine (%)	175	5 (2.9%)
Concomitant Sulfazalazine (%)	175	3 (1.7%)
Concomitant steroids (%)	175	107 (61.1%)
Mean dose (mg/d)		7.75 ± 4.77
Mean time between last infusion and surgery (weeks)	130	4.94 ± 2.6
Mean TCZ dose (mg/month)	174	7.76 ± 0.89
Previous biological DMARD	175	107 (61.1%)
RTX treatment in the previous year	175	20 (11.4%)
Mean number of TCZ courses before surgery	175	9.78 ± 8.1

kg: kilogramme; DAS: Disease Activity Score in 28 joints; ACPA: anti-citrullinated protein antibodies: MTX: methotrexate; DMARDs: disease-modifyng anti-rheumatic drugs; mg: milligramme; d: day; TCZ: tocilizumab; RTX: rituximab.

Results

From 2011 to 2013, 1496 RA patients treated by TCZ initiated after January 1st 2010 have been included from 78 French centres. Five patients had no follow-up. At the time of the analysis, 167 patients included in the REGATE registry underwent 175 surgical procedures: 103 orthopaedic, 29 abdominal and 43 other surgeries. Characteristics of RA patients collected at the last visit preceding the 175 surgery procedures are detailed in Table I. Patients were mainly women (84%), mean age was 58.11±12.83 years (median: 59, range: 22–87 years), and disease duration was 14.96±11.29 years (median: 12, range: 1–67 years). The mean delay between surgery and the last TCZ infusion was 4.94±2.6 weeks (median: 4, range: 0–12 weeks). Most of the surgical procedures were orthopaedics (58.9%), with osteosynthesis or arthrodesis for half of those patients. Surgery of hip and knee represented 42% of the orthopaedic procedures, and foot and ankle surgery 32.0%. Sixty-nine patients (39.4%) received TCZ in monotherapy.

Rate and description of postoperative complications

Fifteen patients experienced 15 postoperative complications (8.6%) with 10 severe infections including 5 surgical site infections and 5 general infections, 1 intestinal obstruction, 1 RA flare, 1 delayed wound healing, 1 venous thromboembolism and 1 haemorrhagic complication. More details of postoperative complications characteristics and management are described in the Supplementary file (Suppl. Tables S1 and S2). The mean delay between the surgery and postoperative complication was 4.23 weeks (median: 3.5, range: 0–12 weeks). For 8 patients, postoperative complications occurred after orthopaedic surgeries and 3 after abdominal procedures. Seven out 10 severe infections occurred following orthopaedic surgery. For 5 patients, TCZ treatment was definitively stopped because of the postoperative complication.

Risk factors of postoperative complications

Comparisons of patient's characteristics with and without complications are shown in Table II (more details in Suppl. Table S3). On univariate analysis, no risk factor was significantly associated with postoperative complications. However, corticosteroids (p=0.096), previous biological treatment (p=0.096) and RTX treatment in the previous year (p=0.07) tended to be associated with postoperative complications. In multivariate analysis, we excluded of the analysis rheumatoid factor and ACPA because of missing data. Moreover, we did not consider middle range DAS28 (from 2.6 to 5.1), since remission DAS28 and high DAS 28 level were not associated with postoperative complications. Finally, hip replacement and chronic lung disease were excluded of the multivariate analysis, as the percentage was higher in the "non-complicated" group. Then, the sex, previous biological treatment, RTX treatment in the previous year, corticosteroids treatment, diabetes mellitus, sDMARDS treatment associated, MTX treatment associated and the foot surgery were considered in multivariate analysis. Only RTX treatment in the previous year was close to be significant in multivariate analysis (OR: 3.27, IC95% 0.92–11.49, 0.06).

Risk factors of postoperative infectious complications

Comparisons of patient's characteristics with and without infectious complications are shown in Table III (more details in Suppl. Table S4). On univariate analysis, no risk factor was found statistically associated with postoperative complications. Only diabetes mellitus (p=0.09), foot surgery (p=0.095) and number of TCZ infusions before surgery (p=0.08), were close to statistical significance. In multivariate analysis, as explained previously, chronic lung disease antecedent, middle range DAS28, and anti-cyclic citrullinated peptide were excluded. We analysed the foot surgery, diabetes mellitus, other surgery, and the mean number of TCZ courses before surgery. Then, foot surgery (OR: 3.17, IC95% 0.82–12.21

Table II. Comparison of RA patients' characteristics at last visit preceding 175 surgery procedures with and without postoperative complications: univariate analysis.

	Data available	Surgery without complications n=160	Surgery with complications n=15	p-value
n. women (%)	175	136 (85 %)	11 (73%)	0.202*
Mean age (years)	175	57.9 ± 12.8	60.8 ± 13.5	0.440
Mean weight (kg)	171	70.9 ± 16	73.6 ± 14.3	0.381
Mean disease duration (years)	167	15.2 ± 11.5	12.3 ± 7.6	0.574
Smoker (%)	166	35 (23%)	3 (20%)	0.537
Diabetes mellitus (%)	175	17 (11%)	3 (20%)	0.236*
Orthopaedic surgery (%)	175	95 (59%)	8 (53%)	0.424
Prosthesis (%)	175	49 (31%)	3 (20%)	0.347
Foot surgery (%)	175	15 (9%)	0 (0%)	0.246
Abdominal surgery (%)	175	26 (16%)	3 (20%)	0.468
Other surgery (%)	175	39 (24%)	4 (25%)	0.528
Concomitant sDMARDs (%)	175	95 (59%)	11 (73%)	0.220*
Concomitant MTX (%)	175	73 (46%)	9 (60%)	0.213*
Concomitant Leflunomide (%)	175	18 (11%)	2 (13%)	0.533
Concomitant Steroids (%)	175	95 (59%)	12 (80%)	0.096
Time since last infusion before surgery (weeks)	130	4.9 ± 2.6	5.5 ± 2.2	0.270
Mean DAS 28	137	3.4 ± 1.7	3.5 ± 2.1	0.711
Previous biological treatment	175	95 (59%)	12 (80%)	0.096*
RTX treatment in the previous year	175	16 (10%)	4 (27%)	0.074*
Mean neutrophil blood count (mm^3)	157	4283 ± 2733	4226.2 ± 2046	0.700
Mean TCZ courses before surgery	175	9.9 ± 7.9	8.67 ± 9.6	0.317

TCZ: Tocilizumab treatment, RTX: Rituximab treatment, sDMARDs: synthetic disease-modifying anti-rheumatic drugs, DAS28: Disease Activity Score in 28 joints.
n procedures: number of procedures with available data.
*p-value<0.25 and involved in multivariate analysis.

Table III. Comparison of RA patients' characteristics at last visit preceding 175 surgery procedures with and without postoperative serious infectious complication: univariate analysis.

	Data available	Surgery without infectious complications n=165	Surgery with infectious complications n=10	p-value
n. women (%)	175	139 (84 %)	8 (80%)	0.497
Mean age (years)	175	57.9 ± 12.8	61.1 ± 13.8	0.324
Mean weight (kg)	171	71.1 ± 15.8	71.2 ± 16.2	0.963
Mean disease duration (years)	167	15.1 ± 11.4	11.6 ± 7.9	0.472
Smoker (%)	166	37 (24%)	1 (10%)	0.286
Diabetes mellitus (%)	175	17 (10 %)	3 (30%)	0.091*
Orthopaedic surgery (%)	175	96 (58%)	7 (70%)	0.349
Prosthesis (%)	175	49 (30%)	3 (30%)	0.489
Foot surgery (%)	175	15 (9%)	0 (0%)	0.095*
Abdominal surgery (%)	175	27 (16.4%)	2 (20%)	0.517
Other surgery (%)	175	42 (26%)	1 (10%)	0.246*
Concomitant sDMARDs (%)	175	98 (59%)	8 (80%)	0.280
Concomitant MTX (%)	175	76 (46%)	6 (60%)	0.297
Concomitant Leflunomide (%)	175	18 (11%)	2 (20%)	0.320
Concomitant Steroids (%)	175	100 (61%)	7 (70%)	0.408
Time since last infusion before surgery (weeks)	130	4.9 ± 2.7	5.0 ± 2.1	0.810
Mean DAS 28	137	3.4 ± 1.7	3.5 ± 1.7	0.602
Previous biological treatment	175	100 (61%)	7 (70%)	0.408
RTX treatment in the previous year	175	18 (11%)	2 (20%)	0.320
Mean neutrophil blood count (mm^3)	157	4315 ± 720.8	3714.7 ± 752	0.690
Mean TCZ courses before surgery	175	9.9 ± 7.8	8.0 ± 11.8	0.084*

TCZ: Tocilizumab treatment; RTX: Rituximab treatment; DMARDs: disease-modifying anti-rheumatic drugs, DAS28: Disease Activity Score in 28 joints. n procedures: number of procedures with available data. *p-value<0.25 and involved in multivariate analysis.

p=0.08) and diabetes mellitus (OR: 3.73, IC95% 0.88–15.79, p=0.06) were near to be significantly associated with infectious postoperative complications.

Discussion

Fifteen cases of postoperative complications out of the 175 surgical procedures were analysed in the REGATE registry (8.6% of procedures). Two third of these complications were serious infections including 5 site infections. Only one delay wound healing was collected. No risk factor was significantly associated to a postoperative complication in univariate or multivariate analysis. This absence of factors significantly associated with complications following surgery in our study may be explained by the one-month delay between stopping TCZ and the surgery procedure. Indeed, the median delay between the last infusion of TCZ before surgery and the time of surgery was 4 weeks, without any difference between patients with and without complication. Previous biological treatment and corticosteroids associated treatment were close to being associated with an increased postoperative complication risk. As expected, the most common complication observed was infections. We therefore examined the factors associated with this specific complication. Foot surgery and diabetes mellitus tended to be associated with severe infections following surgery. It is interesting to note that in a Japanese study retrieving postoperative complications following orthopaedic procedures, foot and ankle surgery was identified as a risk factor of serious site infection (14).

To our knowledge, this is the largest study describing postoperative complications for all surgery procedures in daily practice for RA patients receiving TCZ. In the Japanese observational TOPP study, reporting 161 RA patients treated with TCZ who underwent orthopaedic surgery, 20 delayed wound healing and only 3 surgical site infections were observed (8). In this study, surgeons evaluated themselves postoperative complications, which could explain the higher percentage of delay would healing reported.

The main limit of our study is the lack of a control group of RA patients receiving conventional DMARDs or anti-TNF. Due to this limitation, it was difficult to make any comparisons with other drugs. There are some other limits like the number of missing data, and the relatively limited number of surgical complications, which could result in lack of statistical power. When comparing our results with those reported with TNF inhibitors treatments, the frequency of complications following surgery, are in the same range as observed with TCZ. Thus, in a large retrospective study of 1,219 orthopaedic procedures for RA patients receiving anti-TNF therapy, 8.7% of local infectious complications were reported for those who retained the treatment before surgery and 5.8% for those who stopped treatment 4 half-lives before surgery (15). Compared to the two other French registries AIR-PR and ORA, the frequency of complications was 8.5 % (12/140) for RA patients treated with rituximab and 7% (20/284) for those treated with abatacept (ABA), very similar to the frequency observed in our study (16, 17). In the AIR and ORA French registries, spine surgery and duration of ABA treatment were respectively associated to a higher risk of postoperative complications. Interestingly, in the AIR-PR registry, postoperative complications were mainly infections (89%). This could explain the higher number of infectious complications in patients who received RTX the year before the surgery in our study.

More recently, George *et al*. reported that administering infliximab within 4 weeks of elective knee or hip arthroplasty was not associated with a higher risk of short or long-term serious infection compared to withholding infliximab for longer time periods (5). Steroid use during peri-operative period, especially >10mg/d, was associated with an increased risk of infection. Steroid prescription is more often identified as a risk factor of postoperative infection than anti-TNF (18). These observations combined with ours confirm that a period of 1 month between last administration of bDMARDs (excluding RTX) and surgery does not expose to an increase risk of serious postoperative infection. It supports the last ACR guidelines for the perioperative management of bDMARDs withholding in RA patients undergoing elective total knee or total hip arthroplasty (11). In certain conditions, such as diabetes, history of severe infections, foot surgery, and co-treatment especially steroids and RTX in the year of surgery, patients should be followed-up with greater caution after the procedure.

In conclusion, the frequency of postoperative complications in RA patients receiving TCZ is estimated at 8.6%, very similar to the rate observed with anti-TNF, rituximab, or abatacept. For RA patients treated with TCZ IV, a 1-month delay between last infusion and surgery did not influence the rate of postoperative complications.

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Key messages

- The rate of postoperative complication in rheumatoid treated patients treated with Tocilizumab is 8.6%.
- No risk factor was significantly associated to a postoperative complication in TCZ patients undergoing surgery.
- The delay between the last TCZ infusion and surgery did not influence the postoperative complication risk.

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