

## The perioperative use of synthetic and biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis

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### Summary

Disease-modifying antirheumatic drugs (DMARDs) have become essential treatments in the management of patients with inflammatory rheumatic diseases. Their use has resulted in a marked improvement of disease control and a limitation of joint damage, although some patients still require subsequent corrective or joint replacement surgery. Due to their immunosuppressive effects, some DMARDs are associated with an increased risk of infection. The aim of this review is to discuss the available literature on the management of DMARDs during the perioperative period, particularly in the case of orthopaedic surgery. Conventional synthetic DMARDs such as methotrexate, sulfasalazine, leflunomide, hydroxychloroquine appear to be safe during the perioperative period. Conflicting results on biological DMARDs, mainly tumour necrosis factor antagonists, are reported in the literature, including both increased and unchanged risk of superimposed infections after surgery. Taking into account the available literature, we included some propositions for the management of patients who will undergo surgical interventions.

**Key words:** surgery, perioperative, DMARDs

### Introduction

The first-line treatment of rheumatoid arthritis (RA) comprises various conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) [1]. Methotrexate is the cornerstone csDMARD that is used either as monotherapy or in combination with other DMARDs. If low disease activity or remission is not achieved with csDMARDs, treatment is escalated with the use of biological DMARDs (bDMARDs), including monoclonal antibodies or soluble receptors acting on specific cytokines, co-stimulatory signals and B cells. More recently, targeted synthetic DMARDs (tsDMARDs) blocking cell signalling such as Janus kinase (JAK) inhibitors have been introduced for the management of RA. In addition to their pathogenic role in immune-mediated inflammatory diseases, the pathways targeted by bDMARDs and tsDMARDs contribute to hosting defence

against pathogens [2]. As an example, the use of tumour necrosis factor (TNF) inhibitors is associated with an enhanced risk of infectious complications including various bacterial and viral infections as well as opportunistic infections [3]. Despite recent treatment progresses, some RA patients experience end-stage joint disease with structural damage requiring surgery. One critical question is how to manage immunosuppressive agents in patients who will require surgery, in order to avoid the occurrence of complications after surgery, but also to limit perioperative disease flares. This article aims to review the evidence regarding the use of DMARDs during the perioperative period and provide some guidance to the clinicians caring for patients with RA and other auto-immune diseases. To do this, the Medline database was screened to address the question of drug discontinuation and occurrence of perioperative complications (infection and delayed wound healing) in RA patients treated with cs- or bDMARDs undergoing orthopaedic surgery.

### Rheumatoid arthritis as a risk factor for perioperative complications

Several studies have attempted to examine surgical site complications (wound infection, delayed healing, and deep infection) among RA patients, unfortunately without always taking into account on-going DMARDs treatment. Even so, one would have to deal with factors such as disease activity that cannot be dissociated from DMARDs use, immunity impairment inherent to the disease, and concomitant glucocorticoid use. Table 1 summarises the conclusions of studies that have tried to give an overview of infection risks in RA patients, and aims to reflect the post-operative complications seen in various centres when no drug interruption guidelines are involved.

The largest study on total knee arthroplasties performed between 2006 and 2010 compared the number of infections after surgery in 11 755 RA and 339 348 osteoarthritis (OA) patients and showed that the risk was higher in RA patients (4.5% vs 3.8% infections,  $p < 0.001$ ) [12]. The results from the Nordic Arthroplasty Register Association included 13 384 total hip arthroplasties in RA and in 377 287 OA

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patients [7]. The relative risk (RR) of infectious complications was higher in RA patients who underwent surgery between 2002 and 2010 (RR 1.4, 95% confidence interval [CI] 1.0–1.8;  $p = 0.05$ ) as compared with those who had surgery between 1995 and 2001 (RR 1.1, 95% CI 0.8–1.5;  $p = 0.5$ ). Although not formally proven, the authors raise the fact that this slight increase could be related to the introduction of TNF inhibitors in Scandinavian countries. The Norwegian Arthroplasty Registry [19] reported a significantly increased RR of 1.6 (95% CI 1.06–2.38;  $p =$

0.027) of infectious complications in RA versus OA patients undergoing total hip or knee arthroplasty. In contrast, the risk of infections within 90 days following total hip arthroplasty was not significantly higher in 5565 RA compared with 132 834 non-RA patients (odds ratio [OR] for infection risk 1.47, 95% CI 0.90–2.41;  $p = 0.12$ ) in another study [18]. Despite these contradictory data, the larger studies consistently show a small but significant increase in risk of postoperative infections in RA compared to OA patients.

**Table 1:** Rheumatoid arthritis as a risk factor for postoperative infection.

Studies	Surgical interventions on RA patients	Control group	Orthopaedic procedures	Infection rate	Increased infection risk
Koyama et al. [4]	47	None	Spinal surgery	14.89%	Could not be proven
Kang et al. [5]	40	134	Spinal surgery	47.5 vs 17.1%	Yes
Lo Verde et al. [6]	159	318	TKA	Deep infection: 0 vs 0% Minor infection: 8.2 vs 13.2%	No
Schrama et al. [7]	13 384	377 287	THA	1995–2001: RR 1.1 (95% CI 0.8–1.5; $p = 0.5$ )	Yes, from 2001
Singh et al. [8]	496	33 815	THA, TKA	Readmission within 90 d: 8.5 vs 6.7% Major readmission cause infection: 10.2 vs 5.7%	Yes
Ravi et al. [9]	3855	97 445 OA 14 490 inflammatory arthritis	THA, TKA	RA: 1.3%; inflammatory arthritis: 1.13%; OA: 0.94%	Yes for TKA Not proven for THA
Pedersen et al. [10]	50	50	Foot and ankle surgery	Deep infection: 2 vs 0% Minor infection: 2 vs 0%	No
Carrol et al. [11]	58	906	THA, TKA	Superficial wound complication OR 2.56 (95% CI 1.17–5.58; $p = 0.018$ )	Yes
Stundner et al. [12]	11 755	339 348	TKA	4.5 vs 3.8% $p = 0.001$	Yes
Hsieh et al. [13]	46	300	THA, TKA	44 vs 32% $p = 0.14$	Could not be proven Worse outcomes among RA patients
Pahys et al. [14]	36	965	Cervical spine surgery	Infection OR 6.3 (95% CI 1.5–26.1; $p = 0.027$ )	Yes
Michaud et al. [15]	839	33 685	THA, TKA	4.17 vs 4.15%	No
Bhatia et al. [16]	41	59	Occipito-cervical fixation	5 vs 5.1% Deep infection: 4 vs 0%	No
da Cunha et al. [17]	75	131	THA, TKA	Superficial infection: 8 vs 2.3% Systemic infection: 5.3 vs 7.7%	No No significant result
Soothoo et al. [18]	5565	132 834	THA	90-day infection risk OR 1.47 (95% CI 0.90–2.41; $p = 0.12$ )	Could not be proven
Schrama et al. [19]	6629	102 157	THA, TKA	0.86 vs 0.64%	Yes for TKA Yes for THA only from 2001
van der Heide et al. [20]	58	None	Total ankle arthroplasty	6.90% Infection most important implant cause of failure	Could not be proven
Jämsen et al. [21]	3290	39 859	TKA	1.32% for primary TKA, 3.24% for revision HR 1.86 (95% CI 1.31–2.63) for primary	Yes
Bongartz et al. [22]	462	462	THA, TKA	HR 4.08 (95% CI 1.35–12.33)	Yes
Himanen et al. [23]	751	None	TKA	1.33%	Could not be proven
Ljung et al. [24]	50	None	Capitello-condylar prosthesis	Deep infection: 2% Delayed wound healing: 4%	Could not be proven
Kristensen et al. [25]	71	None	TKA	7% 4 haematogenous /1 postop. skin infection	Could not be proven
Wymenga et al. [26]	No data	3013 in total	THA, TKA	THA: 17/2651 TKA: 9/362 RR infection in TKA: 4.8 (95% CI 1.2–19)	Yes for TKA
Wilson et al. [27]	2076	1857	TKA	2.2 vs 1% ( $p < 0.0001$ )	Yes
Poss et al. [28]	275	382	THA	1.46 vs 1.57%	No
Garner et al. [29]	100	100	All except spinal surgery	13 vs 8% ( $p > 0.4$ )	No
Luessenhop et al. [30]	51 primary prosthesis infection RA prosthesis	None	THA, TKA, SA	19 RA patients among the 27 secondary infections	Yes

CI = confidence interval; OA = osteoarthritis; OR = odds ratio; RA = rheumatoid arthritis; RR = relative risk; SA = shoulder arthroplasty; THA = total hip arthroplasty; TKA = total knee arthroplasty

## Method

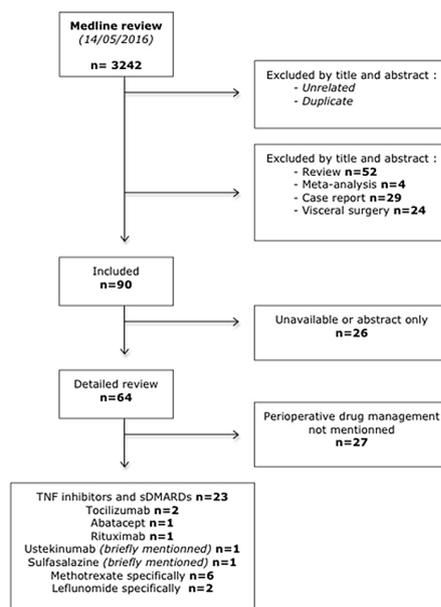
We used a combination of the following MeSH terms: *surgery, arthroplasty, infection, wound healing, surgical wound, rheumatoid arthritis, postoperative complications, perioperative period, orthopaedic surgery, anti-tumour necrosis factor, tocilizumab, abatacept, rituximab, belimumab, anakinra, tofacitinib, apremilast, methotrexate, leflunomide, sulfasalazine*, detailed in appendix 1. We included 37 articles based on the exclusion criteria summarised in figure 1. Based on the titles and the abstracts, our first selection process allowed us to exclude all the studies that did not discuss the link between perioperative complications and immunosuppressive drugs. We did not find any publications on the perioperative use of some DMARDs, such as apremilast, tofacitinib, belimumab and anakinra.

## Conventional synthetic disease-modifying antirheumatic drugs

### Methotrexate

A study examining the perioperative use of methotrexate (median dose 10 mg, 2.5–25 mg) included 388 RA patients who were prospectively randomised into three groups: 88 patients in whom methotrexate was continued, 72 patients in whom methotrexate was discontinued two weeks prior to surgery and resumed two weeks after surgery, and a control group of 228 patients without methotrexate treatment [31]. After a follow-up of one year, there was a significant reduction in the incident rate of infections in patients in whom methotrexate was maintained (2%), as compared to those in whom methotrexate was discontinued (15%,  $p < 0.003$ ) and the control group (10.5%,  $p = 0.026$ ). With-

**Figure 1:** Medline search strategy. sDMARD = synthetic disease modifying antirheumatic drug; TNF = tumour necrosis factor



in six weeks of surgery, RA flares were numerically more frequent in the methotrexate discontinuation group (8%) and the control group (4%) than in the methotrexate maintenance group (0%). A further logistic regression analysis showed a significant risk of infection with use of D-penicillamine, ciclosporin, hydroxychloroquine, chloroquine and prednisone.

Sixty-five patients included in this study were reviewed ten years later, including 23 patients from the methotrexate continuation, 8 from the methotrexate interruption, and 34 from the control groups. This long-term follow-up did not reveal any case of delayed infections [32].

A retrospective study included 122 RA patients undergoing 201 orthopaedic procedures [33]. Methotrexate was maintained in 77 cases and discontinued for more than one week prior to surgery in 21 cases. The remaining patients (103 surgeries) had not been treated with methotrexate. There was no significant difference in terms of postoperative infection (3.9, 4.8 and 3.9, respectively) or occurrence of delayed wound healing (1.3, 9.5 and 7.8%, respectively). There was also no significant difference regarding the incidence of disease flares in the three groups (3.9, 14.3 and 6.8%, respectively). Eighty RA patients undergoing 129 hand surgical procedures without perioperative drug interruption were divided into various treatment groups, including methotrexate monotherapy, glucocorticoids only, methotrexate plus glucocorticoid, and no therapy [34]. The authors observed four wound infections in the methotrexate groups (5%), and two in the group without therapy (4%).

A randomised non-blind prospective study examined the frequency of postoperative complications in 64 RA patients separated into two groups. In group A (32 patients, 50 surgical procedures) methotrexate was discontinued seven days before surgery; in group B (32 patients, 39 procedures), methotrexate was maintained [35]. There was no postoperative infection but prolonged wound healing in six and four cases in groups A and B, respectively (not significant).

A prospective non-randomised study included 32 RA patients undergoing elective total joint arthroplasty who were divided into two groups. In group one, methotrexate was discontinued one week prior to and after surgery ( $n = 19$  with 26 procedures), whereas in group two, methotrexate was maintained throughout the perioperative period ( $n = 13$  with 16 procedures) [36]. Four postoperative infectious complications occurred in group two, including two prosthetic infections, one infected joint fusion, and one deep wound infection, but none was observed in group one ( $p = 0.03$ ). No disease flare was observed in either group.

A systematic review including the studies described above concluded that low dose methotrexate is safe during the perioperative period, and associated with significantly fewer disease flares [37].

### Leflunomide

Two studies provided conflicting results regarding the perioperative safety of leflunomide. A case-control study including 41 RA patients treated with leflunomide (82 orthopaedic procedures) versus 41 patients in whom leflunomide was discontinued four weeks prior to surgery (79 orthopaedic procedures) showed no difference in the infec-

tion percentage (6.1 vs 6.3% local infections, respectively) [38].

A more recent prospective study included 201 patients with RA and psoriatic arthritis who underwent orthopaedic surgery and were treated with various combinations of methotrexate, leflunomide, etanercept, infliximab and glucocorticoids [39]. An increased number of postoperative complications was observed, including infections, impaired wound healing and necrotic scars in patients treated with leflunomide compared to methotrexate (40.6 vs 13.6%). A logistic regression analysis confirmed that the complication risk was significantly higher for leflunomide (OR 3.48, 95% CI 1.31–9.24;  $p = 0.01$ ), but not for the other drugs. Based on these results, the authors recommended stopping leflunomide without providing any specific indication regarding the timing and duration of treatment discontinuation. They also suggested that preoperative cholestyramine administration could help to reduce circulating levels of leflunomide.

### Sulfasalazine

There is no specific study on the safety of sulfasalazine in patients with inflammatory arthritis undergoing orthopaedic surgery. However, a retrospective cohort study compared the number of surgical site infections following 1219 orthopaedic procedures in RA patients, in whom TNF inhibitors were maintained or discontinued four drug half-lives before surgery (infliximab 39 d, etanercept 12 d, adalimumab 56 d) [40]. There was no significant effect of TNF inhibitors on the risk for infection (OR 1.5, 95% CI 0.45–5.2;  $p = 0.53$ ). Interestingly, the risk of infection was lower among those treated concomitantly with sulfasalazine (OR 0.21, 95% CI 0.05–0.89;  $p = 0.035$ ). The authors attributed the protective effect of sulfasalazine to its action on bacterial folic acid synthesis.

### Hydroxychloroquine

Hydroxychloroquine did not show any statistically significant association with either delayed healing or postoperative infections [41].

## Biologic disease-modifying antirheumatic drugs

### TNF inhibitors

The effect of TNF inhibitors on the risk of infectious complications in patients undergoing orthopaedic surgery has been examined in several studies. Most of these are retrospective and very heterogeneous regarding their design and conclusions. They include mainly RA patients and occasionally patients with other rheumatic diseases. Most of these studies compared the rates of infections in patients treated with TNF inhibitors versus csDMARDs without specifying whether the treatment was discontinued during the perioperative period. There is only one prospective randomised clinical trial that specifically compared the perioperative discontinuation versus maintenance of TNF inhibitors [42]. We have arbitrarily divided the presentation of the results into two parts: the first includes all the studies in which the use of TNF inhibitors was associated with an increased risk of infections, and the second describes those that did not find any difference in the number of infectious complications. All these studies are summarised in [table 2](#).

### *The use of TNF inhibitors was associated with an increased risk of infection*

In summary, there are six retrospective [43, 44, 46–49] and one prospective study [45] showing an increased risk for infection. Most of them do not provide information on whether TNF inhibitors treatment was discontinued before surgery. First of all, we describe the prospective study and then the retrospective ones.

A prospective observational non-randomised study evaluated the risk of septic arthritis among patients treated with TNF inhibitors (11 881) or csDMARDs (3673) [45]. Patients treated with TNF inhibitors were more likely to develop septic arthritis than patients on csDMARDs (HR 2.3, 95% CI 1.2–4.4), with 20 events in the csDMARD group and 179 events in the TNF inhibitor group. A subsequent analysis showed that previous arthroplasty was associated with an increased risk of septic arthritis (HR 2.45, 95% CI 1.90–3.17) in both groups.

In a retrospective nonrandomised multicentre study, a significant increase in infectious complications was observed in RA patients treated by bDMARDs (TNF inhibitors, abatacept, tocilizumab) undergoing arthroplasties (OR 2.12, 95% CI 1.48–3.03;  $p < 0.0001$ ) [47]. The prevalence of infections was 2.1% for bDMARDs (out of a total of 1626 arthroplasties) versus 1.0% in patients treated with csDMARDs (on a total of 29 903 arthroplasties). In contrast, the prevalence of infections was the same for other surgical procedures in the bDMARD and csDMARD groups (1.6 vs 1.0%). Timing of discontinuation before surgery was  $26.4 \pm 9.1$  for infliximab and  $14.1 \pm 6.7$  for etanercept. Number of surgical procedures on infliximab was 1616 and on etanercept 1686, with a number surgical site infections of 21 (1.3%) for infliximab and 23 (1.4%) for etanercept.

Ten infections were observed in a retrospective study including 91 RA patients who underwent orthopaedic procedures [43]. 35 patients were on TNF inhibitors at the time of surgery (no information on treatment discontinuation) and 56/91 were TNF inhibitor-naïve. Seven out of these ten infectious complications occurred in patients on TNF inhibitors. In the multivariate analysis, the use of TNF inhibitors was significantly associated with serious infections (OR 5.3, 95% CI 1.1–24.9).

Another retrospective case control study comparing the rates of infectious complications, deep venous thrombosis and RA flares included 64 orthopaedic procedures in 49 patients on TNF inhibitors (35 on infliximab and 29 on etanercept) versus 64 cases of surgery in 63 patients treated with csDMARDs (mainly methotrexate or sulfasalazine) [44]. Etanercept and infliximab were discontinued between two and four weeks, and four weeks, before surgery, as per the British Society of Rheumatology [64] and the Japanese College of Rheumatology [65] guidelines, whereas csDMARDs were not discontinued. The results showed that infections occurred more frequently in patients treated with TNF inhibitors (OR 21.8, 95% CI 1.231–386.1;  $p = 0.036$ ). Likewise, deep venous thrombosis was more frequent in patients treated with TNF inhibitors (OR 2.83, 95% CI 1.10–7.25;  $p = 0.03$ ). Disease flares were observed in 17.2% of all patients and more specifically in 31% of patients treated with etanercept versus 5.7% with infliximab.

Table 2: Overview of studies with TNF inhibitors.

Study	Design	Population	Treatment	Endpoint	Follow-up	Results	Conclusion
<b>Studies showing increased risk of infection</b>							
Giles et al. 2006 [43]	Retrospective	91 patients 35/91 on TNFi, 56 naive		Infection		Infection while on treatment 7/91 Infection in naive 3/91	Interruption recommended
Kawakami et al. 2010 [44]	Retrospective	RA, orthopaedic surgery 64 TNFi interrupted (ETN: 2–4 w, IFX: 4 w) vs 64 csDMARDs		Infection DVT Flare		Infection on TNFi OR 21.8 (95% CI 1.231–386.1; p = 0.036) DVT with TNFi OR 2.83 (95% CI 1.10–7.25; p = 0.03) 31% flares with ETN, 5.7% with IFX	
Galloway et al. 2011 [45]	Prospective	11 881 TNFi 3673 csDMARDs		Septic arthritis		aHR 2.3 (95% CI 1.2–4.4) for TNFi	
Momohara et al. 2011 [46]	Retrospective	RA Orthopaedic surgery		Septic arthritis		Use of bDMARDs OR 5.69 (95% CI 2.07–15.61) Longer RA duration OR 1.09 (95% CI 1.04–1.14)	
Suzuki et al. 2011 [47]	Prospective multicentre study	RA Orthopaedic surgery	bDMARDs	Prevalence of postoperative complications	January 2004 to November 2008	Use of bDMARDs OR 2.12 (95% CI 1.48–3.03; p <0.0001). Infection prevalence: 2.1% for bDMARDs, 1.0% for csDMARDs	
Johnson et al. 2013 [48]	Retrospective	RA TKA	bDMARDs csDMARDs	Prevalence of postoperative complications		7.3% AE including 4.3% infections: with TNFi 2.10%, local infections with csDMARDs	
Scherrer et al. 2013 [49]	Retrospective	Inflammatory rheumatic diseases OA Orthopaedic surgery	bDMARDs csDMARDs	Infection		OA group: 0.8% Inflammatory rheumatic disease group: 2.0% OR 2.58 (95% CI 1.81–3.67; p = 0.001) TNFi given <1 administration interval OR 10.05 (95% CI 1.17–86.29; p = 0.035)	
<b>Studies not showing increased risk of infection</b>							
Bibbo et al. 2004 [42]	Randomised prospective	31 patients: 141 elective foot procedures Gr 1: 16 pts with TNFi continued, 72 operations Gr 2: 15 pts without TNFi, 69 operations	Etanercept: 2.6 d (1–10 d) Infliximab: 20.2 d mean (2–45 d) csDMARD continued in both groups	Wound healing Infection	1 year	Total complications with TNFi < without TNFi Gr 1: 1 superficial infection Gr 2: 3 delayed cicatrizations, 2 nonunions, 1 delayed union, 1 osteomyelitis No respiratory or urinary infection	No interruption
Talwalkar et al. 2005 [50]	Retrospective	11 patients: 16 orthopaedic procedures	Gr A: 4 with TNFi continued Gr B: 12 with TNFi stopped			No systemic or local infection in groups A and B	
Wendling et al. 2005 [51]	Retrospective	30 patients: 50 procedures, mainly orthopaedic 18 TNFi stopped 32 TNFi continued		Infection Flare		No complication in either group Flares more common in interruption group	No interruption
Den Broeder et al. 2007 [40]	Retrospective	768 patients, 1219 orthopaedic procedures	Gp 1: no TNFi Gp 2A: TNFi stopped 4 half-lives before Gp 2B: TNFi continued	Infection		Infection while on TNFi OR 1.5 (95% CI 0.45–5.2)	No interruption Risk factors: skin infection, elbow, ankle, foot surgery Sulfasalazine could be protective OR 0.21 (95% CI 0.05–0.89)
Ruyssen-Wittrand et al. 2007 [52]	Retrospective	127 procedures (mainly orthopaedic), 97 patients (77% RA)	Surgery type Timing of discontinuation			Trend towards more infections with shorter delay before surgery	
Corrao et al. 2007 [53]	Case series	5 RA (ETN)	Without stop			No infection	
Hirano et al. 2010 [54]	Retrospective	RA Orthopaedic surgery 39 on TNFi 74 no TNFi		Wound healing Fever Inflammatory markers		TNFi: 5.1% adverse events on surgical wounds csDMARDs: 6.8% (not statistically significant)	No interruption
Gilson et al. 2010 [55]	Retrospective	RA Orthopaedic surgery 20 cases (infection while on TNFi) 40 controls (TNFi) TNFi interrupted 30 d ADA, 14 d ETN		Risk factors for infection		5 mg/d of GC plus TNFi OR 5 (CI 95% 1.1–21.6; p = 0.03) Previous arthroplasty infection OR 88.3 (95% CI 1.1–7071; p = 0.04)	Minimum doses Interruption recommended
Hayata et al. 2011 [56]	Retrospective	RA Orthopaedic surgery 52 procedures IFX stopped 4 w before surgery		Infection Wound healing		3.8% postoperative infection (2/52)	

Study	Design	Population	Treatment	Endpoint	Follow-up	Results	Conclusion
Barnard et al. 2012 [57]	Retrospective	RA Hand surgery ETN postponed 2–3 w before surgery	bDMARDs csDMARDs	Infection Wound healing Flare		No infection	Continue csDMARDs Stop bDMARDs
Berthold et al. 2013 [58]	Observational	TNFi Rheumatic patients Hand and general orthopaedic procedures	Gp A: 872 procedures stopped TNFi (IFX 8 w, ETN 1 w, ADA 4 w.) Gp B: 671 procedures without stopping TNFi	Infection		No significant difference in infection rates	
Somayaji et al. 2013 [59]	Retrospective	RA Orthopaedic surgery		Infection		No significant difference in infection rates, except for prednisone use OR 21 (95% CI 3.5–127.2; p<0.001) for doses >15 mg/day)	
Kubota et al. 2014 [60]	Retrospective	RA Orthopaedic surgery	bDMARDs with drug interruption 2–4 w before surgery (principally TNFi) Non-biologic (300 joints)	Infection		No significant difference in infection rates	
Abou Zahr et al. 2015 [61]	Retrospective	RA	csDMARDs bDMARDs according to algorithm	Infection		No significant difference in infection rates But increased risk of generalised infection with bDMARDs interrupted after surgery OR 9.2 (95% CI 1.99–42.60; p = 0.005) Increased risk of wound infection OR 14.15 (95% CI 1.76–113.76; p = 0.013)	
Tada et al. 2016 [62]	Retrospective	RA Orthopaedic surgery	csDMARDs bDMARDs with drug interruption 2–4 w before surgery	Infection Wound healing		No significant difference in infection rates	
Kadota et al. 2016 [63]	Retrospective	RA Orthopaedic surgery	bDMARDs (TNFi) with drug interruption 2–4 w before surgery	Infection Wound healing		No significant difference in infection rates Higher infection risk with foot surgery OR 3.167 (95% CI 1.256–7.986; p = 0.015) Delayed wound healing with TKA OR 4.044 (95% CI 1.436–11.389; p = 0.008)	

ADA = adalimumab; AE = adverse event; aHR = adjusted hazard ratio; bDMARD = biologic DMARD; DVT = deep vein thrombosis; CI = confidence interval; csDMARD = conventional synthetic DMARD; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GC = glucocorticoid; IFX = infliximab; OR = odds ratio; TNFi = tumour necrosis factor inhibitor;

This latter result must be interpreted with caution, as csDMARDs were not interrupted perioperatively. Finally, the authors did not observe any delay in wound healing.

A retrospective study analysed all consecutive total hip and total knee arthroplasties. 5.7% developed a superficial wound infection and 0.7% suffered a serious infection leading to removal of the prosthesis [46]. The use of bDMARDs (OR 5.69, 95% CI 2.07–15.61) and longer RA duration (OR 1.09, 95% CI 1.04–1.14) were associated with prosthetic joint infections.

A retrospective cohort study including 268 total knee arthroplasties in 248 RA patients reported adverse events in 7.3% of cases, including an infection rate of 4.3%, more specifically 3/92 (3.26%) local infections and one deep infection in patients on TNF inhibitors, and 3/143 (2.10%) local infections in patients treated with csDMARDs [48].

In a Swiss retrospective study covering 50 359 orthopaedic procedures (inflammatory rheumatic diseases and OA), 373 infections in 47 887 (0.8%) occurred in OA patients, and 49 infections in 2472 (2.0%) in patients with inflammatory rheumatic diseases (OR 2.58, 95% CI 1.81–3.67; p = 0.001) [49]. Within the inflammatory rheumatic disease group, the risk of infection was higher in TNF in-

hibitor than in csDMARD users, with an OR of 2.54 (95% CI 1.08–5.97; p = 0.032) with TNF inhibitors and an OR of 2.49 (95% CI 1.06–5.84; p = 0.036) for csDMARDs. This risk increased when the TNF inhibitors had been given within one administration interval (i.e., without stop) with an OR of 10.05 (95% CI 1.17–86.29; p = 0.035). Furthermore, the highest rate of infections was observed in cases of elbow and foot surgery.

Goodman et al. performed a meta-analysis in 2016 including eight observational and three case-control studies, covering a total of 3681 patients exposed to TNF inhibitors and 4310 with no recent exposure [66]. Results showed a higher risk of infection in the TNF inhibitor group with an OR of 2.47 (95% CI 1.66–3.68; p<0.0001). They did not analyse the continuation or stop of the TNF inhibitors before the operation.

#### ***The use of TNF inhibitors was not associated with increased risk of infection***

We found three prospective studies – two studies in which TNF inhibitors were maintained [42, 58] and another that compared TNF inhibitor discontinuation with a group of patients not receiving a TNF inhibitor [60] – and 11 ret-

rospective studies including three maintaining the TNF inhibitor [40, 50, 51], seven discontinuing [52, 56, 57, 59, 61–63], and one without further specification [54]. First of all, we describe the three prospective studies, and then the retrospective ones.

A prospective, randomised study included 31 RA patients who underwent 141 elective foot and ankle procedures [42]. Patients were divided into two groups: 16 patients on TNF inhibitors and 15 TNF inhibitor-naïve patients who underwent 4.5 and 4.6 mean procedures per patient, respectively, without stopping their treatment (bDMARDs and csDMARDs). Three soft-tissue healing complications were reported (two non-unions and one delayed union), and two cases of infections: one superficial infection in group one, and one osteomyelitis in a TNF inhibitor-naïve patient. There was no deep venous thrombosis reported. Except for a higher number of smokers in TNF inhibitor group, both groups were well matched for demographic characteristics. The authors concluded that TNF inhibitors could be safely administered during the perioperative period because of the same complication number between the two groups.

Rheumatic patients on TNF inhibitors undergoing hand and other orthopaedic procedures were divided in a prospective observational study into the following two groups: the first group (group A: 872 procedures) between 2003 and 2005 in which the TNF inhibitor was stopped (infliximab 8 w, etanercept 1 w, adalimumab 4 w) and another group (group B: 671 procedures) from 2006 to 2009 in which the TNF inhibitor was continued [58]. No significant association was observed between infection rates (total deep and superficial infections) and medical treatment, although 3% infections in the group A compared with 5.3% in the group B were reported.

A study divided RA patients undergoing orthopaedic surgery (total joint arthroplasty) into two groups; one biologic (267 joints) with drug interruption between two and four weeks before surgery according to the Japanese guidelines [65] (principally TNF inhibitors), and one non-biologic (300 joints) [60]. No significant differences in the incidence of complications were observed between the two groups (TNF inhibitor stopped vs csDMARDs continued) in terms of superficial and deep infections, which were observed in 0.37 and 1%, respectively in the biologic group vs 0.67 and 0% in the non-biologic group.

A retrospective study reported 11 patients (10 RA and one psoriatic arthritis) who underwent 16 operations. The TNF inhibitor was discontinued in 12 patients and maintained in four during the perioperative period. There were no serious systemic or wound infections. There was one episode of disease flare in a patient who stopped therapy [50].

In a retrospective study that included 50 surgical procedures in 30 RA patients, TNF inhibitors were maintained in 32 cases and withheld prior to surgery in 18 cases [51]. There was no major complication, but disease flares occurred more frequently in patients who discontinued therapy ( $p = 0.02$ ).

A retrospective parallel cohort included 768 RA patients with 1219 orthopaedic procedures who were divided as follows: group 1, TNF inhibitor-naïve; group 2A, TNF inhibitors stopped (four half-lives), and group 2B, TNF inhibitors continued [40]. There was no significant difference in the occurrence of infections between groups (OR

1.5, 95% CI 0.45–5.2). However, surgical procedures on the elbow, foot or ankle, as well as previous episodes of skin or wound infections, were associated with an increased risk of infectious complications (OR 4.1, 95% CI 1.6–10.1; OR 3.2, 95% CI 1.6–6.5; OR 13.8, 95% CI 5.2–36.7, respectively). Wound dehiscence (RR 2.4, 95% CI 1.1–5.0) and bleeding were more frequent in the TNF inhibitor group.

One retrospective study included 770 patients on biologics, 92 of whom underwent surgery (RA  $n = 71$ , ankylosing spondylitis  $n = 18$ ) [52]. TNF inhibitors included infliximab, etanercept and adalimumab. Patients underwent 127 surgical procedures (orthopaedic  $n = 107$ , 85%; abdominal  $n = 6$ , 4.7%; gynaecological  $n = 2$ , 1.6%; and other  $n = 12$ , 9.4%). Surgical procedures were separated into five groups based on the risk of infections and other complications such as deep venous thrombosis and rate of wound healing. Complication rates were compared based on the type of surgery and timing of TNF inhibitor discontinuation (less than two and up to five circulating half-lives prior to surgery). The total complications rate was 18.9% (24 cases), including 12 infections, 1 deep venous thrombosis and six delayed healings. Patients in whom therapy was discontinued less than two half-lives before surgery showed a higher rate of complications than those in whom discontinuation occurred with more than two (up to five) half-lives (30% vs 16.3, 19.4%), but the difference was not statistically significant ( $p = 0.24$ ).

A retrospective study including 39 RA patients on TNF inhibitors and 74 patients on csDMARDs undergoing orthopaedic surgery (ankle arthrodesis; total hip, knee, elbow or shoulder arthroplasty) found no differences in overall adverse events in wounds (csDMARDs: 6.8%, TNF inhibitors 5.1%,  $p = 1.0$ ), nor in duration of wound healing and fever. This study, however, does not provide sufficient data on discontinuation timing [54].

A case-control study performed within the French national registry RATIO (Research Axed on Tolerance of bioTherapies) included 20 patients with various rheumatic diseases (RA 90%, ankylosing spondylitis, psoriatic arthritis) treated with TNF inhibitors [55]. Patients who presented with infection after a total arthroplasty of a large joint were compared with 40 controls. A rate of 67% of flares was observed. Increased steroid intake was associated with infection (OR 5, 95% CI 1.1–21.6;  $p = 0.03$ ) as was previous arthroplasty infection (OR 88.3, 95% CI 1.1–7071;  $p = 0.04$ ). Neither TNF inhibitor use nor duration of exposure showed a statistically significant increase of infection rate, but infections had a worse outcome in patients on TNF inhibitors.

A retrospective study including RA patients who stopped infliximab four weeks prior to 52 orthopaedic procedures (total hip, knee, elbow or shoulder arthroplasty; foot/hand surgery, arthroscopic synovectomy and fractures) showed that infliximab did not increase the risk of superficial and deep infections [56].

In a study on hand surgery, authors reviewed 35 Swanson's metacarpophalangeal joint arthroplasties performed on RA patients [57]. They only interrupted their biologic treatment (TNF inhibitor, etanercept) two or three weeks prior to surgery and resumed after wound healing, while maintaining the other synthetic DMARDs, steroids or non-steroidal anti-inflammatory drugs (NSAIDs). In addition,

antibiotic prophylaxis was used. They observed no deep infection, only one superficial infection, one late suture granuloma, and one presumed rheumatoid flare.

A multicentre retrospective study reviewed 381 hip and knee arthroplasties performed on RA patients [59]. No further details were provided on the timing protocol for withholding biological agents (94% TNF inhibitors) or synthetic DMARDs except that 67.5% of patients were being treated at the time of surgery. Based on the small numbers of surgical site infections [7], the authors did not find any significant association between treatments and infection, except for prednisone use exceeding 15 mg/day (OR 21, 95% CI 3.5–127.2;  $p < 0.001$ ).

A large retrospective study examined use of DMARDs and biological agents in 6024 RA patients undergoing surgery from the US database of the Veteran Health Administration [61]. To determine the drug-withhold timing, they developed an algorithm. The authors did not report any significant increase in risk of surgical site infection or wound infection between perioperative drug continuation and interruption. However, they found an increased risk of generalised infection with bDMARD interruption after surgery (OR 9.2, 95% CI 1.99–42.60;  $p = 0.005$ ), which may be explained by drug interruption because of an on-going postoperative complication, as well as a significantly higher risk of postoperative wound infection with an OR of 14.15 (95% CI 1.76–113.76;  $p = 0.013$ ).

Risk factors for surgical site infection and delayed wound healing were retrospectively analysed among 332 elective orthopaedic procedures performed on RA patients in various Japanese centres [62]. Their bDMARDs (etanercept, adalimumab, infliximab, tocilizumab, abatacept) and csDMARDs were interrupted prior surgery as per the Japanese College of Rheumatology guidelines [65]. The authors did not find any association of infection or delayed wound healing with bDMARD or csDMARD use. Unfortunately, the small number of patients on new biological drugs (abatacept or tocilizumab) does not allow for any firm conclusions.

Another recent retrospective study of a larger sample examined risk factors for the same parameters (infection and wound healing) after 1036 various orthopaedic procedures on RA patients [63]. TNF inhibitors (etanercept, adalimumab, infliximab, golimumab) were interrupted two to four weeks before surgery, again according to the Japanese guidelines. There was no significant correlation between infection or delayed wound healing and bDMARDs. A higher risk of infection with foot surgery (OR 3.167, 95% CI 1.256–7.986;  $p = 0.015$ ) and delayed wound healing with total knee arthroplasty (OR 4.044, 95% CI 1.436–11.389;  $p = 0.008$ ) was observed.

#### **Tocilizumab: anti interleukin-6 receptor monoclonal antibody**

A retrospective case-control study compared wound healing and inflammatory state in 44 RA patients treated with either tocilizumab or csDMARDs [67] who underwent upper and lower limb total arthroplasties. The mean time from last infusion of tocilizumab was 16.1 days (range 3–27). There were no differences in terms of C-reactive protein (CRP) levels ( $p < 0.001$ ), white blood cell counts, temperature, superficial or deep infections and no wound healing delays.

More recently, a multicentre retrospective study collected 161 cases of orthopaedic surgery (mainly arthroplasties: 89/161 cases) among 122 RA patients treated with tocilizumab [68]. According to the Japanese guidelines [69], treatment was interrupted prior to surgery but with some variability among patients. The mean time between the last infusion and surgery was  $23.5 \pm 12.7$  days, and the time for resuming therapy was  $24.8 \pm 12.7$  days after surgery. The authors reported a small number of surgical site infections – two superficial (1.9%) and one deep (0.6%) infection – as well as a few cases of wound healing delays (14%) and disease flares (22.4%). In a multiple logistic regression analysis, no correlation was found between the duration of treatment interruption and disease flares (OR 1.033, 95% CI 1.013–1.055;  $p = 0.0015$ ). Delays in wound healing were mostly related to concomitant use of prednisolone (OR 5.494, 95% CI 1.026–101.926;  $p = 0.0459$ ). There were also significant correlations between foot and spinal surgery and delayed wound healing with ORs of 3.066 (95% CI 1.009–9.327;  $p = 0.0483$ ) and 158.750 (95% CI 10.521–6993.007;  $p = 0.0002$ ).

#### **Rituximab: anti-CD20 antibody**

The French Auto-Immunity and Rituximab (AIR) registry analysed data that included 94 orthopaedic and 23 abdominal procedures in RA patients [70]. The mean time between the last rituximab infusion and surgery was 6.4 months (4.3–8.7). There were 12 postoperative complications in nine patients: eight surgical site infections, and one fatal case of septic shock. In a univariate analysis, spine surgery was significantly associated with postoperative complications ( $p = 0.048$ ), but no association was reported regarding the timeframe between surgery and the last rituximab infusion.

#### **Abatacept: CTLA4-IgG fusion protein**

A retrospective study included seven RA patients undergoing eight orthopaedic procedures (knee, hand, foot and vertebral surgery) [71]. Abatacept was discontinued on average 15.9 days prior to surgery (mean of 33.1 days in the perioperative period) but concomitant medications (prednisolone, methotrexate, sulfasalazine) were maintained. There was no case of postoperative surgical site infection, delayed wound healing or disease flare.

#### **Ustekinumab: anti-p40 antibody targeting both interleukin-12 and interleukin-23**

A retrospective study was performed on 131 psoriasis patients who underwent various surgical procedures (orthopaedic, cardiovascular, dermatological, dental extraction and neurosurgery) [72]. Only 13 patients were treated with ustekinumab, and 118 patients were on TNF inhibitors (infliximab, adalimumab or etanercept). The treatment (TNF inhibitor or ustekinumab) was maintained in 87 patients and discontinued in 44 patients according to the guidelines of the British Association of Dermatologists, which advises that ustekinumab be interrupted 12 weeks prior to surgery (four half-lives) [73]. Three wound infections were observed without knowing the type of treatment: two in the discontinuation group (knee arthroplasty), and one in the maintenance group (dental implant). Given its small sample, this study seems reassuring as far as the perioperative safety of TNF inhibitors is concerned, but

does not really provide much information on perioperative ustekinumab use.

## Discussion

Our review of the current literature shows that the number of clinical studies on the effect of DMARDs during the perioperative period is scarce. Furthermore, the limited numbers of patients included in most studies, as well as the sometimes poor study design, are major limitations to making recommendations with a good level of evidence. Finally, as several studies were observational, confounding factors may have introduced major bias leading to conflicting results and sometimes, wrong conclusions.

Methotrexate is by far the best studied among all csDMARDs, in particular in prospective randomised clinical trials addressing the question of treatment maintenance during the perioperative period. Based on the results of these studies, it seems reasonable to continue methotrexate administration during the perioperative period. This recommendation is not only supported by the absence of major safety signals, but also aims to avoid disease flares that may ultimately lead to use corticosteroids or an increase their dosage, thus promoting a higher risk of complications. However, one should also bear in mind that low median doses of methotrexate (10 mg/week) were used in most of the studies, and that the safety of larger doses, as currently used, has not been formally examined. The evidence currently suggests that other csDMARDs (HCQ, sulfasalazine) can also continue to be safely administered during the perioperative period.

National recommendations on the use of bDMARDs in patients undergoing surgical procedures have been based primarily on limited evidence and mostly on clinical experience and expert opinions. Some of the recommendations, which vary greatly between countries, are based essentially on bDMARDs half-lives (table 3). In France, the CRI (Club Rhumatisme et Inflammation) adjusts its recommendations to discontinue TNF inhibitors according to the surgical site: two half-lives for interventions in a sterile mi-

lieu such as cataracts, to four to five half-lives for high-risk procedures such as abdominal surgery [74]. In the UK and in Japan, guidelines advise stopping TNF inhibitors between three and five half-lives prior to any surgical procedure [69, 75]. In Spain [76], like in Switzerland (Commission des médicaments des pharmaciens suisses) [77], guidelines recommend stopping administration without any further detail regarding the timing of discontinuation or the type of surgery. The German Rheumatology Society gives further recommendations on synthetic DMARDs, mainly based on expert opinion and drug half-lives. Pre-operative interruption is only recommended for ciclosporin (1–2 days before surgery), mycophenolate mofetil (1–2 days before surgery) and azathioprine (1–2 days before surgery) [78]. In 2017, The American College of Rheumatology published new recommendations with low and moderate level of evidence: they suggest not stopping csDMARDs and stopping bDMARDs based on the timing of administration rather than the half-life, i.e., schedule surgery one week after normal administration, for example 9 weeks for infliximab, and 3 weeks for adalimumab [79]. Various case reports [80, 81] and a case-control study comparing postoperative inflammation [82] reported a lack of inflammatory response (CRP and fever) in patients treated with tocilizumab. These findings are consistent with the well-described role of interleukin (IL)-6 in the control of acute-phase protein production by hepatocytes and body temperature. Thus, physicians should be aware of the specificity of tocilizumab's mode of action when assessing a patient with a postoperative complication. Notably, they should not rely on CRP as a marker of infection since CRP elevation is blunted by IL-6 inhibition. Furthermore, and regardless of surgery, severe infections can occur in tocilizumab-treated patients with an OR of 1.78 (95% CI 0.98–3.23), including mainly skin and subcutaneous infections, when tocilizumab is used in combination with methotrexate. Adverse events were also noticed with tocilizumab 8 mg/kg in combination with csDMARDs, as

**Table 3:** Half-lives of disease-modifying antirheumatic drugs.

Drug	Half-life
<b>bDMARDs</b>	
<b>TNF inhibitors</b>	
Infliximab	8–9.5 days
Etanercept	70 hours (between 7 and 300 hours)
Adalimumab	2 weeks
Golimumab	12 ± 3 days
Certolizumab pegol	14 days
<b>IL6 receptor antagonist</b>	
Tocilizumab	Dependent on concentration: between 6 and 16 days
<b>Anti-CD20</b>	
Rituximab	22 days, range 6.1–52 days
<b>CTLA4-IgG</b>	
Abatacept	13.1 days, range 8–25 days
<b>Anti-p40 antibody targeting both IL-12 and IL-23</b>	
Ustekinumab	Median 3 weeks, range 15–32 days
<b>IL1 receptor antagonist</b>	
Anakinra	Between 4 and 6 hours
<b>csDMARDs</b>	
<b>Half-life</b>	
Methotrexate	6–7 hours, range 3–17 hours
Leflunomide	1–4 weeks

bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; DMARD = disease-modifying antirheumatic drug; IL = interleukin Source: [medicaments.gouv.fr](http://medicaments.gouv.fr)

compared with controls treated with csDMARDs, with an OR of 1.53 (95% CI 1.26–1.86) [83].

Regarding bDMARDs, the preoperative withdrawal will depend on several parameters. Decisions should ideally be made in a multidisciplinary setting involving the rheumatologist, surgeon, and specialist in infectious diseases in certain cases. Points to consider should include individual patient and disease characteristics, including the presence of comorbidities, previous infectious complications, the type of immunosuppressive therapy and the severity of the disease. High disease activity is a risk factor for infection [84], as is the presence of prosthetic joint [45]. The current literature does not clearly address whether bDMARDs should be discontinued according to their half-life or administration interval, and it seems difficult to completely dissociate one from the other. However, the administration interval has the advantage of being easy to use in routine practice. The intrinsic risk of infectious complications associated with the type and site of surgical procedures should be assessed. Particular attention should be given to an articular pathology that is known to be a risk factor for subsequent postoperative complications [85]. The same applies to the type and severity of the autoimmune disease. Indeed, uncontrolled systemic lupus erythematosus may have major consequences on morbidity or even mortality that may preclude the complete cessation of immunosuppressive therapy. The decision of bDMARD discontinuation will also depend on whether bDMARDs are used as monotherapy or in combination with methotrexate or other csDMARDs, since in the latter case the disease may still be controlled by the administration of csDMARDs, whereas patients left without therapy in the former situation are at risk of flares. Finally, it is common practice to withhold bDMARDs before surgery because of the increased risk (or fear) of infection and delayed wound healing. However, the benefits of such an approach should be carefully weighed against the side effects of increasing glucocorticoid doses to treat flares.

### Key messages

- Owing to scarce and limited literature, there are major limitations to recommending the discontinuation of disease-modifying antirheumatic drugs (DMARDs).
- Methotrexate is by far the best studied conventional synthetic DMARD (csDMARD) and it seems reasonable to continue administering methotrexate during the perioperative period.
- National recommendations on the use of biological DMARDs (bDMARDs) vary greatly between countries, but they all propose stopping bDMARDs during the perioperative period.
- Clinicians should be aware of a possible lack of temperature and acute-phase marker elevation in patients treated with the IL-6 inhibitor, tocilizumab.
- Several points should be taken into consideration prior to bDMARD withdrawal, including the presence of comorbidities, previous infectious complications, the use of a concomitant csDMARD, and disease severity.

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## Appendix 1

**Medline search strategy details**

Pubmed database up to 14 May 2016  
 ((surgery) AND infection) AND rheumatoid arthritis:  
 Total : 1841  
 Selected: 56  
 Specific drug  
 Methotrexate: 6  
 Leflunomide: 2  
 Tocilizumab: 2  
 Sulfasalazine: 1  
 Meta-analysis: 4  
 Case report: 18  
 Review: 25  
 (“post-operative complications”) AND “tumor necrosis factor alpha”  
 Total: 593  
 Selected: 4  
 Specific drug: Ustekinumab: 1  
 Already included with previous MeSH terms: 3  
 Visceral surgery: 23  
 Review: 5  
 Case report: 1  
 Unrelated: 1  
 “anti tumor necrosis factor AND orthopedic surgery”:  
 Total: 271  
 Selected: 1  
 Already included with previous MeSH terms: 6  
 Review: 4  
 Case report: 4  
 Unrelated: 2  
 “anti tumor necrosis factor AND orthopedic surgery” AND “wound healing”:  
 Total: 11  
 Selected: 0  
 Already included with previous MeSH terms: 3  
 Case report: 1  
 Review: 2  
 ((surgery) AND infection) AND tocilizumab:  
 Total: 17  
 Selected: 0  
 Already included with previous MeSH terms: 1  
 Case report: 3  
 Review: 1  
 (((“surgery”) OR “arthroplasty”) AND “infection”) AND “wound healing”) AND “anti tumor necrosis factor”  
 Total: 2  
 Selected: 0  
 Already included with previous MeSH terms: 2  
 (abatacept) AND perioperative period

Total: 10  
 Selected: 1  
 Review: 1  
 ((rituximab) AND rheumatoid arthritis) AND operation  
 Total: 52  
 Selected: 1  
 Review: 2  
 ((“surgery”) AND “infection”) AND “rituximab”:  
 Total: 124  
 Selected: 0  
 Review: 3  
 (rituximab) AND perioperative period  
 Total: 18  
 Selected: 0  
 Review: 2  
 (rituximab) AND wound healing  
 Total : 13  
 Selected: 0  
 ((rituximab) OR “anti CD20”) AND “wound healing”  
 Total: 8  
 Selected: 0  
 (rituximab) AND “orthopedic/surgery”  
 Total: 0  
 (((belimumab) OR anakinra) OR tofacitinib) OR apremilast) AND perioperative period  
 Total: 20  
 Selected: 0  
 Review: 1  
 Unrelated: 1  
 (((belimumab) OR anakinra) OR tofacitinib) OR apremilast) AND “surgical wound”  
 Total: 8  
 Selected: 0  
 Already included with previous MeSH terms: 1  
 Review: 1  
 ((“methotrexate”) AND “surgery”) AND “infection”  
 Total: 212  
 Selected: 0  
 Already included with previous MeSH terms: 13  
 Review: 5  
 Visceral surgery: 1  
 Case report: 2  
 Unrelated: 1  
 ((“leflunomide”) AND “surgery”) AND “infection”  
 Total: 27  
 Selected: 0  
 Already included with previous MeSH terms: 2  
 ((“sulfasalazine”) AND “surgery”) AND “infection”  
 Total: 14  
 Selected: 0  
 Already included with previous MeSH terms: 1