# Perioperative Management of Immunosuppressive Medications for Rheumatoid Arthritis

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**Learning Objectives**

Upon completion of this CME activity, the learner will understand:

- The mechanism of action of drugs frequently used in the medical management of rheumatoid arthritis (RA).
- The perioperative considerations and risks of different drugs used in the medical management of RA.
- Current evidence and recommendations for management of different RA medications in patients undergoing elective hand surgery.

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Operations in patients with rheumatoid arthritis are complicated by the fact that most drugs used in medical management have immunosuppressive mechanisms of action, including corticosteroids and conventional synthetic and biologic disease-modifying antirheumatic drugs. In deciding to continue or discontinue these medications perioperatively, surgeons must weigh the relative risk of infection from immunosuppression against the risk of rheumatoid arthritis symptom flares from reduced medical disease control. The objective of this

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article is to review the existing evidence regarding perioperative management of immunosuppressive rheumatoid arthritis medications, with a specific focus on relevance to hand and upper-extremity procedures. *(J Hand Surg Am. 2022;47(4):370–378. Copyright © 2022 by the American Society for Surgery of the Hand. All rights reserved.)*

**Key words** Biologic synthetic disease-modifying antirheumatic drugs, conventional synthetic disease-modifying antirheumatic drugs, corticosteroids, disease-modifying antirheumatic drugs, rheumatoid arthritis.



RHEUMATOID ARTHRITIS (RA) is a progressive, inflammatory, autoimmune joint disease that causes synovial inflammation, destruction of articular cartilage, and periarticular bone erosion. RA affects between 0.5% to 1% of adults worldwide.[1] In addition to symptomatic control with nonsteroidal anti-inflammatory drugs and systemic corticosteroids, medical management of RA relies on the use of disease-modifying antirheumatic drugs (DMARDs) that slow the rate of joint destruction. Care for the disease was further advanced with the introduction of biologic DMARDs (bDMARDs) that target specific molecules in the involved inflammatory pathways.[2] As a result of these improvements in medical management, rates of hand surgery for RA have declined in recent decades.[3] However, hand and upper-extremity arthroplasties, synovectomies, tendon reconstructions, and muscle releases are still performed to alleviate the pain and loss of function associated with advanced disease.

Operations in patients with RA are complicated by the fact that most drugs used in medical management have immunosuppressive mechanisms of action, including corticosteroids, conventional synthetic DMARDs (csDMARDs), and bDMARDs. In deciding to continue or discontinue these medications perioperatively, surgeons must weigh the relative risk of infection from immunosuppression against the risk of RA symptom flares from reduced medical disease control. In 2017, the American College of Rheumatology (ACR) and American Association of Hip and Knee Surgeons (AAHKS) released guidelines for perioperative management of RA medications.[4] However, these guidelines were designed to pertain only to patients undergoing total knee or total hip arthroplasty. The objective of this article is to review the existing evidence regarding perioperative management of immunosuppressive RA medications, with a specific focus on relevance to hand and upper-extremity procedures.

## CORTICOSTEROIDS

Over half of patients with established RA are prescribed systemic corticosteroids.[5] Chronic corticosteroid use is known to increase the risk of postoperative infection, and this risk may be dose-dependent.[6] Perioperatively, the infectious risk of corticosteroid continuation must be balanced against the risk of intraoperative hemodynamic stability from hypothalamic-pituitary-adrenal axis suppression if steroids are withheld.

Evidence suggests that patients on low-dose daily corticosteroids and undergoing minor surgeries may safely continue their baseline regimen throughout the surgical period without any need for stress-dose supplementation. A systematic review of studies assessing the need for stress-dose steroids in noncardiac surgery found overall low-quality evidence and no studies identifying a substantial difference in outcomes when stress-dose steroids were or were not given.[7] Friedman et al[8] evaluated outcomes in 28 chronically corticosteroid-treated patients undergoing 35 hand surgeries while continuing their usual steroid with no planned stress-dose supplementation. The included patients used a mean dose of 10 mg prednisone daily for a mean of 7 years prior to surgery. No patient required exogenous steroids intraoperatively, and there were no instances of unexplained or unexpected hypotension, hyponatremia, or fever. Urine studies showed that 19/26 (73%) of patients had appropriately increased urinary cortisol following surgery, indicating an adequate adrenal response. Patients without increased urinary cortisol did not exhibit any clinical symptoms of abnormal adrenal function.[8]

Due to the low quality of the current evidence and a dearth of studies stratifying patients by the individual risk of adrenal suppression, previous authors recommended intravenous administration of a stress dose of 50 mg hydrocortisone before incision for patients who do not fall into a low risk category.[9,10] Risk is determined based on both the intensity of the operation and the patient's baseline corticosteroid

dose. Most hand surgeries are considered minor and are not expected to require supplementation. A stress dose may be needed for intermediate-intensity surgeries, such as total joint arthroplasty. For these higher-intensity surgeries, a baseline corticosteroid dose should be considered. Patients at low risk for adrenal suppression who do not require supplementation are those using corticosteroids for less than 3 weeks preoperatively and taking prednisone at $\leq$5 mg/day or $\leq$10 mg every other day or taking an equivalent drug.[9] High-risk patients expected to require stress doses are those on >20 mg prednisone daily for more than 3 weeks or with clinical signs of Cushing syndrome. Intermediate-risk patients are those whose daily corticosteroid dose falls between these values.[9] Intermediate-risk patients may undergo cosyntropin testing prior to surgery to evaluate their adrenal response. If supplemental intravenous corticosteroids are given, 25 mg intravenous hydrocortisone should be continued every 8 hours for 24 hours or until the patient is able to tolerate oral administration of the usual baseline medication.[9,10]

## SYNTHETIC DMARDS

### Conventional synthetic DMARDs

The csDMARDs are a class of well-established medications that improve physical function in patients with RA and slow the progression of joint destruction.[1] For many of the csDMARDs, the molecular targets and mechanisms of action that result in their benefit in RA have not yet been fully elucidated, and each drug may have multiple beneficial effects.

Methotrexate is the most commonly used csDMARD and is considered the cornerstone of RA treatment.[2,5,11] It is often used in combination with corticosteroids, other csDMARDs, and bDMARDs, as doing so improves disease control compared to monotherapies.[1] Methotrexate is safe to continue throughout the perioperative period, as it does not increase the infection risk and continuation may reduce postoperative RA flares. Grennan et al[12] conducted a prospective randomized controlled trial of methotrexate continuation in patients with RA undergoing a variety of hand surgeries. Patients who continued methotrexate had lower rates of infection, other complications, and postoperative RA disease flares than both patients who discontinued methotrexate 2 weeks prior to surgery and patients with RA who had not received methotrexate.[12] Similarly, Jain et al[13] retrospectively reviewed outcomes of hand and wrist surgeries in which patients continued DMARDs perioperatively, and found no difference in postoperative wound infection rates between methotrexate users and nonusers and no influence of methotrexate dose on infection risks.

Recommendations regarding perioperative management of leflunomide vary due to conflicting findings regarding postoperative complications. A randomized controlled trial of patients continuing leflunomide perioperatively or discontinuing use for 2 weeks before and 2 weeks after total joint arthroplasty found no difference in postoperative infection rates between the 2 groups (6.1% in those who continued vs 6.3% in those who discontinued).[14] However, a prospective cohort study comparing patients continuing leflunomide or methotrexate perioperatively found a significantly higher infection rate in the leflunomide group (40.6% vs 13.1% in the methotrexate group).[15] Reviewing this evidence and considering the known infection risk with leflunomide use in nonsurgical patients, Goodman[16] recommended discontinuing leflunomide for 1 week preoperatively. Conversely, the ACR/AAHKS guidelines recommend continuing leflunomide throughout the perioperative period.[4]

Limited evidence exists assessing the perioperative effects of other common csDMARDs, such as azathioprine, sulfasalazine, and hydroxychloroquine, individually. Studies of patients with RA continuing any of these csDMARDs during the perioperative period have not found an association with infection risks.[13,17–19] One retrospective analysis suggested that sulfasalazine continuation decreases the likelihood of perioperative infection.[20] Thus, previous reviewers and the ACR/AAHKS guidelines recommend continuing these drugs at the current dose.[4,16] While these drugs may be continued, surgeons should be aware that concurrent use of multiple csDMARDs has been associated with an increased risk of postoperative infection compared to monotherapy.[17,21]

### Tofacitinib

Unlike other csDMARDs, Tofacitinib (Xeljanz) has a specific molecular target, and thus has been classified as the first drug in a new category: the targeted synthetic DMARDs.[1,2] However, like the biologic agents, it is a second-line therapy indicated for RA refractory to csDMARD treatment. Tofacitinib has a short half-life and is a synthetic, small-molecule inhibitor of the Janus Kinase 1 and Janus Kinase 3 signaling pathways.[2,22] There is limited information on the impact of tofacitinib on outcomes in hand surgical populations. A small, retrospective case series of 11 hand surgeries in patients with RA treated with tofacitinib found no instances of surgical site

infection (SSI) and one instance of delayed wound healing. However, patients had variable lengths of drug discontinuation prior to surgery.[22] The ACR/AAHKS guidelines recommend withholding tofacitinib for 7 days prior to surgery, based on trials in nonsurgical patients and translational studies suggesting that immune responses return to normal within this time frame.[4]

## BIOLOGIC DMARDS

Biologic DMARDs are targeted protein drugs that disrupt the action of a specific molecule or pathway involved in the pathogenesis of RA.[1,2] Biologics are indicated for patients who continue to have high disease activity and progressive joint destruction despite csDMARD treatment.[1] These drugs are typically given in combination with csDMARDs, usually methotrexate. Tumor necrosis factor α (TNFα) inhibitors (TNFαi) were the first class of bDMARDs introduced for RA, and remain the most commonly used biologic drugs.[5,11] Several other biologics with alternative molecular targets have also been adopted. Despite this variety of mechanisms, evidence in total joint replacement patients shows no difference in postoperative infection risks between the various bDMARDs.[6]

### TNFαi

Inhibition of TNFα disrupts multiple key inflammatory signaling pathways and reduces local bone destruction.[2] The most frequently prescribed TNFαi in patients with RA are etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humera).[5,11] All TNFαi produce similar biomolecular effects and have been shown to have similar efficacy and safety profiles.[2]

Individual studies of orthopedic patients have found conflicting results regarding the risks of continuing TNFαi perioperatively. A large, retrospective review by Scherrer et al[17] of all hand surgeries in patients with inflammatory rheumatic diseases at a single institution found that bDMARD use within 3 months of surgery was associated with an increased infection risk (odds ratio, 2.54). Among those patients with a biologic dose within 3 months, the infection risk was substantially increased when surgery was performed within one administration interval of the biologic drug (odds ratio, 10.05).[17] Conversely, Den Broeder et al[20] compared outcomes in patients with RA undergoing surgery within >4 (discontinuing) or ≤4 (continuing) drug half-lives of TNFαi administration, and found no difference in rates of SSIs. However, patients who continued treatment with TNFαi perioperatively were significantly more likely to have wound dehiscence.[20] Continuation of infliximab may not be associated with an increased infection risk. A large, claims-based analysis of Medicare patients undergoing total hip or knee arthroplasty found no difference in rates of serious infection or periprosthetic joint infection when surgery was performed within <4, 4 to 8 (1 dosing interval), 8 to 12, 12 to 16, or >16 weeks after the last infliximab infusion.[23]

Meta-analyses combining data from these investigations and others generally suggest that TNFαi use increases the infection risk and that the risk is higher if the drugs are not discontinued before surgery. Goodman et al[24] showed that in patients undergoing total joint arthroplasty, a SSI was more likely when a TNFαi was given within 3 months of surgery (odds ratio, 2.47). The meta-analysis by Clay et al[25] considered patients undergoing any hand surgery and found decreased risks of both overall complications (relative risk, 0.60) and SSIs specifically (relative risk, 0.62) when TNFαi were discontinued. Mabille et al[26] found a higher infection rate in orthopedic patients who continued biologic use in the perioperative period (6.63% vs 3.99%), but this difference was not significant. The findings of these meta-analyses are limited by the substantial variation in the biologic discontinuation periods used in the included studies and by differences in disease severity between patients treated with TNFαi or csDMARDs only.

### Other biologics

Abatacept (Orenica) is a fusion protein of cytotoxic T-lymphocyte antigen 4 and immunoglobulin G1 that acts as a competitive inhibitor of CD28 at the CD80/CD86 T-cell receptor to disrupt the costimulation signal required for T-cell activation.[2] A case series of abatacept-treated patients with RA undergoing surgery at a mean of 5.3 weeks after the last infusion found that complications occurred in 6.7% of surgeries, with a longer duration of abatacept use being associated with a lower complication rate.[27] The complication rate in hand surgery cases (2.6%) was lower than the overall complication rate. A recent claims-based analysis of abatacept-treated patients with RA undergoing total joint arthroplasty suggests that the length of abatacept discontinuation may not have an impact on outcomes. The study found no difference in rates of postoperative hospital infections, periprosthetic joint infections, or 30-day readmission rates between patients who underwent surgery less or more than 4 weeks (1 dosing interval) after abatacept infusion.[28] When surgery was performed within 2 weeks of infusion, patients had numerically, though not statistically significantly,

higher rates of infection, periprosthetic joint infection, and readmission.

Rituximab (Rituxan) is a monoclonal antibody against CD20 that depletes the peripheral B-cell population. Because of its long half-life and treatment effect, rituximab infusions are typically given every 6 months. A retrospective case-control study of 133 patients with RA treated with rituximab found that complications occurred following 8.5% of surgeries overall and 7.4% of hand surgeries, but there were no complications following 19 hand or wrist procedures. While there was no difference in the mean time between the last infusion and surgery in patients with and without complications (6.43 months vs 6.49 months, respectively), 66% of complications occurred when surgery was performed between 6 and 12 months after the last infusion.[29]

Tocilizumab (Actemra) is a humanized monoclonal clonal antibody against the interleukin-6 receptor. Outcomes of hand surgeries in patients with RA treated with tocilizumab have been reported in 2 case series. Momohara et al[30] reviewed 161 orthopedic operations, the majority of which were total joint arthroplasties, in patients who discontinued tocilizumab for 23.5 days prior to surgery on average. Postoperative SSIs occurred following 1.9% of operations and delayed wound healing occurred in 12.4%.[30] However, they found no association between either outcome and the length of tocilizumab discontinuation. RA flares occurred after surgery in 22.4% of cases and were more likely in patients with a longer interval between the last infusion and surgery (30.0 days in those with flares vs 21.6 in those without).[30] Morel et al[31] reviewed 167 patients with RA undergoing any surgery from a prospectively collected registry of tocilizumab users. On average, surgery was performed 4.96 weeks after the last tocilizumab infusion. They found an overall complication rate of 8.6%, with the majority of complications being due to infection and only 1 patient experiencing a postoperative RA flare. No single factor, including the discontinuation interval, was found to be a significant risk factor for experiencing a complication in a multivariable analysis.[31]

Anakinra (Kineret) is a monoclonal antibody that binds to the interleukin-1 receptor.[2] Anakinra is among the least commonly prescribed bDMARDs for RA.[5,11] Its effects on surgical outcomes have not been studied in a cohort of patients with RA. As anakinra is typically a daily medication, the ACR and AAHKS recommend surgery be performed on the second day following the last anakinra dose.[4]

## EVIDENCE IN HAND SURGERY

Hand surgeons face a challenge in interpreting the existing evidence on perioperative RA drug management and implementing current guidelines, because the majority of studies have evaluated patients undergoing total joint arthroplasty or other procedures not related to the hand or upper extremity. The evidence base for existing recommendations relies primarily on surgeries that may have higher baseline perioperative risks than the majority of hand and upper-extremity procedures.

The few studies that have assessed hand surgery specifically suggest that the perioperative infection risk from DMARD continuation may be low. Jain et al[13] retrospectively assessed the infection risks associated with perioperative continuation of csDMARDs and corticosteroids in 129 patients undergoing hand or wrist surgery. All medications were continued perioperatively. They found no differences in infection rates between methotrexate users and nonusers or between corticosteroid users and nonusers. The methotrexate dose, prednisolone dose, and use of other csDMARDs were also not associated with the likelihood of infection.[13] Barnard et al[18] reviewed 28 patients with RA (35 hands, 140 wounds) undergoing metacarpophalangeal joint arthroplasty at a single center who continued csDMARDs and corticosteroids perioperatively, although the 4 patients using etanercept discontinued that medication 2 to 3 weeks preoperatively and resumed once all wounds were healed. They reported no serious complications and only 4 minor complications: 1 instance of delayed wound healing, 1 superficial infection, 1 RA flare, and 1 suture granuloma.[18] Menchaca-Tapia et al[21] retrospectively reported outcomes from 130 hand surgeries in 96 patients who continued all RA medications perioperatively, and found that intensive treatment with concurrent use of $\geq$2 DMARDs and a corticosteroid was a significant predictor of postoperative complications, whereas less intensive regimens did not influence the complication rate. They did not distinguish between csDMARDs and bDMARDs in their analysis. Most recently, Klifto et al[19] compared complications in elective hand and upper-extremity procedures between 61 patients who continued all RA medications (including bDMARDs) and 27 patients with RA not taking any RA medications at the time of surgery. They considered bDMARDs to be continued if surgery occurred within 1 dosing interval. Among the patients continuing RA medications, 100% used at least 1 csDMARD, 31% used corticosteroids, and 5% used a bDMARD. Complication

**TABLE 1. Common Immunosuppressive Medications for rheumatoid arthritis and Recommended Management**

| Drug | Mechanism | Typical Dosing Regimen* | Continue or Withhold Perioperatively* | ACR/AAHKS Recommendation for Surgery Timing* | Evidence in Hand/Upper-Extremity Surgery |
|---|---|---|---|---|---|
| Corticosteroids | Inhibit inflammation | Daily | Continue | Stress dosing not required | Continuation may not increase infection risk[†] |
| Synthetic DMARDs | | | | | |
| Hydroxychloroquine | Various | Daily (1−2 doses) | Continue | | Continuation does not increase infection risk; use of ≥2 drugs with steroid may increase infection risk[†,‡] |
| Leflunomide | Various; inhibits dihydroorotate dehydrogenase (pyrimidine synthesis) | Daily | Continue | | |
| Methotrexate | Various; inhibits dihydrofolate reductase (purine synthesis) | Weekly | Continue | | |
| Sulfasalazine | Various | Daily (1−2 doses) | Continue | | |
| Tofacitinib (Xeljanz) | Inhibits JAK1 and JAK3 signaling pathways | Daily (1−2 doses) | Withhold 7 days before surgery | 7 days after last dose | None |
| Anti-TNFα bDMARDs | | | | | |
| Adalimumab (Humira) | TNFα inhibition | Weekly or every 2 weeks | Withhold 1 dosing interval | Week 2 (weekly dosing) or week 3 (every 2 weeks dosing) after last dose | None |
| Certolizumab (Cimzia) | TNFα inhibition | Every 2 weeks or every 4 weeks | Withhold 1 dosing interval | Week 3 (every 2 weeks dosing) or week 5 (every 4 weeks) after last dose | None |
| Etanercept (Enbrel) | TNFα inhibition | Weekly or twice weekly | Withhold 1 dosing interval | Week 2 after last dose | None |
| Golimumab (Simponi) | TNFα inhibition | Every 8 weeks (intravenous) or every 4 weeks (SQ) | Withhold 1 dosing interval | Week 9 (intravenous) or week (5) after last dose | None |
| Infliximab (Remicade) | TNFα inhibition | Every 4, 6, or 8 weeks | Withhold 1 dosing interval | Week 5 (every 4 weeks dosing), week 7 (every 6 weeks), or week 9 (every 8 weeks) after last dose | None |
| Other bDMARDs | | | | | |

(Continued)

**TABLE 1. Common Immunosuppressive Medications for rheumatoid arthritis and Recommended Management (Continued)**

| Drug | Mechanism | Typical Dosing Regimen* | Continue or Withhold Perioperatively* | ACR/AAHKS Recommendation for Surgery Timing* | Evidence in Hand/Upper-Extremity Surgery |
|---|---|---|---|---|---|
| Abatacept (Orencia) | Inhibits CD28/CTLA4 system; inhibits T-cell costimulation | Monthly (intravenous) or weekly (SQ) | Withhold 1 dosing interval | Week 5 (intravenous) or week 2 (SQ) after last dose | None |
| Anakinra (Kineret) | IL-1 inhibition | Daily | Withhold 1 dosing interval | Day 2 after last dose | None |
| Rituximab (Rituxan) | CD20 inhibition; depletes B cells | 2 doses 2 weeks apart every 4–6 months | Withhold 1 dosing interval | Month 7 after last dose | None |
| Tocilizumab (Actemra) | IL-6 inhibition | Every 4 weeks (intravenous) or weekly (SQ) | Withhold 1 dosing interval | Week 5 (intravenous) or week 2 (SQ) after last dose | None |

CTLA-4, Cytotoxic T-lymphocyte antigen 4; IL, interleukin; SQ, subcutaneous.
*Goodman et al.[4]
†Jain et al.[13]
‡Barnard et al,[18] Menchaca-Tapia et al,[21] and Klifto et al.[19]

rates were higher in patients not taking any RA medications (19%) than those continuing medications perioperatively (5%), but this difference was not statistically significant. They concluded that patients undergoing elective hand surgery may safely continue RA medications without an increased risk of complications or unintended disease progression.

## RECOMMENDED MANAGEMENT STRATEGY

Low-dose corticosteroids (≤5 mg/day) and csDMARDs are safe to continue throughout the perioperative period (Table 1). For most hand and upper-extremity procedures, planned perioperative stress-doses corticosteroids are not required. However, patients on high daily corticosteroid doses (>20 mg/day) or undergoing more intensive surgeries should be evaluated individually. Patients may continue their regular dose of csDMARDs, including methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, and azathioprine.

Due to the lack of specific evidence in hand surgery populations, we defer to current ACR/AAHKS guidelines regarding bDMARDs and tofacitinib. Because of studies in nonsurgical patients showing that the durations of the immunosuppressive effects of bDMARDs do not correspond to their serum half-lives, the ACR/AAHKS guidelines instead use the dosing cycle to determine the optimal timing for surgery. For all bDMARDs, they recommend scheduling surgery in the first week of the first withheld dose (eg, week 5 for a drug dosed every 4 weeks) of the patient's typical dosing regimen, as this point represents the expected nadir of the drug effect.[4] Tofacitinib should be withheld for 7 days prior to surgery.[4]

Biologics can be restarted when the surgical wound shows evidence of healing, all sutures or staples have been removed, and there are no signs of infection at the surgical site or systemically.[4] The decision to restart a bDMARD should be made in collaboration with the patient's rheumatologist and clearly communicated to both the rheumatologist and the patient. A recent study found that after withholding bDMARDs for hand surgery, some patients did not restart medications for up to 3 months after surgery because of scheduling challenges and miscommunications.[19] Prolonged bDMARD discontinuation may increase the risk of experiencing an RA flare and unnecessary disease progression.

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## JOURNAL CME QUESTIONS

### Perioperative Management of Immunosuppressive Medications for Rheumatoid Arthritis

1. What is the most appropriate recommendation regarding corticosteroids and conventional synthetic disease-modifying antirheumatic drugs (DMARDs [methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, and azathioprine]) in the perioperative period?

a. Safe to continue throughout the perioperative period
b. Should be discontinued for 1 week prior to surgery
c. Should be discontinued for 1 month prior to surgery
d. Should be discontinued for 1 day prior to surgery
e. None of the above

2. How long after stopping a biologic DMARD (bDMARD) does the American College of Rheumatology and American Association of Hip and Knee Surgeons recommend scheduling surgery?

a. One day after last dose
b. Within the first week of the first withheld dose.
c. One month after last dose
d. Could be continued through the perioperative period
e. None of the above

3. When should biologic DMARDs be restarted after surgery?

a. When the surgical wound is healed and there are no signs of infection.
b. Immediately after surgery
c. 1 week after surgery and there are no signs of infection.
d. 1 month after surgery and there are no signs of infection.
e. None of the above

4. Prolonged bDMARD discontinuation may increase the risk of experiencing a rheumatoid arthritis (RA) flare and unnecessary disease progression. How can prolonged discontinuation be avoided?

a. Letting patients manage their own perioperative DMARD regimen
b. The decision to restart a bDMARD should be made in collaboration with the patient's rheumatologist.
c. All patients to resume bDMARD immediately after surgery
d. None of the above

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