SH3: What is the appropriate management of disease modifying drugs (DMARDs, kinase inhibitors, etc) in the perioperative period?

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Answer: Unknown. There are currently no studies that investigates the management of disease modifying drugs specifically for total shoulder arthroplasty. The best recommendations are to extrapolate the recommendations for lower extremity total joint arthroplasty most recently updated in 2022.

Strength of Recommendation: Limited

Rationale: A comprehensive literature review was performed to identify all studies on the use of disease modifying drugs in the setting of total joint arthroplasty. Comprehensive search across PubMed, Google Scholar and Cochrane database was performed with assistance of a medical librarian to search for studies related to use of disease modifying drugs in the setting of total joint arthroplasty or orthopedic surgery. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence). Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies with less than <10 patients in the sample size, studies without clinical follow-up, and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. Of the 411 studies initially identified, 35 were included for review.

Total shoulder arthroplasty, usually in the form of reverse shoulder arthroplasty in patients with rheumatoid arthritis (RA) or other immunosuppressive conditions, historically has promising outcomes in terms of pain relief, functional improvement, and implant survival[1,2]. Complications reported on 9-13%, and can include unique complications such as infection, delayed in growth of implants or intra-operative/post-operative fracture due to poor bone quality. Additionally, there is evidence to suggest an increased infection rate in shoulder arthroplasty in patients with inflammatory arthritis (reported 1-5%), and a reported 50% increased risk of periprosthetic infection (PJI) in total knee and hip arthroplasty[1–3].

Disease modifying drugs have provided remarkable improvements in the management of patients with inflammatory arthritis and other rheumatologic disease such as systemic lupus erythematous. Despite these advances, joint arthroplasty is still needed for end stage arthritic conditions. Several of the disease modifying drugs alter the immune system, potentially increasing risk of PJI[3,4]. Given the increased risk of PJI in this patient population, there have been several attempts to provide recommendations/guidelines for modifying various drugs in the perioperative settings. Unfortunately, the current literature is sparse without any level I studies, and there are not studies specifically investigating perioperative use of these drugs in shoulder arthroplasty. The most recent recommendations for total knee and hip arthroplasty were published in 2022 by the American College of Rheumatology/American Association of Hip and Knee Surgeons[5]. The below tables summarize the findings of this group and provides the best recommendations for shoulder arthroplasty.

Tables[4]

Tables[4]

Table 2. Medications included in this 2022 guideline update*

	Dosing interval	Recommended timing of surgery since last medication dose
Medications to continue through surgery		
DMARDs: continue these medications through surgery (all patients)		
Methotrexate	Weekly	Anytime
Sulfasalazine	Once or twice daily	Anytime
Hydroxychloroquine	Once or twice daily	Anytime
Leflunomide (Arava)	Daily	Anytime
Doxycycline	Daily	Anytime
Apremilast (Otezla)	Twice daily†	Anytime†
Severe SLE-specific medications: continue these medications in the perioperative period in consultation with the treating rheumatologist‡		
Mycophenolate mofetil	Twice daily	Anytime
Azathioprine	Daily or twice daily	Anytime
Cyclosporine	Twice daily	Anytime
Tacrolimus	Twice daily (IV and PO)	Anytime
Rituximab (Rituxan)	IV every 4–6 months†	Month 4–6†
Belimumab SC (Benlysta)	Weekly†	Anytime†
Belimumab IV (Benlysta)	Monthly†	Week 4†
Anifrolumab (Saphnelo)§	IV every 4 weeks†	Week 4†
Voclosporin (Lupkynis)§	Twice daily†	Continue†
Medications to withhold prior to surgery¶		
Biologics: withhold these medications through surgery		
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Adalimumab (Humira)	Every 2 weeks	Week 3
Etanercept (Enbrel)	Every week	Week 2
Golimumab (Simponi)**	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Abatacept (Orencia)	Monthly (IV) or weekly (SC)	Week 5; week 2
Certolizumab (Cimzia)	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4–6 months	Month 7
Tocilizumab (Actemra)	Every week (SC) or every 4 weeks (IV)	Week 2; week 5
Anakinra (Kineret)	Daily	Day 2
IL-17 secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Ixekizumab (Taltz)§	Every 4 weeks†	Week 5†
IL-23 guselkumab (Tremfya)§	Every 8 weeks†	Week 9†
JAK inhibitors: withhold this medication 3 days prior to surgery#		
Tofacitinib (Xeljanz)	Daily or twice daily†	Day 4†
Baricitinib (Olumiant)§	Daily†	Day 4†
Upadacitinib (Rinvoq)§	Daily†	Day 4†
Not severe SLE: withhold these medications 1 week prior to surgery		
Mycophenolate mofetil	Twice daily	1 week after last dose†
Azathioprine	Daily or twice daily	1 week after last dose
Cyclosporine	Twice daily	1 week after last dose†
Tacrolimus	Twice daily (IV and PO)	1 week after last dose†
Rituximab (Rituxan)	Every 4–6 months	Month 7
Belimumab IV (Benlysta)	Monthly†	Week 5†
Belimumab SC (Benlysta)	Weekly†	Week 2†

* Dosing intervals obtained from prescribing information provided online by pharmaceutical companies. Adapted from the 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline (26). DMARDs = disease-modifying antirheumatic drugs; SLE = systemic lupus erythematosus; IV = intravenous; PO = by mouth; SC = subcutaneous; IL-17 = interleukin-17.
** Correction added on 24 August 2022, after first online publication on 20 June 2022. One of the biologic medications to withhold prior to surgery was omitted from Table 2. Golimumab (Simponi) and the corresponding dosing/timing have been added.
† Recommendation that has changed since 2017.
‡ Severe SLE indicates organ-threatening disease.
§ Drug added for 2022 update.
¶ For patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or all SLE for whom antirheumatic therapy was withheld prior to undergoing total joint arthroplasty, antirheumatic therapy should be restarted once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days.
# Recommendation pertains to infection risk and does not account for risk of cardiac events or venous thromboembolism.

A shared decision model should be employed by surgeons and patients to determined optimal timing of holding and restarting these medications. Despite the increased risk of PJI in this patient population, there is also potential risk of causing an inflammatory flare that can cause total body pain if these medications are held, especially if the disease burden is significant[4]. Currently there are no recommendations for how to best balance the risk of flare based on a patient's disease severity[4].

Table 3. Recommendations for perioperative management of antirheumatic drug therapy in patients with inflammatory arthritis and those with systemic lupus erythematosus (SLE) undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA)*

Recommendation/strength of recommendation	Level of evidence
For patients with RA, AS, PsA, JIA, or all SLE undergoing THA or TKA, continuing the usual dosing of the following DMARDs through surgery is **conditionally** recommended: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and/or apremilast.†	Low to moderate
For patients with RA, AS, PsA, or JIA undergoing THA or TKA, withholding all biologics, including rituximab, prior to surgery and planning the surgery after the next dose is due is **conditionally** recommended.	Low
For patients with RA, AS, PsA, or JIA undergoing THA or TKA, withholding tofacitinib, baricitinib, and upadacitinib for at least 3 days prior to surgery is **conditionally** recommended.‡	Low
For patients with SLE (not severe) undergoing THA or TKA, withholding the current dose of mycophenolate mofetil, mycophenolic acid, azathioprine, cyclosporine, mizoribine, or tacrolimus 1 week prior to surgery is **conditionally** recommended.	Low
For patients with SLE (not severe) undergoing THA or TKA, withholding the usual dose of belimumab and rituximab prior to surgery is **conditionally** recommended.	Low
For patients with severe SLE who have been deemed appropriate to undergo THA or TKA, continuing the usual dose of mycophenolate mofetil, mycophenolic acid (Myfortic), azathioprine, mizoribine, cyclosporine, or tacrolimus, anifrolumab, and voclosporin through surgery is **conditionally** recommended.‡	Low
For patients with severe SLE undergoing THA or TKA, continuing belimumab and planning surgery in the last month of the dosing cycle of rituximab is **conditionally** recommended.‡	Low
For patients with RA, AS, PsA, or all SLE for whom antirheumatic therapy was withheld prior to undergoing TJA, antirheumatic therapy should be restarted once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days, is **conditionally** recommended.	Low
For patients with RA, AS, PsA, or all SLE undergoing THA or TKA who are receiving glucocorticoids for their rheumatic condition, continuing their current daily dose of glucocorticoids rather than administering supraphysiologic doses of glucocorticoids on the day of surgery is **conditionally** recommended.	Low

* RA = rheumatoid arthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; DMARDs = disease-modifying antirheumatic drugs; TJA = total joint arthroplasty.
† Apremilast is a change from the prior recommendation.
‡ Indicates a change from the prior recommendation.

References:

1. Mangold DR, Wagner ER, Cofield RH, Sanchez-Sotelo J, Sperling JW. Reverse shoulder arthroplasty for rheumatoid arthritis since the introduction of disease-modifying drugs. *Int Orthop*. 2019;43(11):2593-2600. doi:10.1007/s00264-019-04373-3
2. Lévigne C, Chelli M, Johnston TR, et al. Reverse shoulder arthroplasty in rheumatoid arthritis: survival and outcomes. *J Shoulder Elbow Surg*. 2021;30(10):2312-2324. doi:10.1016/j.jse.2021.01.033
3. Goodman SM, Springer BD, Chen AF, et al. 2022 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. *Arthritis Care Res (Hoboken)*. 2022;74(9):1399-1408. doi:10.1002/acr.24893
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5. Goodman SM, Bykerk VP, DiCarlo E, et al. Flares in patients with rheumatoid arthritis after total hip and total knee arthroplasty: Rates, characteristics, and risk factors. *Journal of Rheumatology*. 2018;45(5):604-611. doi:10.3899/jrheum.170366