G18: Should disease modifying antirheumatic drugs (DMARDs) be stopped prior to major orthopedic procedures?

Hyonmin Choe, Paul N Smith, Ben Kendrick, Hironori Yamane, Kosuke Sumi, James N Powell, Yasuhito Tanaka, Armita A Abedi, Javad Parvizi, Susan M Goodman,

---

RESPONSE/RECOMMENDATION: Yes, biological and targeted synthetic disease modifying antirheumatic drugs (DMARDs) should be stopped prior to major orthopedic procedures. The exact time to withhold the drugs depends on the half-life of these drugs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE:

Rationale: Disease-modifying antirheumatic drugs (DMARDs) are classified in this paper as proposed at the European League Against Rheumatism (EULAR) in 2013[1]. This classification categorizes DMARDs based on their method of production into synthetic DMARDs and biological DMARDs (bDMARDs). Synthetic DMARDs are subdivided into conventional synthetic DMARDs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs)[2]. These immunosuppressive and immunomodulatory therapies are used across a broad spectrum of rheumatic and musculoskeletal diseases (RMDs) [3]. These conditions include spondyloarthritis (SpA), juvenile idiopathic arthritis (JIA), autoimmune or connective tissue disorders such as systemic lupus erythematosus (SLE), and inflammatory bowel disease as well as RA[4, 5]. It is common to encounter patients undergoing major orthopedic procedures, such as total joint arthroplasty, who are taking DMARDs [6, 7]. Patients with inflammatory arthritis, such as RA, are known to have an increased risk of infections, and the use of DMARDs may further elevate this risk [3, 8-15]. However, as active RA is also a risk factor for infection, balancing infection risk in the peri-operative period is challenging [8, 16]. Other complication such as hip dislocation, venous thromboembolism (VTE), acute kidney damage, and cardiac complications are also higher in patients with inflammatory arthritis compared to those with osteoarthritis (OA) [9, 17].

The current question explores the potential risk between DMARDs and subsequent risk of SSI after major orthopedic procedures. We conducted a systematic review, using specific MESH terms developed by librarians, to identify all relevant publications in the Medline and Embase databases, covering studies published up to November 2024. Search Results yielded 426 publications in English language. Two of the authors went through title and abstract screening and discrepant results were adjudicated by a third person. Then 142 full articles were reviewed. Finally, 70 articles were included in this systematic review and 38 articles were referenced in this manuscript. Particular attention was given to the new evidence and updated recommendations that have emerged since the previous international consensus meeting (ICM) in 2018. One author prepared the initial draft, and all contributors reviewed, provided feedback, and approved the final version.

DMARDs play a crucial role in controlling disease activity and improving daily function in patients with inflammatory conditions, but careful monitoring is essential to mitigate potential adverse effects, especially the surgical site infection (SSI) during major orthopedic procedures[3, 9, 10, 14]. While the use of DMARDs may increase the risk of infections, discontinuation of DMARDs carries the potential to trigger disease flare-ups since

RA patients with high disease activity are reported to experience frequent postoperative flare-ups predicted flaring by 6 weeks [9, 18-20].

In 2017, Goodman et al. in collaboration with the American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons (AAHKS) developed evidence-based recommendations for continuing or withholding both conventional and biologic DMARDs perioperatively for total hip arthroplasty (THA) and total knee arthroplasty (TKA)[18]. This content has been directly adopted in the ICM2018. In addition, British Society for Rheumatology also published safety guidelines related to DMARDs in 2019. Russell et al also published consensus statement for perioperative management of medication for rheumatologic and HIV disease in 2022 as a practical guideline from society for perioperative assessment and quality improvement[21]. In their document, it was recommended to take most immunosuppressant medications perioperatively including on day of surgery, except for cyclophosphamide that was to be held for 4weeks. For bDMARDs, most biologic agents were recommended to hold for an entire one dosing cycle except belimumab for severe SLE, and anti-interferon agent of anifrolumab that were recommended for continuing. tsDMARDs (JAK inhibitors) was recommended to hold for 3 days preoperatively[21]. There is some evidence suggesting that tsDMARDs may increase the risk of thrombotic events, raising concerns about whether patients receiving tsDMARDs therapy should be considered high-risk for DVT/PE and managed with appropriate prophylaxis[22]. Further investigation on this matter is warranted.

The first ACR/AAHKS recommendation was updated in 2022 by convened a panel of rheumatologists, orthopedic surgeons, and infectious disease specialists. This updated guideline includes recently introduced immunosuppressive medications[23]. In the 2022 ACR/AAHKS recommendations, the use of csDMARDs remained unchanged, with the addition of apremilast as a medication. The guideline continues to conditionally recommend their perioperative continuation. On the other hand, regarding bDMARDs, various new drugs have become available since the 2017 guidelines, and several revisions have been made concerning their perioperative use. The summary of the 2022 ACR/AAHKS recommendations are presented in Table 1.

In 2023, Albrecht et al in corroboration with German Society for Rheumatology published an updated recommendation regarding perioperative DMARDs use[24]. They recommended reducing the glucocorticoid dose to as low as possible 2–3 months before elective surgery (in any case <10mg/day) but keeping the dose stable 1–2 weeks before and on the day of surgery. They recommended continuing csDMARDs, exceptions being a reduction of high methotrexate (MTX) doses to ≤15mg/week and washout of leflunomide in patients at high risk of infection. They recommended that azathioprine, mycophenolate and ciclosporin should be paused 1–2 days prior to surgery, tsDMARDs should be paused 3-4 days prior to surgery, and in patients undergoing bDMARDs treatment, surgery should be scheduled for the end of each treatment interval.

In 2024 James et al published a perioperative management of systemic immunomodulatory agents in patients with psoriasis and psoriatic arthritis[25]. In this review, TNF-a inhibitors, abatacept, MTX, and cyclosporine were recommended to be continued through low-risk surgery. On the other hand, in patients undergoing TKA or THA, the recommendations align with the 2022 ACR/AAHKS guideline to hold TNF-a inhibitors for one full dosing interval. Some studies have reported that the continuation of bDMARDs is not associated with an increased risk of infection[26, 27], however, a 2024 meta-analysis reported that the continued use of bDMARDs increases the risk of postoperative infection in

orthopedic surgeries[12]. Ongoing clinical studies are being conducted to ensure the safer use of DMARDs, and further evidence is anticipated to be established[28].

The reviewed studies and guidelines also focus on major orthopedic procedures that include upper-extremity surgery, foot and ankle surgery, and spine surgery, but the evidence remains limited[29-32]. Saunders et al. conducted a critical analysis review in 2021 on the use of DMARDs in RA and SLE patients undergoing foot and ankle surgery. Their recommendations align closely with the 2017 ACR/AAHKS guidelines. They recommended the continuation of csDMARDs, withholding bDMARDs and tsDMARDs prior to surgery, and resuming bDMARDs and tsDMARDs only after the surgical wound shows signs of healing. Additionally, they highlighted differences in the duration of drug discontinuation between severe and non-severe SLE. For glucocorticoids, they recommended tapering to ≤20 mg/day whenever possible[33]. Hresko et al. conducted a review in 2022 on the use of DMARDs in hand and upper-extremity procedures for RA patients. Their recommendations are also adapted from the 2017 ACR/AAHKS guidelines, suggesting the continuation of low-dose corticosteroids (≤5 mg/day) and csDMARDs, withholding bDMARDs for one dosing interval, and discontinuing tsDMARDs for 7 days before surgery. For high daily corticosteroid doses(>20 mg/day), individualized evaluation is recommended[34].

Despite the existence of various guidelines for major orthopaedic procedure, evidence and expert consensus about recommendations for perioperative management of DMARDs in spine surgery has been limited. Several original and review articles have aimed to determine the association between DMARDs use and clinical outcomes in patients undergoing spine surgery[35, 36]. In 2021, Gaudiani et al. conducted a retrospective review to evaluate the association between preoperative DMARDs use within 90 days before surgery and reoperation rates in patients undergoing spinal fusion[37]. The study included 90 patients in the TNF-alpha inhibitor group, 90 in the other DMARD group, and 123 in the control group. The odds of reoperation within one year were 3.1 (95% confidence interval [CI]: 1.4−7.0) and 2.2 (95% CI: 0.96−5.3) times higher in the TNF-alpha inhibitor and other DMARD groups, respectively, compared to the control group. This study highlights the potential risk of DMARD use for reoperation in patients with RMDs undergoing spinal fusion. Streufert et al. conducted a systematic review and meta-analysis in 2022. This meta-analysis included 703 patients with RA and 2,569 patients without RA from nine studies, comprising seven retrospective cohort studies, one prospective cohort study, and one case-control study[38]. The analysis revealed that the relative risk of infection was 2.29 times higher in patients with RA compared to those without RA. Additionally, the management of antirheumatic medication in the perioperative period for spine surgery was reviewed in seven articles, encompassing a total of 226 patients undergoing spine surgery. The findings indicated significant variability in the timing, cessation or continuation, and types of medications used, making it challenging to derive conclusive recommendations. However, it was emphasized that all RA patients should be perioperatively co-managed by a rheumatologist. The study also noted that, as in other areas of surgical practice, spine surgery requires further investigation to develop specific, patient-centered guidance for perioperative medication management to optimize patient outcomes and minimize risks.

In conclusion, many current guidelines recommend the continuation of csDMARDs, while suggesting a temporary discontinuation period for bDMARDs and tsDMARDs. There are conflicting results regarding the discontinuation of bDMARDs, and future studies with higher levels of evidence may lead to changes in optimal usage. However, based on our understanding of all the available evidence, we present our recommendations as outlined in Table 2.

References

[1] Smolen, J.S., et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis, 2014;73(3):p. 492-509.
[2] Rezaieyazdi, Z., M. Sahebari, and M. Khodashahi, Preoperative Evaluation and Management of Patients Receiving Biologic Therapies. Arch Bone Jt Surg, 2019;7(3):p. 220-228.
[3] Gualtierotti, R., M. Parisi, and F. Ingegnoli, Perioperative Management of Patients with Inflammatory Rheumatic Diseases Undergoing Major Orthopaedic Surgery: A Practical Overview. Adv Ther, 2018;35(4):p. 439-456.
[4] van der Heijde, D., et al., Common Language Description of the Term Rheumatic and Musculoskeletal Diseases (RMDs) for Use in Communication With the Lay Public, Healthcare Providers, and Other Stakeholders Endorsed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). Arthritis Rheumatol, 2018;70(6):p. 826-831.
[5] Lin, C.H., W.S. Liu, C. Wan, and H.H. Wang, Effectiveness of tofacitinib in patients with ulcerative colitis: an updated systematic review and meta-analysis of real-world studies. BMJ Open Gastroenterol, 2024;11(1):p.
[6] Mertelsmann-Voss, C., et al., US trends in rates of arthroplasty for inflammatory arthritis including rheumatoid arthritis, juvenile idiopathic arthritis, and spondyloarthritis. Arthritis Rheumatol, 2014;66(6):p. 1432-9.
[7] Nikiphorou, E., et al., Hand and foot surgery rates in rheumatoid arthritis have declined from 1986 to 2011, but large-joint replacement rates remain unchanged: results from two UK inception cohorts. Arthritis Rheumatol, 2014;66(5):p. 1081-9.
[8] Au, K., et al., High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis, 2011;70(5):p. 785-91.
[9] Ravi, B., et al., Increased risk of complications following total joint arthroplasty in patients with rheumatoid arthritis. Arthritis Rheumatol, 2014;66(2):p. 254-63.
[10] Richardson, S.S., et al., Inflammatory Arthritis Is a Risk Factor for Multiple Complications After Total Hip Arthroplasty: A Population-Based Comparative Study of 68,348 Patients. J Arthroplasty, 2019;34(6):p. 1150-1154 e2.
[11] Ito, H., et al., Postoperative complications in patients with rheumatoid arthritis using a biological agent - A systematic review and meta-analysis. Mod Rheumatol, 2015;25(5):p. 672-8.
[12] Imam, M.S., et al., A Meta-Analysis Examining the Effect of Perioperative Biologic Disease-Modifying Anti-Rheumatic Medications on Postoperative Wound Complications in Various Orthopedic Surgeries. J Clin Med, 2024;13(18):p.
[13] Cordtz, R.L., et al., Incidence of hip and knee replacement in patients with rheumatoid arthritis following the introduction of biological DMARDs: an interrupted time-series analysis using nationwide Danish healthcare registers. Ann Rheum Dis, 2018;77(5):p. 684-689.
[14] Cordtz, R.L., et al., Predictors of revision, prosthetic joint infection and mortality following total hip or total knee arthroplasty in patients with rheumatoid arthritis: a nationwide cohort study using Danish healthcare registers. Ann Rheum Dis, 2018;77(2):p. 281-288.
[15] Goodman, S.M., et al., Management of perioperative tumour necrosis factor alpha inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis. Rheumatology (Oxford), 2016;55(3):p. 573-82.

[16] Mehta, B., et al., Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. RMD Open, 2019;5(1):p. e000935.
[17] Lin, J.A., et al., Adverse outcomes after major surgery in patients with systemic lupus erythematosus: a nationwide population-based study. Ann Rheum Dis, 2014;73(9):p. 1646-51.
[18] Goodman, S.M., et al., 2017 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. J Arthroplasty, 2017;32(9):p. 2628-2638.
[19] Goodman, S.M., et al., Flares in Patients with Rheumatoid Arthritis after Total Hip and Total Knee Arthroplasty: Rates, Characteristics, and Risk Factors. J Rheumatol, 2018;45(5):p. 604-611.
[20] Goodman, S.M., et al., Rheumatoid Arthritis Flares After Total Hip and Total Knee Arthroplasty: Outcomes at One Year. Arthritis Care Res (Hoboken), 2020;72(7):p. 925-932.
[21] Russell, L.A., et al., Preoperative Management of Medications for Rheumatologic and HIV Diseases: Society for Perioperative Assessment and Quality Improvement (SPAQI) Consensus Statement. Mayo Clin Proc, 2022;97(8):p. 1551-1571.
[22] Charles-Schoeman, C., et al., Risk of Venous Thromboembolism With Tofacitinib Versus Tumor Necrosis Factor Inhibitors in Cardiovascular Risk-Enriched Rheumatoid Arthritis Patients. Arthritis Rheumatol, 2024;76(8):p. 1218-1229.
[23] Goodman, S.M., 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. J Arthroplasty, 2022;37(9):p. 1676-1683.
[24] Albrecht, K., et al., Perioperative management of patients with inflammatory rheumatic diseases : Updated recommendations of the German Society for Rheumatology. Z Rheumatol, 2023;82(Suppl 1):p. 1-11.
[25] James, W.A., et al., Full Guidelines-From the Medical Board of the National Psoriasis Foundation: Perioperative management of systemic immunomodulatory agents in patients with psoriasis and psoriatic arthritis. J Am Acad Dermatol, 2024;91(2):p. 251 e1-251 e11.
[26] George, M.D., et al., Timing of Abatacept Before Elective Arthroplasty and Risk of Postoperative Outcomes. Arthritis Care Res (Hoboken), 2019;71(9):p. 1224-1233.
[27] Borgas, Y., A. Gulfe, M. Kindt, and A. Stefansdottir, Anti-rheumatic treatment and prosthetic joint infection: an observational study in 494 elective hip and knee arthroplasties. BMC Musculoskelet Disord, 2020;21(1):p. 410.
[28] Brady, S., et al., PERI-operative biologic DMARD management: Stoppage or COntinuation during orthoPaEdic operations (the PERISCOPE trial) - a study protocol for a pragmatic, UK multicentre, superiority randomised controlled trial with an internal pilot, economic evaluation and nested qualitative study. BMJ Open, 2024;14(6):p. e084997.
[29] Berthold, E., P. Geborek, and A. Gulfe, Continuation of TNF blockade in patients with inflammatory rheumatic disease. An observational study on surgical site infections in 1,596 elective orthopedic and hand surgery procedures. Acta Orthop, 2013;84(5):p. 495-501.
[30] Diaper, R., E. Wong, and S.A. Metcalfe, The implications of biologic therapy for elective foot and ankle surgery in patients with rheumatoid arthritis. Foot (Edinb), 2017;30(53-58.
[31] Klifto, K.M., B.H. Cho, and S.D. Lifchez, The Management of Perioperative Immunosuppressant Medications for Rheumatoid Arthritis During Elective Hand Surgery. J Hand Surg Am, 2020;45(8):p. 779 e1-779 e6.
[32] Gupta, P., T. Quan, M.A. Wright, and A.M. Murthi, Risks of chronic steroid or immunosuppressive therapy on total shoulder arthroplasty patients. Shoulder Elbow, 2023;15(4):p. 373-380.

[33] Saunders, N.E., J.R. Holmes, D.M. Walton, and P.G. Talusan, Perioperative Management of Antirheumatic Medications in Patients with RA and SLE Undergoing Elective Foot and Ankle Surgery: A Critical Analysis Review. JBJS Rev, 2021;9(6):p.
[34] Hresko, A.M., C.J. Got, and J.A. Gil, Perioperative Management of Immunosuppressive Medications for Rheumatoid Arthritis. J Hand Surg Am, 2022;47(4):p. 370-378.
[35] Mamaril-Davis, J.C., et al., Managing Disease-Modifying Antirheumatic Drugs (DMARDs) for Patients Undergoing Elective Spine Surgery: A Pilot Survey. Spine Surg Relat Res, 2024;8(1):p. 35-42.
[36] Joaquim, A.F., S.A. de Oliveira, S. Appenzeller, and A.A. Patel, Spine Surgery and Ankylosing Spondylitis: Optimizing Perioperative Management. Clin Spine Surg, 2023;36(1):p. 8-14.
[37] Gaudiani, M.A., et al., The association of preoperative TNF-alpha inhibitor use and reoperation rates in spinal fusion surgery. Spine J, 2021;21(6):p. 972-979.
[38] Streufert, B.D., et al., Rheumatoid Arthritis in Spine Surgery: A Systematic Review and Meta-Analysis. Global Spine J, 2022;12(7):p. 1583-1595.

Table 1: The summary of the 2022 ACR/AAHKS recommendations for the Perioperative Management of DMARDs in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

	Dosing Interval	Timing of surgery since last medication dose
I. Medications to continue through surgery		
csDMARDs: continue 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
Glucocorticoids (All patients) [#]	Daily	Anytime
Severe SLE-specific medications: continue these medications in the perioperative period in consultation with the treating rheumatologist		
Mycophenolate	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 monthsb	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	Anytime
II. Medications to withhold prior to surgery [##]		
bDMARDs (All patients)		
Infliximab (Remicade)	Every 4, 6 or 8 weeks	Week 5, 7 or 9
Adalimumab (Humira)	Every 2 weeks	Week 3
Etanercept (Enbrel)	Weekly	Week 2
Golimumab (Simponi)	Every 4 weeks (SQ) or 8 weeks (IV)	Week 5 or Week 9
Abatacept (Orencia)	Monthly (IV) or weekly (SC)	Week 5 or 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 4 weeks (IV) or weekly (SC)	Week 5 or Week 2
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
Secukinumab (Cosentyx) 150 mg	Every 4 weeks	Week 5
Belimumab (Benlysta) 10 mg/kg	Every 4 weeks	Week 5
tsDMARDs (JAK inhibitors)(All patients)		
Tofacitinib (Xeljanz)	Daily or twice daily	Day 4**
Baricitinib (Olumiant)	Daily	Day 4**
Upadacitinib (Rinvoq)	Daily	Day 4**

Not severe SLE		
Mycophenolate	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

Data was reproduced based on 2017, 2022 ACR/AAHKS guideline and 2018 International consensus meeting (ICM)[4].

Abbreviations: IV, intravenous; SC, subcutaneous; PO, oral

*Medications added from ICM 2018; **Recommendations that has changed since ICM 2018

[#]Continuing their current daily dose rather than administering supraphysiologic doses of glucocorticoids on the day of surgery

[##]Resuming medications withheld before surgery is conditionally recommended once the wound shows evidence of healing, typically about 14 days after surgery. Evidence of healing includes the absence of sutures or staples out, swelling, erythema, or drainage, and signs of surgical site infection.

Table 2: The Current Recommendations of the International Consensus Meeting (2025)

Patients with RA, AS, PsA, or JIA undergoing THA or TKA, continuation of csDMARDs, withholding biological DMARDs for one dose cycle, and with holding tsDMARDs (Janus Kinase Inhibitors) at least 3 days before surgery is conditionally recommended.
Patients with SLE undergoing THA or TKA, continuation of csDMARDs is conditionally recommended but depending on the severity of SLE, recommendations for continuing or withholding immunosuppressive or biological medications differ and final decisions should be made in consultation with the treating rheumatologist.
Patients with RA, AS, PsA, or SLE undergoing THA or TKA and receiving glucocorticoids for their rheumatic condition, continuation of the current daily dose of glucocorticoids rather than administering supraphysiologic doses of glucocorticoids on the day of surgery is conditionally recommended.
For other major orthopedic procedures (e.g., upper limb or foot and ankle surgeries, and spinal surgeries), where evidence is limited, decisions should be made in consultation with the treating rheumatologist, referencing the optimization strategies used for THA and TKA until evidence specific to that procedure becomes available.
Resuming medications withheld before surgery is conditionally recommended once the wound shows evidence of healing, typically around 14 days post-surgery.