Authors: Susan Goodman, Bryan D. Springer, Jasvinder Singh, Adolph J. Yates

QUESTION 8: Do immunomodulatory disease-modifying medications (e.g., methotrexate or antitumor necrosis factor (anti-TNF) agents) need to be withheld preoperatively to reduce the risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION:

For adults with inflammatory arthritis (rheumatoid arthritis (RA), psoriatic arthritis (PsA), adults with juvenile idiopathic arthritis (JA), ankylosing spondylitis (AS) or systemic lupus erythematosus (SLE)), all biologic anti-rheumatic medications including TNF inhibitors and IL-6 blockers (see Table 1 for complete list) should be withheld for a full dosing cycle prior to total hip (THA) and total knee arthroplasty (TKA), and the surgery should be timed to the week following the withheld dose. These medications can be restarted no less than two weeks after surgery if the wound is healing well, all sutures are out and there are no non-surgical site infections.

For adults with inflammatory arthritis or SLE, synthetic disease-modifying anti-rheumatic drugs (DMARDs; see Table 1), including methotrexate, can be continued through the perioperative period.

For adults with severe SLE, immunomodulatory medications (see Table 1) can be continued through the perioperative period.

For adults with mild SLE, immunomodulating medications (with the exception of tacrolimus) should be withheld prior to surgery and restarted at a minimum of 14 days after surgery if the wound is healing well and all sutures are out and there is no surgical site or non-surgical site infection.

For adults with RA, SLE, AS, PsA and JIA receiving glucocorticoids (GCs) for treatment of their rheumatic disease, who did not receive GCs during development and are not receiving replacement therapy, we recommend that the usual daily GC dose be given on the day of surgery rather than supra-physiologic ("stress dose") GCs.

LEVEL OF EVIDENCE: Limited, based on moderate to low-quality indirect evidence

DELEGATE VOTE: Agree: 87%, Disagree: 3%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

While arthroplasty provides important benefits for those with inflammatory arthritis and SLE, these patients are at increased risk of complications including infection [1–3]. To provide guidance, the American Association of Hip and Knee Surgeons (AAHKS) and the American College of Rheumatology (ACR) convened a panel of stakeholders including rheumatologists, orthopaedists, patients, infectious disease experts and methodologists. We systematically reviewed the relevant literature in Embase (1974 +), the Cochrane Library and PubMed (mid-1960s +) from January 1, 1980 through March 6, 2016 and synthesized the evidence, reaching consensus on the recommendations listed above, to balance the risk of infection against the risk of disease flare [4]. An additional literature search was conducted from March 1, 2016 through February 28, 2018 and additional relevant articles were added to this discussion.

For synthetic non-biologic DMARDs there is evidence from randomized controlled trials revealing no increase in infection when these medications are continued through the perioperative period. Although there are no surgical trials directly comparing infection and flare for biologic anti-rheumatic medications including TNF inhibitors and IL-6 blockers, there are numerous trials that demonstrate an increase in infection associated with these medications in non-surgical settings. Because patients with mild SLE can be carefully monitored after surgery and medications can be restarted for flares, we recommend withholding all immunomodulating medications at the time of surgery. For patients with severe or potentially life or organ-threatening SLE, perioperative complications may be linked to active disease, so we recommended continuing immunomodulating medications through surgery, in consultation with the patient's rheumatologist.

TABLE 1. Medications included in this guideline

DMARDs: CONTINUE these medications through surgery.	Dosing Interval	Continue/Withhold
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide (Arava)	Daily	Continue
Doxycycline	Daily	Continue

BIOLOGICS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence wound healing problems, surgical site infection or systemic infec tion.	**Dosing Interval**	**Schedule Surgery (relative to last biologic dose administered)**
Adalimumab (Humira) 40 mg	Every 2 weeks	Week 3
Etanercept (Enbrel) 50 mg or 25 mg	Weekly or twice weekly	Week 2
Golimumab (Simponi) 50 mg	Every 4 weeks (SQ) or Every 8 weeks (IV)	Week 5 Week 9
Infliximab (Remicade) 3 mg/kg	Every 4, 6 or 8 weeks	Week 5, 7 or 9
Abatacept (Orencia) weight-based 500 mg; IV 1000 mg; SQ 125 mg	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Rituximab (Rituxan) 1000 mg	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra) IV 4 mg/kg; SQ 162 mg	Every week (SQ) or Every 4 weeks (IV)	Week 3 Week 5
Anakinra (Kineret) SQ 100 mg	Daily	Day 2
Secukinumab (Cosentyx) 150 mg	Every 4 weeks	Week 5
Ustekinumab (Stelara) 45 mg	Every 12 weeks	Week 13
Belimumab (Benlysta) 10 mg/kg	Every 4 weeks	Week 5
Tofacitinib (Xeljanz) 5 mg: STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose
SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period.	**Dosing Interval**	**Continue/Withhold**
Mycophenolate	Twice daily	Continue
Azathioprine	Daily or twice daily	Continue
Cyclosporine	Twice daily	Continue

Tacrolimus	Twice daily (IV and PO)	Continue
NOT-SEVERE SLE: DISCONTINUE these medications in the perioperative period.	**Dosing Interval**	**Continue/Withhold**
Mycophenolate	Twice daily	Withhold
Azathioprine	Daily or twice daily	Withhold
Cyclosporine	Twice daily	Withhold
Tacrolimus	Twice daily (IV and PO)	Continue
Dosing intervals obtained from prescribing information provided online by pharmaceutical companies.		
*2016 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Anti-rheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty		

IV, intravenous; SQ, subcutaneous; PO, oral
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Tofacitinib is a unique oral immunomodulator that increases infection risk, so we recommended withholding tofacitinib for seven days prior to surgery. Immunocompromised status is linked to high-dose biologic therapy, so we based the period of drug withholding on the dose interval, to reflect the period of effective immunosuppression that is not reflected in the serum pharmacokinetic half-life. For example, rituximab has a serum half-life of 18 to 32 days, yet B-lymphocyte depletion may persist ≥ 6 months after an infusion. This suggests that the optimal time for surgery is at the end of the dosing cycle at the drug immunosuppressive nadir.

Glucocorticoids (GCs) are typically administered at supra-physiologic doses ("stress-dose corticosteroids") to patients receiving long-term GCs at the time of THA and TKA, despite the consistent association with increased infection, out of concern for hemodynamic instability. Based on randomized control trials as well as observational studies that do not demonstrate hypotension when usual dose GCs are administered, we recommended continuing the usual dose rather than "stress-dose corticosteroids." This recommendation applies only when the GCs are given for a rheumatic conditions and not to those who received GCs during development or those receiving GCs as replacement therapy for other medical conditions.

Since this publication, the background assumption of increased infection risk for patients with RA has been confirmed in a large registry-based THA/TKA cohort study of 3,913 patients with RA compared with 120,499 patients with osteoarthritis (OA) [5]. Patients with RA had an increased risk of PJI (subhazard ratio (SHR): 1.46, 95% confidence interval (CI) 1.13 to 1.88). Biologics were administered within 90 days of surgery in 345 of 1,946 patients but did not increase the risk of PJI (SHR: 1.61, CI 0.70 to 3.69). A second retrospective cohort study analyzed surgeries in 4,288 patients with inflammatory bowel disease and inflammatory arthritis on chronic infliximab who received an infusion within 6 months of THA and TKA [6]. Exploiting the precision of infusion billing records, they determined that infliximab when given within four weeks of surgery compared to infliximab given > six months prior to surgery did not increase the risk of serious infection within 30 days after surgery (odds ratio (OR): 0.90, CI 0.60 to 1.34) or PJI within one year (OR: 0.98, CI 0.52, 1.87). Glucocorticoid dose > 10 mg significantly increased the risk of 30 day infection (OR: 2.11, CI 1.30 to 3.40) and PJI (HR: 2.70, CI 1.30 to 5.60). In a retrospective case control study using data from a large commercial database, 55,861 patients with OA or RA undergoing arthroplasty were identified, including 1,127 infected TJA cases that were matched to 1,106 controls. RA patients were 47% more likely to have a postoperative infection than OA patients (OR: 1.47, CI 1.04 to 2.08). Use of perioperative immunosuppressive medications did not increase the risk (OR: 1.12, CI 0.84 to 1.50). Perioperative prednisone use was again found to be a significant risk factor for infection (OR: 1.59, CI 1.28 to 1.97) [7].

These observational studies indicate that addressing infection risk for rheumatic disease patients remains important, and support our recommendation to give the usual dose of GCs, not supraphysiologic doses, at the time of THA and TKA. While biologics were not a risk factor for infection after surgery, unmeasured confounders may play a role in observational studies. These studies provide further justification for needed research in the future.

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