Perioperative Management of Rheumatic Disease and Therapies

Diane Zisa, MD[a], Susan M. Goodman, MD[a,b,*]

KEYWORDS

• Rheumatic disease • Perioperative care • Perioperative medication management

KEY POINTS

- Rates of orthopedic surgery use among patients with rheumatic disease remain high despite improvements in diagnosis and treatment.
- Patients with rheumatoid arthritis (RA), systemic lupus erythematous (SLE), and spondyloarthritis (SpA) are complex surgical candidates because of their diseases and their use of immunosuppressant medications and are at higher risk of adverse events after surgery.
- Existing systemic manifestations of the rheumatic diseases must be identified and carefully evaluated by the internist during the preoperative assessment.
- The goal of perioperative management of rheumatic therapies is to balance the risks of infection and delayed wound healing when continued with the potential for disease flare when withheld.
- Optimization of these patients before surgery often requires collaboration among multiple specialists.

INTRODUCTION

Patients with rheumatic disease are undergoing orthopedic procedures in considerable numbers, most often to alleviate pain and restore function after years of accrued joint damage. These are medically complex patients because of the potential organ damage from their diseases and their use of immunosuppressant therapy. Thus, these patients demand careful perioperative management and, often, interdisciplinary collaboration. These therapies constitute a rapidly advancing field, and, as such, the medical providers most often tasked with completing the preoperative consultation may be less experienced in their use. This article presents the relevant considerations to managing this challenging population of patients, particularly those with systemic

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[a] Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA; [b] Hospital for Special Surgery, Weill Cornell Medicine, 535 East 70th Street, New York, NY 10021, USA
* Corresponding author.
E-mail address: goodmans@hss.edu

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lupus erythematous (SLE), rheumatoid arthritis (RA), and spondyloarthritis (SpA), through the perioperative period. Special emphasis is given to the principles surrounding the management of conventional synthetic disease-modifying agents and targeted therapies, including biologics, so as to improve patient outcomes and mitigate postoperative risks.

Scope of the Problem

Major orthopedic surgeries, such as total joint arthroplasties, continue to be highly used procedures among patients with SLE, RA, and SpA despite the substantial advances in diagnosis and treatment.[1–5] More specifically, even with the extensive implementation of the disease-modifying antirheumatic drug (DMARD) methotrexate by 1990, and the arrival of the biologics to the treatment armamentarium by 1998, the rate of large joint arthroplasties for patients with RA has remained high, although surgery seems to have been delayed because patients are now older at the time of arthroplasty.[1,3,6] A recent study using a national database of 13,961 patients with RA in England found that this cohort had approximately double the lifetime risk of knee and hip replacements compared with that of the general population.[2] Similarly high use rates are seen for patients with SLE and SpA, the latter of which includes patients with ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, and inflammatory bowel disease–associated arthritis.[3,4]

Although rates of arthroplasty remain high, complications are also higher in these patients than for patients with osteoarthritis (OA), and include infection and hip dislocation, and venous thromboembolism (VTE), acute kidney damage, and cardiac complications in patients with SLE.[7,8] This article discusses the specific risks that are increased in these patients by virtue of their underlying inflammatory diseases and medications. Additionally, it discusses our approach to the preoperative evaluation to address modifiable risk factors and optimize them, when possible, before surgery.

PREOPERATIVE CONSIDERATIONS

Anesthesia

Patients with RA and AS can have cervical spinal involvement that presents challenges for anesthesiologists during intubation for general anesthesia. Cervical spine instability and subluxation in RA is usually seen in association with severe, erosive disease and can be asymptomatic, as demonstrated in a study of 154 patients with RA awaiting orthopedic surgery, in which 44% of them were identified as having cervical spine involvement (subluxation or prior surgical fusion) by radiographs.[9] About one-third of patients with cervical spine subluxations did not report associated symptoms.[9] Although gait and balance may be affected in patients with an unstable spine with spinal cord compression, patients with advanced arthritis of the hip or knee may not report this, but signs of myelopathy, such as hyperreflexia, a positive Babinski reflex, or loss of fine motor function in the hands may point to the diagnosis and is easily checked before surgery. Thus, consideration of preoperative screening cervical spine radiographs (with lateral flexion and extension views) should be given to patients with severe, erosive, highly active, and/or long-standing disease before undergoing anesthesia, because manipulation of an unstable cervical spine can result in spinal cord injury or death.[9,10]

Moreover, patients with severe RA can have involvement of the upper airway, particularly arthritis of the cricoarytenoid joints and temporomandibular joints. Hoarseness in the patient with RA is a clue to involvement of the cricoarytenoid joints. If present, it necessitates preoperative consultation with anesthesiologists for a safe and

informed plan of care, because trauma during intubation can lead to severe edema and airway obstruction.[11]

Conversely, patients with AS may suffer from cervical spinal fusion and severe osteoporosis, which increases the risk of fracture during endotracheal intubation. These patients can additionally develop restricted chest wall expansion caused by fusion of the costovertebral joints and thoracic spine, to which they adapt by becoming diaphragmatic breathers.[12] Attention to bowel function postoperatively is important in these patients, because a distended abdomen can prevent the diaphragmatic excursion needed for ventilation.[12]

Cardiopulmonary Disease

Inflammation is now recognized as a contributor to the development of atherosclerotic cardiovascular disease in all populations. Unsurprisingly, patients with SLE, RA, and SpA are at higher risk of cardiovascular disease compared with age- and sex-matched control subjects.[13–16]

Total joint arthroplasties are major surgical procedures with potential cardiopulmonary complications, and patients with underlying cardiovascular disease are at increased risk for poor outcomes. The rate of postoperative myocardial infarction in 7600 inpatient orthopedic operations was reported to be 0.6%, but this rate increased to 6.4% in patients with known or risk factors for ischemic heart disease.[17]

RA was not independently associated with an increase in perioperative cardiac events or death when compared with patients with diabetes mellitus or control subjects in a study of noncardiac surgeries using the Nationwide Inpatient Sample of more than 7 million cases or when compared with patients with OA using a Veterans Affairs database.[18,19] However, a study of Taiwan's National Health Insurance Research database found that patients with SLE undergoing surgery (of which approximately 30% were orthopedic surgeries) had higher 30-day postoperative mortality, and that inpatient care, a likely proxy for active SLE, within 6 months of surgery predicted worse outcomes.[7] However, similar to the RA study, cardiovascular events, particularly acute myocardial infarction, did not differ significantly between the SLE and non-SLE groups.[7] Yet, when evaluating patients with SLE undergoing arthroplasty specifically, patients with SLE had a two-fold to seven-fold increased risk of inhospital mortality postoperatively compared with control subjects.[20] In regard to the spondyloarthropathies, the evidence for increased cardiovascular risk after total joint arthroplasty is mixed, particularly in patients with AS.[21,22] Taken together, although data for increased cardiovascular risk in these patients are clear, the same cannot be said for risk of postoperative cardiac events, particularly in patients with RA.

Arthroplasties are categorized as intermediate risk surgeries, with an associated 1% to 5% incidence of cardiac death and nonfatal myocardial infarction, by the American College of Cardiology/American Heart Association.[23,24] Patients with systemic inflammatory diseases may be unable to perform exercise and activities equivalent to four metabolic equivalent tasks secondary to their accrued joint damage, which limits the ability to accurately assess functional capacity.[24,25] Current risk assessment tools, such as the Revised Cardiac Risk Index, or use of traditional risk factors, such as cholesterol levels, may further underestimate the cardiac risk in these patients.[13,24] It is important to have a high index of suspicion for potential subclinical and asymptomatic cardiac disease in patients with rheumatic disease, particularly in RA and AS, when conducting a preoperative assessment, because patient history and traditional risk assessment algorithms alone may not reflect true cardiac risk. Additional evaluation may include a preoperative stress test, with postoperative troponin screening for subclinical cardiac events.[13]

Finally, pulmonary diseases in patients in rheumatic disease range from the more common entities, such as asthma and chronic obstructive pulmonary disease, to the less frequent, including interstitial lung disease and pulmonary hypertension. The latter, pulmonary hypertension, can be fatal in the perioperative context, particularly after the administration of anesthetic agents.[26] Consultation with cardiology, pulmonology, and anesthesiology preoperatively is imperative to anticipate and mitigate risk in affected patients.[13]

Venous Thromboembolism

Patients with systemic inflammatory diseases have higher risks of VTE, including deep venous thrombosis and pulmonary embolism (PE), compared with the general population, particularly at times of high disease activity.[27–32] A review of a Swedish database of all hospital admissions of patients with an autoimmune disorder found that the risk of PE was high and persists beyond the period immediately after hospitalization; for some conditions, the risk lasts for greater than 10 years.[27] This suggests that hypercoagulability associated with the inflammatory disorder itself is likely responsible aside from traditional VTE risk factors.[27]

As potentially fatal complications of total joint arthroplasties, VTE has received considerable attention by the American Association of Orthopedic Surgeons and the American College of Chest Physicians.[33,34] Perhaps because of this additional diligence, patients with RA have not consistently been found to develop VTE at higher rates after arthroplasties, although they do suffer thrombosis at higher rates for medical hospitalizations.[8,35,36] Rates of deep venous thrombosis and PE after total joint arthroplasty in patients with spondyloarthropathies, particularly AS and psoriatic arthritis, however, are mixed, because studies have demonstrated increased and similar rates compared with OA control subjects.[21,37]

Alternatively, patients with SLE do have elevated postoperative risk of VTE that is highest when SLE is active, as demonstrated in patients with preoperative SLE-related inpatient care within 6 months of surgery.[7,38] Patients with SLE with concomitant antiphospholipid syndrome (APS) are at particular risk for VTE.[39–41] APS is characterized by either venous or arterial thrombosis or pregnancy morbidity in the setting of persistent antiphospholipid antibody positivity.[39–41] Patients with SLE with known antiphospholipid antibody positivity or a positive lupus anticoagulant who do not meet criteria for APS are, like all patients with SLE, treated as high risk for VTE, even if they have no history of thrombosis. Although mild thrombocytopenia may accompany APS, it is not typically severe, and the risk of VTE for these patients is not lessened. The goal in the perioperative setting for patients with APS is to formulate a plan that will decrease the patient's risk of thrombosis by minimizing the time spent off anticoagulation, while simultaneously not increasing bleeding risk.[40] Thus, preoperative communication and cooperation among medical, surgical, and anesthesiology teams is necessary to achieve this delicate balance.

Infection

Overall, infection risk is higher in patients with RA, SpA, and SLE, and susceptibility is multifactorial, including disease activity and severity and the use of immunosuppressive treatments.[25] Infections, including periprosthetic joint infection and surgical site infection (SSI), have been shown to occur more frequently after total joint arthroplasty in patients with RA relative to patients with OA, with risks consistently 50% higher.[8,21,37,42–44] However, analysis of a cohort of validated patients with RA at a major referral center with high RA-specific surgical experience did not find a difference in infection rate between patients with RA and OA at 90 days post total knee

arthroplasty, supporting prior work that surgeon experience with patients with RA is potentially a mitigating factor in poor outcomes.[35,45] Nasal colonization with *Staphylococcus aureus* has been recognized as a substantial risk factor for SSI.[46] In a recent study, patients with RA treated with biologic therapies were found to have an increased risk of *S aureus* nasal colonization compared with those with RA not on biologics and patients with OA.[47] Although not considered standard of practice, perioperative decolonization of patients with RA on biologics may be considered to lower the risk of infectious complications.[47] Decolonization protocols include either Bactroban ointment applied to nares for 5 days before surgery, twice a day, or chlorhexidine shower or bath daily for 5 days before surgery and drying with a clean towel. Although there is no definitive proof of an impact of *S aureus* decolonization on SSI, it is reasonable in settings with high risk of infection in immunocompromised patients including orthopedic procedures where arthroplasty hardware is implanted.

Efforts should also be taken to optimally manage psoriatic skin lesions close to the surgical site to minimize infectious complications given the known high rates of bacterial colonization found in psoriatic plaques.[42,48]

Finally, patients with SLE have a significantly higher risk of complications, including infection, after undergoing total hip arthroplasty, but not older patients with SLE undergoing total knee arthroplasty who may have less active disease, when compared with control populations.[38,49–51] When postoperative complications for various surgeries in addition to orthopedic were evaluated in a large cohort of patients with SLE, there were higher rates of septicemia and pneumonia, although not SSI.[7] This suggests that the infection risk may be attributable to the systemic disease.[7,25]

PERIOPERATIVE MANAGEMENT OF RHEUMATIC THERAPIES

In addition to the increased risk of infection in patients with RA and SLE inherent to their altered immune function, these diseases are often managed using immunosuppressive medications, thereby further increasing that risk. These medications are categorized as conventional synthetic DMARD (csDMARD), or as targeted therapies, including biologics and Janus kinase inhibitors, which are agents that selectively target specific mediators involved in the inflammatory process.[25] The use of csDMARDs and biologics, and these classes of drugs in combination, is becoming more prevalent and, surprisingly, use of biologics has not had an impact on need for arthroplasty.[1,52,53] As a result, most patients with RA, SpA, and SLE are using these potent immunosuppressants around the time of surgery.[35,44,52,54] As such, careful attention must be paid to the management of these medications during the preoperative evaluation. The goal of perioperative management of rheumatic therapies is to balance the risks of infection and delayed wound healing when continued with the potential disease flare, and resultant threat to postoperative rehabilitation, when discontinued.

csDMARDs, including hydroxychloroquine, sulfasalazine, leflunomide, and methotrexate, have been studied in the perioperative period and overall seem to be safe.[5,55] An older prospective randomized trial in which patients with RA were randomized to either continue or discontinue methotrexate before elective orthopedic surgery, and then compared with patients with RA who had never been on methotrexate, found that patients who discontinued methotrexate before surgery had higher infection rates and higher flare rates.[56] Studies on the safety of leflunomide perioperatively have been mixed, although current consensus is to continue without interruption.[5,57] Because hydroxychloroquine is not immunosuppressive, it should be continued through the perioperative period.[42]

Although ample data support an increased frequency of infection with the use of biologics in nonsurgical settings, direct evidence on the risks of biologics in the setting of surgery is limited. A meta-analysis that pooled data from 11 articles totaling 3681 patients with recent use of tumor necrosis factor inhhibitors and 4310 without recent use found that those with recent tumor necrosis factor inhhibitor use had a higher risk of developing SSI at the time of elective orthopedic surgery, but this may reflect the increased severity of RA in those receiving biologics.[55] However, studies using administrative data where careful timing of the interval between biologic infusions and surgery could be determined using billing records have not found a relationship between biologics and postoperative infection, although chronic glucocorticoid use was a significant risk factor for infection.[5,58] Consensus recommendations from the American College of Rheumatology and the American Association of Hip and Knee Surgeons suggest that these therapies should be discontinued before surgery and that the procedure should be scheduled at the end of the dosing cycle for the particular medication, thus minimizing the time off drug before surgery, and restarting as soon as the wound is closed after surgery. Normally, the biologic may be restarted once the wound is healing well without any sign of infection and the sutures have been removed, at a minimum of 14 days after surgery.[5]

For patients with SLE, the severity of the disease manifestations informs the recommendations on continuation or cessation of disease-controlling therapies in the perioperative period. Patients with more severe SLE, characterized by severe cardiopulmonary, renal, hematologic, gastrointestinal, ocular, and/or central nervous system involvement, should continue their medications through the perioperative period given the substantial risk of organ- or life-threatening flare should they be discontinued. However, delaying elective surgery until optimal disease control is achieved should be considered when possible.[5] For those patients with SLE without severe manifestations, medications should be discontinued for 1 week before the scheduled surgical procedure and restarted approximately 3 to 5 days after surgery if there are no signs of infectious complications locally or systemically.[5]

Recognizing the need for a consensus-based approach for the perioperative management of rheumatic therapies, members of the American College of Rheumatology and the American Association of Hip and Knee Surgeons published an evidence-based guideline in 2017 developed for use in the setting of total hip or knee arthroplasty.[5] **Table 1** summarizes the medication recommendations set forth in the guidelines, organized by medication class and discussed briefly previously. It additionally includes recommendations regarding appropriate timing of surgery based on dosing schedule of the biologics. It is important to consider the type of surgery when interpreting these recommendations; in patients undergoing minor procedures, such as arthroscopy, continuing all treatment through the perioperative period may be reasonable. However, this would not apply to procedures in which orthopedic hardware is implanted or procedures with a high risk for infection.

Glucocorticoid Management

Glucocorticoid management in the perioperative setting was also addressed in these guidelines.[5] Glucocorticoids have been conclusively shown to increase the rates of infectious and wound healing complications. In a recent retrospective cohort study using national databases of patients with RA having elective total joint arthroplasty, glucocorticoids were strongly associated with a dose-dependent increase in infectious risk postoperatively, even at modest doses of 5 to 10 mg/d.[58]

As part of the preoperative evaluation, therefore, attention should be focused on optimization of glucocorticoid dosing by tapering the dose before surgery to less

Table 1
Medications included in the 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

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 Before Surgery and Schedule Surgery at the End of the Dosing Cycle. Resume Medications at Minimum 14 d After Surgery in the Absence of Wound Healing Problems, Surgical Site Infection, or Systemic Infection.	Dosing Interval	Schedule Surgery (Relative to Last Biologic Dose Administered)
Adalimumab (Humira) 40 mg	Every 2 wk	Week 3
Etanercept (Enbrel) 50 mg or 25 mg	Weekly or twice weekly	Week 2
Golimumab (Simponi) SQ 50mg; IV 2mg/kg	Every 4 wk (SQ) or every 8 wk (IV)	Week 5 Week 9
Infliximab (Remicade) 3-5mg/kg	Every 4, 6, or 8 wk	Week 5, 7, or 9
Abatacept (Orencia) weight-based IV 500-1000mg; SQ 125 mg	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Rituximab (Rituxan) 1000 mg	2 doses 2 wk apart every 4–6 mo	Month 7
Tocilizumab (Actemra) IV 4 mg/kg; SQ 162 mg	Every wk (SQ) or every 4 wk (IV)	Week 2 or Week 5
Anakinra (Kineret) SQ 100 mg	Daily	Day 2
Secukinumab (Cosentyx) 150 mg	Every 4 wk	Week 5
Ustekinumab (Stelara) 45 mg	Every 12 wk	Week 13
Belimumab (Benlysta) IV 10mg/kg	Every 4 wk	Week 5
Tofacitinib (Xeljanz) 5 mg: stop this medication 7 d before surgery	Daily or twice daily	7 d 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)	Withhold

Dosing intervals obtained from prescribing information provided online by pharmaceutical companies.

Abbreviations: IV, intravenous; PO, by mouth; SQ, subcutaneous.

From Goodman SM, Springer B, Guyatt G, 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. Arthritis Rheumatol 2017;69(8):1541; with permission.

than 20 mg/d whenever possible.[5] Although pharmacoepidemiologic data support the increase in risk for patients receiving daily glucocorticoid therapy, a decrease in risk with preoperative dose reduction has not been proven.[58] Furthermore, as a challenge to the widely entrenched implementation of "stress-dose" or supraphysiologic dose administration at the time of surgery to avoid adrenal insufficiency with hypotension and shock in chronically glucocorticoid-treated patients, these guidelines suggest that continuation of the patient's usual daily dose of glucocorticoid is generally sufficient in patients undergoing arthroplasty unless the patient began glucocorticoid therapy in childhood. This recommendation is supported by a systematic review on the topic.[5,59,60] As such, usual dosing of glucocorticoids should be continued perioperatively and given on the day of surgery in most arthroplasty surgeries, although prolonged cases or cases under general anesthesia may require additional glucocorticoids. Close monitoring postoperatively for hypotension or alternative signs of adrenocortical insufficiency can prompt administration of additional exogenous glucocorticoid, if necessary. For first case scenarios, where there is concern for drug absorption before starting the surgery, the glucocorticoid dose is administered intravenously in the operating room or holding area.

SUMMARY

Despite advances in treatment, orthopedic surgery for patients with RA, SLE, and SpA remains necessary for a substantial number of patients. These complex patients present challenges in the perioperative period by virtue of their diseases and their immunosuppressant therapies. Multidisciplinary collaboration and thorough evaluations by internists, rheumatologists, surgeons, and anesthesiologists in the preoperative period are therefore necessary for successful outcomes.

CLINICS CARE POINTS

- Cervical spine disease in RA and AS can increase the risk of endotracheal intubation.
- Screening cervical spine flexion/extension radiographs and consultation with an anesthesiologist preoperatively should be considered.
- Patients with SLE are at increased risk for cardiovascular complications after surgery, whereas patients with RA are not, and the risk for those with SpA has not been quantified.

- Cardiac imaging and noninvasive testing may be required to assess preoperative cardiac risk because many patients with RA, SLE, or SpA may not be able to exercise sufficiently to demonstrate their cardiac status.
- Patients with RA do not have higher rates of VTE after arthroplasty.
- Data in patients with SpA are mixed regarding postoperative VTE risk.
- Patients with SLE have a higher risk of postoperative VTE, particularly those with concurrent APS, and thus require careful preoperative planning among specialists.
- Physicians should be aware of the increased risk for infectious complications in patients with SLE, RA, and SpA undergoing total joint arthroplasties.
- csDMARDs can be continued through the perioperative period, whereas targeted therapies including biologics should be discontinued before surgery with surgery planned for the end of the dosing cycle.
- Biologics are restarted when there is evidence of appropriate wound healing with no evidence of infection, typically at approximately 14 days after surgery.
- Minimizing glucocorticoid use before surgery is a critical part of perioperative risk management for patients with rheumatic disease.

DISCLOSURE

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