Perioperative Management of Rheumatoid Medications in Orthopedic Surgery

Kunal Sindhu, BA; Brian Cohen, MD; Joseph A. Gil, MD

abstract

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder known to cause progressive joint destruction. Over time, untreated RA can lead to pain and increasing disability, making orthopedic intervention necessary. The treatment of RA revolves around a variety of medications that blunt the overall immune response. However, this may increase the risk of infection and impair wound healing. Given the nature of this disease, orthopedists frequently encounter patients with RA in the operative setting. To optimize surgical outcomes, orthopedists must carefully manage and pay special attention to the adverse side effects of the complicated medication regimens of these patients perioperatively. [Orthopedics. 2017; 40(5):282-286.]

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that affects 0.1% to 0.5% of individuals in the United States.¹ The disease classically affects the joints, leading to their progressive destruction, pain, and disability. However, RA is a systemic disease affecting every organ system in the body. In particular, patients with RA have several extra-articular manifestations, including interstitial lung disease, cardiovascular disease, rheumatoid nodules, cervical spine disease, and decreased immunity.² To slow the progression of this insidious disease, prompt therapy is essential. Orthopedists must understand the complexities of these treatments because 58% of patients with RA will ultimately undergo orthopedic surgery, with nearly 24% undergoing large-joint arthroplasty (Table).³

Nonsteroidal anti-inflammatory drugs, glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor-alpha (TNF-α) inhibitors, and interleukin-1 (IL-1) antagonists all play a role in the treatment of RA. Although these medications can significantly improve the quality of life and survival of patients with RA, they present some difficult challenges to physicians and to orthopedists in particular, who frequently treat these patients. All of these medications are anti-inflammatory in nature, thereby interfering with the overactive immune response that underlies the development of RA. However, in suppressing the body’s natural immune response, these medications can increase the risk of infection and decrease the potential for wound healing, which can lead to unsuccessful outcomes in the postoperative period.² Although a seemingly natural response to this conundrum would be to simply discontinue these medications prior to surgery, doing so is not without significant risk of a rheumatoid flare. Thus, a careful, balanced approach is needed prior to planning a surgical intervention for a patient with RA. The purpose of this review is to present guidelines on how orthopedists should proceed in managing the medication regimens of patients with RA in the perioperative period.

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**Preoperative Evaluation of the Patient With Rheumatoid Arthritis**

Patients with RA must be screened for cardiovascular, hematologic, hepatic, and pulmonary function prior to surgery. These patients should receive special consideration regarding cardiovascular health and cervical spine stability. Additionally, orthopedists must also carefully review the medication regimens of these patients prior to considering surgical intervention.4

Patients with RA have a 60% higher risk of cardiovascular-related death as compared with the general population.5,6 Unfortunately, they often present with fewer symptoms of cardiovascular disease.4,7 In low-risk elective procedures and emergencies, no specific additional cardiac evaluation is necessary for this population. However, prior to moderate- and high-risk elective procedures, it is critical to more thoroughly screen these patients for cardiovascular risk. In particular, for patients who are unable to complete activities requiring an intensity of 4 metabolic equivalents (roughly equal to the effort needed to walk up a flight of stairs), further consultations, coupled with risk stratification, are necessary before surgical intervention can be undertaken.3

Patients with RA presenting for orthopedic procedures are more likely to be at high risk for cervical instability as compared with the general population.8 For patients with RA undergoing joint replacement, this risk has been estimated to be as high as 61%.9 Clinicians should be acutely aware of the possibility of cervical instability in these patients, as it can often present asymptotically. Thus, preoperatively, it is important to check both flexion and extension lateral cervical radiographs of patients with RA.10 If screening radiographs show abnormalities concerning for instability, further evaluation by magnetic resonance imaging is necessary.11 A thorough neurological examination should be performed for symptomatic patients, with neurological findings prompting further imaging and perhaps consultation with a spine surgeon. A multidisciplinary approach centered on frequent communication with anesthesiologists is crucial because cervical instability could influence positioning, type of anesthesia, and intubation technique during anesthesia.5

**Types of Medications**

**Nonsteroidal Anti-inflammatory Drugs**

Nonsteroidal anti-inflammatory drugs remain the first-line treatment for pain and stiffness in patients with RA.2 Aspirin and nonsteroidal anti-inflammatory drugs inhibit the action of the cyclooxygenase (COX) family of enzymes, thereby decreasing the synthesis of prostaglandins and exerting an anti-inflammatory effect on the body. However, another consequence of their action is an increased risk of bleeding secondary to their anticoagulative effect.12 In contrast, COX-2 inhibitors, including celecoxib, do not appear to significantly increase the risk of bleeding, but they have been found to significantly increase cardiovascular risk.12,13

Given the risk of bleeding, it is prudent for surgeons to discontinue aspirin and nonspecific COX inhibitors prior to surgery. Aspirin, which irreversibly interferes with the action of COX, should be discontinued 10 days prior to surgery. It may, however, be restarted immediately after surgery, as the risk of bleeding is decreased at this time. Nonsteroidal anti-inflammatory drugs, which can have a reversible effect on COX, should be discontinued 5 half-lives prior to surgery and may be restarted 7 to 14 days after surgery.12,13 The data surrounding COX-2 inhibitors are less clear. However, COX-2 inhibitors have previously been continued in the perioperative period because of the

<table>
<thead>
<tr>
<th>Medication</th>
<th>Half-life</th>
<th>Continue Through Surgery?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2-30 h</td>
<td>Hold 10 d prior to surgery, may restart immediately after</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Varies</td>
<td>Hold for 5 half-lives prior to surgery, restart 7-14 d after</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>11 h</td>
<td>May continue through surgery, but evidence is unclear</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Varies</td>
<td>Continue through surgery; consider administering physiologic dose, followed by taper</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>3-15 h</td>
<td>Continue through surgery</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>7-15 h</td>
<td>Continue through surgery</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>32-50 d</td>
<td>Continue through surgery</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>14-18 d</td>
<td>Hold 1 wk prior to surgery, restart 1 wk after</td>
</tr>
<tr>
<td>TNF-alpha inhibitors</td>
<td>Varies</td>
<td>ACR recommends holding for at least 1 wk prior to surgery; BSR recommends holding for 3-5 half-lives prior to surgery. Consider restarting only after wound has healed.</td>
</tr>
<tr>
<td>Anakinra</td>
<td>4-6 h</td>
<td>Howe et al11 recommended holding 1-2 d prior to surgery and restarting 10 d after. Mushtraq et al17 recommended holding 1 wk prior to surgery and restarting after wound closure.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACR, American College of Rheumatology; BSR, British Society of Rheumatology; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.
decreased risk of bleeding associated with them as compared with nonspecific COX inhibitors.\textsuperscript{13}

**Corticosteroids**

Corticosteroids remain a popular treatment for the symptoms of RA. Nearly 66\% of patients with RA overall, and 80\% undergoing arthroplasty, have used corticosteroid therapy.\textsuperscript{14,15} The popularity of corticosteroids hinges on their rapid onset of action, resulting in quicker symptom relief than treatment with DMARDs.\textsuperscript{16} However, with chronic use, corticosteroids suppress the hypothalamic–pituitary–adrenal axis, thereby decreasing physiologic cortisol production. Abrupt withdrawal of glucocorticoids may result in adrenal crisis for chronic users, especially those undergoing surgery.\textsuperscript{12} The risk of adrenal crisis necessitates that patients taking these medications continue to receive them during the perioperative period.

Corticosteroids also may increase the risk of infection, weaken bone, and impair wound healing. Because of the potentially devastating consequences of these side effects for surgical outcomes, it is crucial that surgeons manage each patient’s corticosteroid regimen individually. Some patients receiving long-term corticosteroid regimens may require higher than normal doses of corticosteroids preoperatively to minimize the risk of perioperative adrenal crisis.\textsuperscript{4} Abnormal results on a preoperative adrenocorticotropic hormone stimulation test may indicate that stress-dose corticosteroids are required prior to surgery.\textsuperscript{17} Saleh et al\textsuperscript{2} reported that an appropriate regimen requires the administration of a physiologic dose of glucocorticoids followed by a gradual taper to preoperative levels prior to surgery.

**Disease-Modifying Antirheumatic Drugs**

Disease-modifying antirheumatic drugs are a mainstay of management for patients with RA. It has been estimated that 75\% to 84\% of patients with RA undergoing arthroplasty receive traditional or biologic DMARD therapy.\textsuperscript{18} Methotrexate, in particular, has become the primary treatment for many patients with RA.\textsuperscript{19} It is crucial that surgeons operating on these patients be familiar with the management of DMARDs in the perioperative period.

In general, DMARDs appear to be safe during the perioperative period. Scherrer et al\textsuperscript{20} reviewed more than 50,000 orthopedic procedures and compared patients having degenerative and posttraumatic conditions with patients having inflammatory rheumatic diseases, including RA. They found a higher risk of infection in the inflammatory group among patients taking DMARDs or TNF-\(\alpha\) inhibitors. However, there was no increased risk of infection with monotherapy DMARD treatment in the inflammatory group. Rather, the risk of infection increased only with the use of multiple DMARDs or a biologic.\textsuperscript{20}

Methotrexate, a folate analog with a dose-dependent half-life of 3 to 15 hours, is used frequently for its efficacy and tolerability in treating RA.\textsuperscript{3,4} Fortunately, given its ubiquity in this population, methotrexate may be safely continued in the perioperative period. Grennan et al\textsuperscript{21} reviewed 388 patients with RA who underwent surgery. They found that patients who continued methotrexate during the perioperative period had fewer complications, infections, and RA flares than patients who discontinued methotrexate for the period 2 weeks before and after surgery.\textsuperscript{21}

Most studies support the continuation of methotrexate therapy through the perioperative period for otherwise healthy patients.\textsuperscript{4} However, for patients at high risk of postoperative infection, including those with impaired vascular flow, surgeons may consider discontinuing methotrexate in the perioperative period.\textsuperscript{22} Special consideration must be paid to those patients who develop renal dysfunction postoperatively, as toxicity to methotrexate may develop quickly in this population.\textsuperscript{13}

Both sulfasalazine, an inhibitor of nuclear factor kappa-B with a half-life of 7 to 15 hours, and hydroxychloroquine, an immunomodulator with a half-life of 32 to 50 days, have been less extensively studied during the perioperative period.\textsuperscript{3,4,23} However, the available data support the continuation of both medications in the perioperative period.\textsuperscript{5,24,25} In one retrospective study of patients with RA who underwent elective orthopedic procedures, sulfasalazine was associated with a lower risk of perioperative infection.\textsuperscript{26} However, renal function must be monitored in these patients to ensure adequate elimination of the drug.\textsuperscript{3,4}

In contrast, the perioperative data regarding the use of leflunomide, a pyrimidine synthesis inhibitor with a half-life of 14 to 18 days, are controversial.\textsuperscript{13} One study showed no difference in complication rates between patients who continued and those who discontinued leflunomide during the perioperative period, whereas another study showed a significantly increased risk of wound infections for patients who continued leflunomide.\textsuperscript{27,28} Given this contradictory evidence, it is not surprising that recommendations regarding the perioperative use of leflunomide differ. Müller and Pippi-Ludwig\textsuperscript{29} suggested continuing leflunomide alone for patients undergoing low-risk procedures and co-treating patients undergoing high-risk procedures with cholestyramine. Goodman\textsuperscript{1} suggested holding leflunomide for 1 week prior to surgery.

**Biologic Agents**

**Tumor Necrosis Factor-Alpha Antagonists.** Tumor necrosis factor-alpha is a cytokine involved in the body’s generation of a systemic inflammatory response. It has been implicated in the pathogenesis and progression of RA. Thus, TNF-\(\alpha\) inhibitors, including etanercept, adalimumab, and infliximab, play important roles in slowing the process of joint destruction that is a hallmark of RA.\textsuperscript{13} However, therapy with TNF-\(\alpha\) inhibitors is not without significant risk. By suppressing the body’s immune response, these medications in-
crease patients’ risk of infection. A retrospective review found that the use of etanercept (odds ratio, 9.16) and infliximab (odds ratio, 9.80) was associated with a significantly increased risk of infection for patients with RA undergoing total hip and knee arthroplasties. Additionally, Scherrer et al., in their study comparing patients having noninflammatory conditions with patients having inflammatory conditions undergoing orthopedic surgery, found that patients operated on within one drug administration interval (which varies by TNF-α inhibitor and dose) had a higher risk of infection as compared with patients operated on after 3 administration intervals had passed. Although this risk supports the recommendation to discontinue these medications prior to surgery, doing so also increases the risk of RA flares postoperatively, potentially jeopardizing patients’ adherence to rehabilitation regimens and overall surgical outcomes. Additionally, some studies have shown that patients with RA using TNF inhibitors have a low risk of infection and have suggested that stopping TNF inhibitors may not be ideal.

Surgeons and physicians treating patients with RA must be aware of and must carefully consider the risks of discontinuing TNF-α inhibitors prior to surgery. The American College of Rheumatology and the British Society of Rheumatology offer differing recommendations regarding when to discontinue these medications. The American College of Rheumatology recommends holding them for at least 1 week prior to and after surgery, whereas the British Society of Rheumatology recommends holding them for 3 to 5 half-lives prior to and after surgery. In practice, Goodwin has suggested that etanercept, with a half-life of 3 to 5 days, be held for 2 weeks prior to surgery; adalimumab, with a half-life of 10 to 20 days, be held for 3 weeks prior to surgery; and infliximab, with a half-life of 7 to 12 days, be held for 6 weeks prior to surgery. Although the data are limited regarding when to restart these medications postoperatively, Goodwin has suggested waiting until the wound has completely healed. Barnard et al., on evaluation of their experience with patients with RA who underwent hand surgery procedures, concurred with this assessment. They concluded that there was little risk of infection or wound healing complications when continuing most rheumatologic medications. However, they suggested stopping anti-TNF medications 2 to 3 weeks prior to surgery and restarting them after the surgical wound had healed.

**Interleukin-1 Antagonists.** Anakinra, an IL-1 antagonist used to treat RA, is administered daily in the form of subcutaneous injections. Although IL-1 plays an important role in host immunity, the use of anakinra does not appear to significantly increase the risk of infection. However, Howe et al. recommended that anakinra be held 1 to 2 days prior to and 10 days after surgery because of a theoretical risk of suppressing immune system function. Mushtaq et al. citing animal models that suggested that IL-1 antagonists adversely affect wound healing, recommended that the medication be held 1 week prior to surgery and restarted only after wound closure has occurred.

**CONCLUSION**

The treatment of RA, which leads to progressive joint destruction over time, can present orthopedic surgeons with significant challenges related to medication management. Although the prognosis associated with this disease has significantly improved with the advent of improved therapies, patients with RA still often require orthopedic intervention. Orthopedists must consider the complex trade-offs associated with manipulating these patients’ medication regimens during the perioperative period. Methotrexate, which is widely used as a first-line DMARD treatment for patients with RA, may be continued throughout the perioperative period. However, other DMARDs, including leflunomide, TNF-α inhibitors, and IL-1 antagonists, should be held. Additionally, to decrease the risk of bleeding, nonsteroidal anti-inflammatory drugs and aspirin should also be held. By carefully managing these patients’ medications, orthopedists can maximize the odds of attaining successful surgical outcomes.

**REFERENCES**

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18. Goodman SM, Ramsden-Stein DN, Huang WT, et al. Patients with rheumatoid arthritis are more likely to have pain and poor function after total hip replacements than patients with osteoarthritis. J Rheumatol. 2014; 41(9):1774-1780.


