

# Perioperative Medication Management for the Patient With Rheumatoid Arthritis

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## Abstract

The treatment of rheumatoid arthritis has improved dramatically in recent years with the advent of the latest generation of disease-modifying antirheumatic drugs. Despite these advances, in some patients inflammation is not diminished sufficiently to prevent irreversible musculoskeletal damage, thus requiring surgical intervention to reduce pain and improve function. In these cases, the orthopaedic surgeon frequently encounters patients on a drug regimen consisting of nonsteroidal anti-inflammatory drugs, glucocorticoids, methotrexate, and biologic agents (disease-modifying antirheumatic drugs). Consultation with a rheumatologist is recommended, but the surgeon also should be aware of these medications that could potentially affect surgical outcome. Prudent perioperative management of these drugs is required to optimize surgical outcome. A balance must be struck between minimizing potential surgical complications and maintaining disease control to facilitate postoperative rehabilitation of patients with rheumatoid arthritis.

Rheumatoid arthritis (RA) is a chronic progressive disease characterized by symmetric polyarticular synovitis and joint destruction. Even with aggressive medical management and the early institution of disease-modifying antirheumatic drugs (DMARDs), musculoskeletal damage may still occur. Advanced-stage RA can eventually lead to intractable pain and deformity, requiring surgical intervention through joint reconstruction, tendon rupture repair, joint fusion, or tenosynovectomy.

The patient with RA presents a unique set of problems for the orthopaedic surgeon. The infection rate in total joint arthroplasty is approxi-

mately 2.6 times greater in this population than in patients who undergo surgery for management of osteoarthritis.<sup>1</sup> In addition, these patients typically have a drug regimen that frequently includes nonsteroidal anti-inflammatory drugs (NSAIDs), prednisone, methotrexate, and biologic agents, all of which have the potential to adversely affect surgical outcome by increasing the infection rate or compromising wound healing. Attention to RA disease activity is important, however, because uncontrolled inflammation may negatively impact surgical outcome by compromising participation in rehabilitation. Knowledge of these drugs and their recommended

**Table 1****Perioperative Medication Recommendations**

Medication	Important Drug Interactions	Comments
NSAIDs	If using COX-2 agents for postoperative pain, consult a pharmacist. May affect function of antihypertensive agents and increase INR in older patients taking warfarin	Discontinue 5 half-lives before surgery. Aspirin should be stopped 7-10 days before surgery.
Corticosteroids	Corticosteroid use with fluoroquinolones increases the risk of tendon rupture. Antifungal agents and clarithromycin may increase levels of corticosteroids	Perioperative use depends on level of potential surgical stress
Methotrexate	Methotrexate along with intravenous penicillins may lead to neutropenia	Continue perioperatively for all procedures. Consider withholding 1 to 2 doses of methotrexate for patients with poorly controlled diabetes; the elderly; and those with liver, kidney, or lung disease who are undergoing moderate or intensive procedures
Leflunomide	Leflunomide may elevate levels of warfarin and rifampin	Continue for minor procedures. Withhold 1-2 days before moderate and intensive procedures and restart 1-2 weeks later
Sulfasalazine	May increase INR in patients on warfarin	Continue for all procedures
Hydroxychloroquine	None	Continue for all procedures
TNF antagonists	Avoid live vaccines in patients taking these agents; otherwise, no significant perioperative drug-drug interactions	Continue for minor procedures. For moderate to intensive procedures, withhold etanercept for 1 week, and plan surgery for the end of the dosing interval for adalimumab and infliximab. Restart 10-14 days postoperatively
IL-1 antagonist	None	Continue for minor procedures. Withhold 1-2 days before surgery and restart 10 days postoperatively for moderate to intensive procedures

IL = interleukin, INR = international normalized ratio, NSAIDs = nonsteroidal anti-inflammatory drugs, TNF = tumor necrosis factor

perioperative usage is important to ensure a proper balance between disease modification and reduction of perioperative complication risks.

Few evidence-based guidelines have been established for the traditional antirheumatic drugs. Even NSAID usage has come under increased scrutiny with the recent withdrawal of two of the cyclooxygenase (COX)-2 inhibitors. Few data exist to support evidence-based recommendations regarding perioperative use of the newer biologic agents. However, based on the limited information currently available, the following recommendations have been formulated (Table 1).

### Nonsteroidal Anti-inflammatory Drugs

NSAIDs decrease inflammation and pain through two known mechanisms. The first mechanism consists of inhibiting COX-1 and -2, thereby inhibiting the transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes.<sup>2,3</sup> The effect of NSAIDs on prostaglandins is responsible for the inhibition of platelet function. The second known mechanism of action is inhibition of white cell activation and function via the insertion of NSAID molecules into the lipid bilayer of in-

flammatory cells and the interruption of signaling and protein-protein interactions.<sup>3</sup> With most NSAIDs, this occurs only at the higher dosing range.

In general, NSAIDs should be discontinued from 3 to 5 half-lives before surgery because of their ability to increase bleeding time and the subsequent potential for increased blood loss.<sup>4</sup> There is evidence, however, that NSAIDs only moderately increase intra- and postoperative bleeding and that transfusion requirements, morbidity, and mortality are not increased.<sup>5,6</sup> To ensure elimination of the drug, medications with short half-lives (eg, ibuprofen, indomethacin) should be discontin-

**Table 2****Half-life of Commonly Used Nonsteroidal Anti-inflammatory Drugs (NSAIDs)\***

NSAID	Half-life (hr)
Ibuprofen	1.6-1.9
Diclofenac	2
Indomethacin	4.5
Etodolac	6-7
Celecoxib	11
Naproxen	12-15
Nabumetone	24-29
Piroxicam	30

\* NSAIDs are generally cleared within 5 half-lives.

ued 1 to 2 days before surgery; drugs with longer half-lives (eg, naproxen, piroxicam) should be discontinued 3 days and 6 days, respectively, before surgery (Table 2). For the patient who needs an NSAID, a short-acting agent can be substituted for a longer-acting agent and discontinued 5 half-lives before surgery. NSAIDs can be restarted 7 to 14 days after major surgery, depending on individual circumstances. The control of pain and inflammation without NSAIDs can generally be accomplished with acetaminophen, narcotics, and/or low-dose corticosteroids until satisfactory healing occurs.

Aspirin irreversibly inhibits platelet cyclooxygenase; because platelets cannot generate new cyclooxygenase, the effect is seen for the duration of the platelets' lifetime.<sup>7</sup> Aspirin should be discontinued 7 to 10 days before surgery to allow regeneration of unaffected platelets. Continuing aspirin therapy may prevent perioperative myocardial infarction, but there are no well-designed human trials showing clinically significant prophylaxis. Decisions about low-dose aspirin therapy for cardiac protection should be made in conjunction with the patient's primary care physician or cardiologist.

The newer selective COX-2 inhibitors were developed to avoid compli-

cations resulting from COX-1 inhibition, namely antiplatelet activity and gastrointestinal complications. Originally, in a comprehensive review of the use of COX-2 agents for postoperative pain, Romsing and Moiniche<sup>8</sup> did not find any significant hematologic, gastrointestinal, or renal side effects with the use of COX-2 agents for short-term postoperative pain relief. Studies included subjects undergoing arthroscopy, total knee arthroplasty, and total hip arthroplasty.

In September 2004, rofecoxib (Vioxx; Merck, Whitehouse Station, NJ) was voluntarily removed from the market secondary to accumulating evidence of cardiovascular toxicity. The APPROVe study, a long-term Merck trial evaluating the efficacy of rofecoxib for prophylaxis of colorectal polyps, reported that subjects taking rofecoxib were 2.8 times more likely to have a myocardial infarction and 2.3 times more likely to have a cerebrovascular event than subjects taking placebo.<sup>9</sup>

In April 2005, the Food and Drug Administration (FDA) asked Pfizer (New York, NY) to withdraw valdecoxib (Bextra) from the market because of cardiovascular concerns. Valdecoxib had been shown to have an increased incidence of cardiovascular events when used for postoperative pain control in patients undergoing coronary artery bypass surgery compared with standard postoperative anesthesia (risk ratio, 3.7).<sup>10</sup> Finckh and Aronson<sup>11</sup> reported that those at greatest risk of cardiotoxicity secondary to COX-2 agents were men older than age 65 years who were taking higher doses of COX-2 agents and who had at least one cardiovascular risk factor or had had a previous cardiovascular event.

Celecoxib (Celebrex, Pfizer) is the only remaining selective COX-2 inhibitor on the market. The cardiovascular safety of celecoxib, and indeed the entire class of NSAIDs, is under ever-increasing scrutiny. The FDA now requires black box warnings on all NSAIDs regarding poten-

tial cardiovascular toxicity.

Substantial evidence exists that both traditional NSAIDs and the newer selective COX-2 inhibitors may be detrimental to bone healing when used perioperatively. The mechanism has been elucidated through rodent models that suggest that bone healing is affected via inhibition of osteoblasts at the endosteal bone surface accompanied by reduction of the immune and inflammatory responses.<sup>12-14</sup> In opposition to these findings, Reuben and Ekman<sup>15</sup> were unable to demonstrate a deleterious effect of perioperative COX-2 inhibitors when attempting spinal fusion. The subject is controversial, and currently only limited human or animal data are available to explain the effect of NSAIDs on rates of bone fusion and fracture healing, or their effect on porous ingrowth prostheses.

We recommend discontinuing non-COX-2-specific NSAIDs 5 half-lives before surgery. When an NSAID is important to pain control and the patient is on a long-acting agent, we substitute a short-acting NSAID (eg, ibuprofen), then discontinue it 1 to 2 days before surgery. Aspirin is generally stopped 7 to 10 days before surgery unless deemed critical for cardiac protection. Perioperative use of the COX-2 agent celecoxib for pain management is popular, but concern exists about potential cardiovascular toxicity.

## Corticosteroids

The management of corticosteroids perioperatively in the patient with RA involves striking a balance between the minimal amount of corticosteroids necessary to reduce joint inflammation and unnecessarily high levels that might lead to perioperative complications. Excessive use of corticosteroids can produce immunosuppression, a stifled inflammatory response, which would affect wound healing, and increased protein catabolism, leading to poor bone and soft-tissue wound healing. Conversely,

inadequate corticosteroid levels can lead to disease flares and, although rare, adrenal insufficiency (AI).<sup>16</sup>

Under normal circumstances, the body produces 10 to 12 mg of cortisol per day. With moderate stress, cortisol production is approximately 25 to 50 mg/day; with major stress, 75 to 150 mg may be released into the circulation. Levels of cortisol generally return to baseline within 24 to 48 hours following stress. Secondary or tertiary AI may develop in patients treated with long-term corticosteroid use ( $\geq 20$  mg of prednisone for 3 weeks). Secondary AI develops as a result of suppression of corticotropin-releasing hormone from the hypothalamus, leading to a decrease in adrenocorticotropic hormone production and release from the pituitary gland. Eventually, tertiary iatrogenic AI can develop as the adrenal glands atrophy; the phenomenon can take up to 1 year to completely resolve.<sup>16,17</sup> Traditionally, patients with suspected AI were given 200 to 300 mg of hydrocortisone perioperatively; studies have demonstrated that patients safely tolerate much lower doses, however.<sup>18,19</sup>

The more severe manifestations of AI are caused by primary AI, in which aldosterone production is affected. Aldosterone undersecretion can lead to nausea, vomiting, hypotension, and vascular collapse. Aldosterone production is under the control of renin-angiotensin from the kidney and thus is spared in corticosteroid-associated adrenal suppression. Symptoms of secondary AI (ie, corticosteroid insufficiency) include psychiatric symptoms, myalgia, fatigue, and biochemical changes (ie, hyponatremia, hypoglycemia).

Development of AI is rare in corticosteroid-treated patients undergoing surgery. Two studies in particular bring into question the need for perioperative stress-dose steroids. In 1991, Bromberg et al<sup>18</sup> prospectively studied 40 renal transplant patients admitted to the hospital with physiologic stress categorized as sep-

sis, metabolic abnormalities, and surgery. Although baseline prednisone doses were not changed (5 to 10 mg/day), clinical AI developed in none of the patients even though cosyntropin stimulation tests, which measure responsiveness of the hypothalamus-pituitary-adrenal axis, were abnormal in 63%. In addition, Friedman et al<sup>19</sup> prospectively studied 28 glucocorticoid-treated patients who underwent a total of 35 major orthopaedic operations without traditional stress-dose steroids. The patients had been taking doses of prednisone ranging from 1 to 20 mg daily from 6 months to 32 years. None of the 28 patients had evidence of clinical AI, and 18 of the 19 patients with complete data demonstrated an appropriate biochemical response to stress.

Although our practice is to mimic the normal physiologic dose of corticosteroids in the perioperative period, each patient must be viewed as a unique case; limited information is available to establish firm recommendations. All patients who have been on chronic corticosteroids should receive their regular dose of corticosteroids perioperatively.<sup>20</sup> Patients who take 5 mg/day of prednisone or its equivalent preoperatively do not need additional corticosteroids when the procedure takes <1 hour or requires only local anesthesia.<sup>17,21,22</sup> The data also suggest that minimally stressful procedures, such as routine knee arthroscopy, require 25 mg of hydrocortisone (5 mg of methylprednisone intravenously) on the day of the procedure only (Table 3). Moderately stressful procedures, such as an anterior cruciate ligament reconstruction or primary arthroplasties, require 50 to 75 mg of hydrocortisone (10 to 15 mg of methylprednisone intravenously) on the day of the procedure, with expeditious tapering over 1 or 2 days to the usual dose. Patients with severe stress from complex surgeries (eg, challenging revisions, bilateral arthroplasties, extended spine cases) who are on chronic corticosteroid

therapy require 100 to 150 mg of hydrocortisone (20 to 30 mg of methylprednisone intravenously) on the day of the procedure, with expeditious tapering over 1 or 2 days to the usual dose. The critically injured patient, commonly seen following trauma, will require either 50 to 100 mg of hydrocortisone intravenously every 6 to 8 hours or 0.18 mg/kg/hr as a continuous infusion, plus 50  $\mu$ g/day of fludrocortisone until shock resolves, which may take days to weeks. The steroids are gradually tapered with careful observation of vital signs and serum sodium.<sup>22</sup> In these patients, intravascular volume and a normal serum sodium level can be used to assess the response to corticosteroid supplementation.<sup>16,17</sup> Common corticosteroids are listed in Table 4, with their levels of potency and biologic half-life.

Corticosteroids can also be used in low doses (ie, 5 to 10 mg of prednisone) perioperatively to control inflammatory disease in patients with RA to replace other medications (eg, NSAIDs) that have been discontinued. Certain antibiotics (eg, antifungals, clarithromycin) may require increased levels of corticosteroids when used concurrently.

## Disease-modifying Antirheumatic Drugs

### Methotrexate

Methotrexate is a commonly used DMARD that has been a mainstay of therapy in RA and other inflammatory joint diseases since the 1970s because of its long-term efficacy, tolerability, and response rate >60%.<sup>23</sup> Methotrexate is a folate analogue with anti-inflammatory properties linked to inhibition of neovascularization as well as a decrease in cytokine production, including interleukin (IL)-1, IL-8, and tumor necrosis factor (TNF). Once inflammation is controlled with methotrexate, the patient runs the risk of flares when the medication is discontinued. Most patients whose inflammation is con-

**Table 3**  
**Supplemental Hydrocortisone for Surgical Stress Levels**

Procedure Class/ Level of Stress	Procedure	Recommended Supplemental Hydrocortisone
Minor/ minimal	Carpal tunnel release Tenosynovectomy Knee arthroscopy Hammer toe correction First metatarsophalangeal fusion	25 mg hydrocortisone on day of procedure only (prednisone, 5 mg)
Moderate/ moderate	Hip arthroplasty Knee arthroplasty Ankle arthroplasty Shoulder arthroplasty Elbow arthroplasty Metacarpophalangeal arthroplasty Complex foot reconstruction with arthrodesis and tendon transfer Anterior cruciate ligament reconstruction	50-75 mg hydrocortisone on day of procedure with expeditious tapering over 1-2 days to the preoperative dose (prednisone, 10-15 mg)
Intensive/ significant	Multiple-trauma patient Bilateral knee arthroplasty Revision arthroplasty Multiple level spinal fusion	100-150 mg hydrocortisone on day of procedure with expeditious tapering over 1-2 days to the preoperative dose (prednisone, 20-30 mg)

**Table 4**  
**Equivalencies for Commonly Used Corticosteroids**

Corticosteroid	Relative Anti-inflammatory Potency	Equivalent Dose (mg)	Biologic Half-life (hr)
Hydrocortisone	1	20	8-12
Cortisone	0.8	25	8-12
Prednisone	4	5	12-36
Methylprednisolone	5	4	12-36
Prednisolone	5	4	12-36
Dexamethasone	20-30	0.75	36-54

trolled with methotrexate experience a flare within 4 weeks of drug cessation. Postoperatively this can translate into joint pain, stiffness, and swelling, contributing to a reduction in rehabilitation progression and poorer surgical outcomes.

Perioperative use of methotrexate in patients with RA was initially influenced by studies that reported fewer complications with the cessation of methotrexate from 2 weeks before through 2 weeks after surgery compared with patients who continued taking methotrexate perioperatively.<sup>24-26</sup> These results came under scrutiny with the work

of Grennan et al,<sup>27</sup> who prospectively randomized 388 patients with RA into three groups. One group continued methotrexate while undergoing elective orthopaedic procedures, another group discontinued methotrexate from 2 weeks before through 2 weeks after surgery, and a third group, which consisted of patients who had not received previous methotrexate treatment, took no methotrexate. The group that continued with the methotrexate therapy had significantly fewer infections and complications compared with the two other groups ( $P < 0.003$ ). This group was also void of flares; in

contrast, flares occurred in 8% of those discontinuing methotrexate before surgery and in 2% of those not treated with methotrexate.

The continuation of methotrexate perioperatively appears warranted but must be approached with a great deal of caution. The patient with renal dysfunction is particularly at risk; thus, the withholding of methotrexate in patients with mild renal insufficiency who are undergoing surgery is recommended. Patients with significant renal disease do not generally receive methotrexate, but when renal insufficiency develops postoperatively, methotrexate should be withheld and medicine or rheumatology services consulted. Symptoms of methotrexate toxicity include oral ulcers and bone marrow suppression. Toxicity can be managed by the use of folic acid supplementation. Folate supplementation should be considered for patients taking methotrexate who may have no oral intake for a prolonged period or reduced oral intake, because low folate levels lead to methotrexate toxicity, especially bone marrow suppression. Other groups at risk include elderly pa-

tients, those with poorly controlled diabetes, patients with significant lung or liver disease, and those with a history of significant alcohol use. For these patients and those with renal disease who are undergoing moderate and intensive procedures, withholding the dose of methotrexate the week before and the week of surgery is recommended.<sup>28</sup> Important drug interactions include intravenous penicillins that may affect methotrexate clearance and result in neutropenia.

### Leflunomide

Leflunomide (Arava; sanofi aventis, Bridgewater, NJ), an inhibitor of pyrimidine synthesis, was recently approved for the management of RA. It appears to work through a multitude of mechanisms including, but not limited to, inhibition of IL-1A and TNF- $\alpha$ .<sup>29</sup> Its primary effect is inhibition of pyrimidine synthesis. Leflunomide is an important component in DNA synthesis and targets rapidly dividing cells, such as lymphocytes. Because of its relatively recent introduction, there are few objective data concerning leflunomide and potential perioperative risks. The data on methotrexate suggest that it is not unreasonable to continue DMARD therapy for many procedures.<sup>27</sup> We recommend that leflunomide be continued for minor procedures and withheld 1 to 2 days before surgery for more intensive procedures. With its long half-life (approximately 2 weeks), the DMARD effects will still be present without the potential acute side effects of the drug (eg, diarrhea, nausea) that may interfere with other medications commonly used perioperatively, such as antibiotics and narcotics. Based on the limited information available, it appears reasonable to restart leflunomide once the patient is stable, antibiotic therapy is complete, and narcotic pain medication is minimized (within 1 to 2 weeks). Leflunomide can be urgently reversed, if necessary, by use of cholestyramine via the protocol included in the package insert. Drug interactions that may af-

fect perioperative management include an elevation in the circulating levels of warfarin and rifampin when leflunomide is present.

### Sulfasalazine

Sulfasalazine, a combination of sulfapyridine and 5-aminosalicylic acid, was first developed in the 1930s and has been used to treat both inflammatory arthritis and inflammatory bowel disease. Sulfasalazine is a potential adjunct to other DMARDs. The exact mechanism of action with regard to its therapeutic properties for inflammatory arthritis is unknown. However, its administration is associated with a decrease in the erythrocyte sedimentation rate and serum concentrations of C-reactive protein. Although its use is generally well tolerated perioperatively, when combined with other DMARDs, it has the potential to increase the international normalized ratio in patients taking warfarin. Also, sulfonamide concentration may increase in patients taking NSAIDs.

### Hydroxychloroquine

Hydroxychloroquine (Plaquenil; sanofi-synthelabo, Bridgewater, NJ) is an antimalarial drug that has been used since the 1950s to manage RA. It has relatively low potency but also low toxicity. Its major side effects are gastrointestinal and cutaneous, with very rare ocular and muscle toxicity. It has a large area of distribution and, once stopped, may be detected up to 1 year later. Hydroxychloroquine is safe to continue during most surgical procedures and has been used perioperatively by orthopaedic surgeons for prophylaxis against postoperative thromboembolic disease.<sup>30</sup> No interactions of importance with other medications that are generally used in the perioperative period have been reported in recent literature.

## Biologic Agents

### TNF Antagonists

The novel biologic agents etaner-

cept (Enbrel; Amgen, Thousand Oaks, CA), adalimumab (Humira; Abbott Laboratories, Abbott Park, IL), and infliximab (Remicade; Centocor, Horsham, PA) are directed against TNF- $\alpha$ , an important proinflammatory cytokine that plays a central role in the pathogenesis of RA and that is instrumental in causing joint destruction, the clinical hallmark of the disease (Table 5). All three agents are becoming important in the management of RA.

Etanercept is a TNF- $\alpha$  receptor fusion protein that binds to TNF- $\alpha$ . It has a short half-life and is administered subcutaneously once or twice weekly. Etanercept has shown evidence of being at least as efficacious, if not more so, and more rapid in onset than methotrexate.<sup>23</sup> The combination of etanercept and methotrexate appears to be superior to either drug used as a monotherapy.<sup>31</sup>

Adalimumab is a human anti-TNF- $\alpha$  monoclonal antibody with a 10- to 13-day half-life. It is administered subcutaneously once every 2 weeks. Adalimumab has proved to be safe and efficacious alone and in combination with methotrexate, prednisone, and NSAIDs.<sup>32</sup> There is also evidence of the superiority of adalimumab used in combination with methotrexate compared with methotrexate alone in slowing the radiographic progression of degenerative changes in patients with RA.<sup>33</sup>

Infliximab is a human mouse chimeric anti-TNF- $\alpha$  monoclonal antibody. This agent, which has a long dosing interval, is administered intravenously every 8 weeks. Infliximab has proved to be efficacious as a monotherapy as well as a potent adjunct to methotrexate in retarding the inflammatory disease process, including joint destruction.<sup>34</sup>

TNF- $\alpha$  inhibition may contribute to reported increases in opportunistic infections, such as tuberculosis, *Pneumocystis carinii* pneumonia, histoplasmosis, aspergillosis, and candidiasis. Musculoskeletal infections, including psoas abscess and

**Table 5****Comparison of Biologic Agents**

Agent	Half-life	Binding Target	Construct	Administration
Etanercept (Enbrel)	3-4.8 days	TNF- $\alpha$ and lymphotoxin- $\alpha$	Recombinant human soluble receptor	Twice weekly, subcutaneous
Infliximab (Remicade)	8-9.5 days	TNF- $\alpha$	Recombinant chimeric monoclonal antibody	Every 4 to 8 weeks, intravenous
Adalimumab (Humira)	10-13.6 days	TNF- $\alpha$	Recombinant human monoclonal antibody	Every 1 to 2 weeks, subcutaneous
Anakinra (Kineret)	4-6 hours	IL-1	Recombinant human receptor antagonist	Daily, subcutaneous

IL = interleukin, TNF = tumor necrosis factor

septic bacteremia, have been reported.<sup>35</sup> In one recent report, 31 patients with RA who were undergoing foot and ankle procedures were divided into two groups based on use of anti-TNF agents and followed for issues related to healing and infection.<sup>36</sup> All patients continued DMARD therapy, including anti-TNF agents. After approximately 10 months of follow-up, the group taking the anti-TNF agents had fewer infectious complications and problems with healing than did those taking traditional DMARDs, mirroring the experience with methotrexate. The only other data regarding this topic are in abstract form; the results presented show cause for concern. Giles et al<sup>37</sup> retrospectively evaluated 91 patients with RA for early, deep postoperative infection within 30 days of the orthopaedic procedure. Infection developed in 7 of 35 patients treated with TNF inhibitors before surgery (20%), compared with 3 of 56 patients treated with other DMARDs (5%) ( $P = 0.029$ ). This infection rate seems excessively high; it is hoped that more details will become available.

In the absence of extensive data, we recommend that TNF-inhibiting agents be continued for minor procedures and temporarily withheld for moderate to intensive procedures. Etanercept can be withheld for 1 week preoperatively and restarted 10 to 14 days postoperatively. Surgery

should be planned for the end of the dosing interval of adalimumab and infliximab, with the next dose delayed until 10 to 14 days after surgery.

### IL-1 Antagonist

Anakinra (Kineret), another recently approved agent for managing RA (Table 5), is a recombinant form of the naturally occurring human IL-1 receptor antagonist.<sup>38</sup> It is administered daily via subcutaneous injection. The risk of serious adverse reactions appears to be minimal, with an infection rate similar to that of placebo.<sup>39,40</sup> Furthermore, the unusual opportunistic infections (eg, tuberculosis, histoplasmosis, aspergillosis) seen with use of anti-TNF- $\alpha$  agents have not been reported. However, IL-1 plays an important role in the host defense against infection. Thus, in the absence of data, we suggest that for moderate to intensive orthopaedic procedures, anakinra be withheld 1 to 2 days before surgery and for 10 days postoperatively.

### Summary

Managing the perioperative drug regimen of the patient with RA can be challenging, but it is essential in order to optimize surgical outcome. Perioperative consultation and collaboration with the patient's rheumatologist or internist is recommended. In patients with RA, correct timing

of discontinuation of NSAIDs in preparation for surgery may avoid patient discomfort without risking complications resulting from cyclooxygenase inhibition. Corticosteroid management depends on the type of orthopaedic procedure and must be part of perioperative planning. The goal of perioperative management of DMARDs is to reduce the risk of infection and optimize wound healing while minimizing the chance of a disease flare that could compromise recovery. Currently, methotrexate is the only medication with evidence-based data supporting continuing treatment through surgery. Without data to the contrary, we recommend that the more powerful biologic agents should be used as described in Table 1. These recommendations may change as experience and data accumulate.

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*Evidence-based Medicine*: Level I or II studies: references 9, 10, 23, 24, 27, 31-34.

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