HSSJ (2006) 2: 141–147
DOI 10.1007/s11420-006-9012-5

ORIGINAL ARTICLE

Perioperative Management of Medications Used in the Treatment of Rheumatoid Arthritis

Carla R. Scanzello, MD, PhD · Mark P. Figgie, MD · Bryan J. Nestor, MD · Susan M. Goodman, MD

Published online: 9 June 2006

Abstract Patients with rheumatoid arthritis (RA), an inflammatory arthritis that can destroy joint structures, are often on multiple medications to control disease activity. These medications may have significant toxicities and side effects. Over the course of their lifetime, patients with this disease often require orthopedic procedures, including total joint arthroplasty, and the medications they are taking present management issues specific to the perioperative period. As many of these medications are immunosuppressive, the concern for postoperative infection and delayed wound healing are particularly worrisome. We conducted a review of the available literature pertaining to the perioperative use of the most commonly prescribed medications for RA. Although the existing data directly addressing perioperative complications in orthopedic surgery is sparse, information on relevant complications resulting from the general use of these drugs may be used as a basis for conservative recommendations.

Key words Rheumatoid arthritis · perioperative management · corticosteroids · methotrexate · anti-TNF · rituximab

Introduction

Rheumatoid arthritis (RA), the most common form of inflammatory arthritis, can lead to significant pain, disability, and deformity, and is a multisystem autoimmune disorder. The hallmark of this disease, erosive joint destruction, results from unchecked synovial inflammation, which can damage articular cartilage and bone, with resultant loss of joint function. Advances in medical treatment and surgical reconstruction have dramatically improved the clinical outlook for RA patients. Disease-modifying antirheumatic drugs (DMARD), including biological agents such as the tumor necrosis factor (TNF) inhibitors, have altered the natural history of this disease; however, many of these treatments may cause significant immunosuppression. Although not considered DMARDs, corticosteroids still play a major role in treatment of this disease and are also known to slow down wound healing and predispose patients to infection. Despite improved medical therapy, many RA patients still require orthopedic surgery, most frequently total joint arthroplasty. These surgical techniques have also improved, with infectious complications seen in primary arthroplasty dropping from over 10% to 20% in the earliest series to the current rates of <1% [1]. However, given that patients with RA may be at risk for infections both due to their underlying disease and the use of immunosuppressive medical therapy, concern for complications following orthopedic procedures in these patients remains high. This article will review the available information about corticosteroids, DMARDs, and biological therapies commonly used in the treatment of RA, and address their potential to increase infectious or other surgical complications in the perioperative period. The data regarding the incidence of adrenal suppression with chronic corticosteroid use will also be presented. For the majority of these medications, there is insufficient data in patients undergoing orthopedic procedures with which to make evidence-based recommendations. However, careful synthesis of the available data regarding infection risk and wound healing in other patient populations allows us to make practical suggestions on the management of RA patients who are undergoing orthopedic procedures.

Supported by the Hospital for Special Surgery Frankenthaler Fellowship in Restorative Mobility (C.R. Scanzello).

C. R. Scanzello, MD, PhD (✉) · S. M. Goodman, MD
Department of Rheumatology
Hospital for Special Surgery,
535 East 70th Street, New York, NY 10021, USA
e-mail: scanzelloc@hss.edu

M. P. Figgie, MD · B. J. Nestor, MD
Department of Orthopedic Surgery
Hospital for Special Surgery,
New York, NY 10021, USA

Corticosteroids

Cortisone was introduced into clinical practice in 1949 and, because of its striking anti-inflammatory effect, has been widely used for the treatment of inflammatory diseases such as RA. Shortly after its introduction, cases of adrenal

insufficiency in patients maintained on cortisone were reported, and a practice of administering supraphysiologic doses during times of stress was adopted ["stress dose" steroids (SDS)]. However, despite the common clinical practice of administering SDS to patients who have been on low-dose corticosteroids for ≥6 months or patients who have been on intermediate to high doses for greater than 3 weeks, the data suggest that it is very difficult to predict who is truly at risk for adrenal insufficiency based on steroid dosage or length of treatment [2]. Furthermore, steroid therapy has been shown to increase infection rates [3] and impede wound healing (reviewed in [4]), adding to perioperative risk. A recent study [5] has tried to reassess the risks versus the benefits of SDS in the perioperative setting, but little data address orthopedic surgery directly.

Renal transplant patients are a useful surrogate for RA patients as they too are often on long-term, low-dose corticosteroid therapy as well as other immunosuppressants. Mathis et al. [5] retrospectively compared renal transplant patients who either did or did not receive SDS in the setting of lymphocele repair. Although mean prednisone dose did not differ between the two groups, no information was given on the preoperative length of steroid treatment, which may have influenced the decision to use SDS in this retrospective study. In the 24-h postoperative period, there were no hemodynamic differences between the groups. No cases of significant hypotension or mental status changes were noted. Twenty-five percent of the SDS group and 10% of the others had recurrence of the lymphocele, suggesting a detrimental impact on wound healing, and blood sugar was higher in the SDS group as expected. Of note, only one patient in each group showed evidence of impaired skin wound healing. The authors of this retrospective analysis concluded that there was no apparent benefit in administering SDS. However, it is important to note that although the patient population may be similar in many ways to RA patients, the nature of the surgical intervention is quite different from total joint arthroplasty, as 58% of patients in this study had undergone a laparoscopic procedure.

Previous studies have shown that the hypothalamic–pituitary–adrenal axis can be suppressed by as little as 20 mg of prednisone per day for 5 days in some patients, whereas use of lower doses of corticosteroid or alternate day dosing may reduce the incidence of this side effect. However, in clinical practice, it is difficult to predict whether an individual patient is at risk for adrenal insufficiency based on dosage of steroid or length of treatment [2]. A prospective study in renal allograft recipients was conducted to address this question [6]. Forty patients receiving chronic, low-dose (5–10 mg daily) prednisone treatment were admitted with significant physiologic stress, such as surgery, sepsis, or metabolic abnormalities. Although patients received only their usual daily prednisone dose, and 63% had evidence of adrenal insufficiency (as measured by the consyntropin stimulation test), no patient developed clinical adrenal insufficiency. In a second prospective study, 18 patients taking at least 7.5 mg prednisone daily and undergoing various surgeries (joint replacements or abdominal operations) were randomized to receive either saline alone or saline plus stress-dose hydrocortisone, in addition to their usual daily dose of prednisone [7]. All patients in this study had secondary adrenal insufficiency defined by response to adrenocorticotropic hormone (ACTH) stimulation testing, yet there were no significant hemodynamic differences between groups. These studies suggest that physiologic needs are adequately met in low-dose, steroid-treated renal transplant patients by the administration of the usual daily steroid dose without the addition of SDS. It is likely, but not definite, that these results are generalizable to RA patients on low-dose chronic steroid therapy. However, the magnitude of the surgical stress does influence the level of cortisol production necessary to maintain homeostasis and must be considered as well. For example, arthroplasty may induce up to a 17-fold increase from baseline endogenous cortisol production in nonsuppressed patients, whereas arthroscopy does not induce increased cortisol production at all [8]. The similarity of the various surgical interventions included in these studies to total arthroplasty is unclear.

Concerning perioperative infection risks, another analogous patient population can be found in the gastroenterology literature. Patients with inflammatory bowel disease (IBD) are frequently treated with steroids and may require bowel resection as a result of their disease. One retrospective review of 397 Crohn's disease (CD) patients undergoing bowel resection suggested that steroid therapy had no impact on perioperative complication rates [9]. When comparing patients receiving high dose (≥20 mg prednisolone/day), low dose (<20 mg prednisolone/day), or no steroid therapy, no difference was seen in morbidity, mortality, anastomotic leaks, wound infections, or abscess formation. However, another retrospective study of IBD patients (both CD and ulcerative colitis) reached a different conclusion. One hundred and fifty-nine IBD patients undergoing bowel surgery at the University of Pennsylvania were identified using ICD-9 codes [10]. Fifty-six patients were receiving corticosteroids alone, 18 were being treated with 6-mercaptopurine or azathiaprine alone, 34 were receiving both steroids and 6-mercaptopurine or azathiaprine, and 51 were not on any immunosuppressive therapy. A significantly increased risk of major infections (odds ratio 5.54, 1.12–27.26) in the steroid-treated group was observed, whereas no increase was observed with the addition of 6-mercaptopurine or azathiaprine. No prospective data are available to clarify the discrepancies in the results of these two studies, but differences in the outcomes measured and patient populations likely contribute to the disparate results. For instance, the second retrospective analysis had a broader definition of postoperative infectious complications (including postoperative pneumonias, peritonitis, urinary tract infections, and fever of unknown origin), whereas the first study included only wound dehiscence, sepsis, and abscess formation. Furthermore, neither of these studies considered the use of SDS administration.

There is little information on perioperative complication rates and steroid usage in orthopedic procedures and the data available come from retrospective analyses in divergent patient populations. Jain et al. [11] investigated the rate of postoperative wound infections in 80 RA

patients undergoing hand surgery (a total of 129 procedures). They recorded only one infection in 60 procedures (1.7%) in patients on prednisolone (mean dose 8.8 mg) compared with 5 in 69 procedures (7.2%) in patients not taking prednisolone. This difference was not statistically significant, and the authors concluded that steroids did not influence the development of wound infections in RA patients undergoing hand surgery. However, the use of other DMARDs was not evenly distributed between these two groups, making direct comparison difficult. Similarly, in patients with systemic lupus erythematosis undergoing hip arthroplasty, delayed wound healing (15%) and wound infections (10%) were observed, but were unrelated to the use of corticosteroids [12]. A smaller study of seven liver transplant patients undergoing 12 arthroplasties for osteoarthritis, osteonecrosis, or fracture also showed no short- or long-term complications, in spite of prolonged corticosteroid therapy in most of the patients [13]. In contrast, a retrospective study of 62 patients who underwent fusion for metastatic disease of the spine (a high-risk procedure in a high-risk population) corticosteroid administration appeared to increase the risk of infection. Intraoperative blood loss and protein deficiency were also found to be risk factors for wound infections in this study [3]. Three of these four studies demonstrated no increased risk of postoperative infections attributable to steroid usage; however, the steroid dosages were generally low, and the indications for steroids, patient populations, and surgical procedures varied.

Due to the lack of good prospective data, conclusive recommendations regarding the use of SDS in steroid-treated RA patients undergoing orthopedic surgery are difficult to make, although the following would seem reasonable. RA patients on low dose (i.e., ≤7.5 mg/day) or on any dose of steroids for <3 weeks should be given their usual daily dose of corticosteroids perioperatively. There appears to be no need to add SDS in these patients unless specific clinical events or additional risk factors suggest their need. The usefulness and feasibility of ACTH stimulation testing is unclear, and the benefit of SDS seems minimal in these patients. In patients who have been on chronic moderate- to high-dose therapy (≥20 mg/day prednisone for ≥3 weeks), most physicians would assume secondary adrenal suppression and treat with SDS. In patients on intermediate doses (i.e., 7.5–20 mg daily), the available data suggest that we are greatly overusing supraphysiologic steroid doses in the perioperative setting. We therefore recommend that SDS should not be routinely prescribed, but should be individualized based on the chronicity of steroid treatment, the estimated stress of the surgery, and the presence of additional risk factors that may increase postoperative complications and infection risk (i.e., anemia, hypoalbuminemia, other immunosuppressants, and diabetes).

Methotrexate

Methotrexate (MTX, trade names Trexall™ and Rheumatrex™) is the most commonly used DMARD in the treatment of RA, in up to 80% of patients in some studies. MTX is a folic acid analog, which when administered in high doses blocks purine and pyrimidine synthesis. However, in RA, its anti-inflammatory activity may be due to multiple mechanisms [14]. It has well-proven efficacy and safety, and has been shown to decrease mortality in treated patients compared with RA patients who have not received the drug [15]. Patients remain on MTX longer than other DMARDs, which is an excellent indicator of benefit [14–16]. It is usually used as an initial agent, adding other medications if efficacy is inadequate. Previously, more modest dosing was used, but modern rheumatologists have become more comfortable with rapidly increasing up to a maximum dose of 25 mg weekly to control disease activity. Patients frequently flare, however, when MTX is discontinued, which can complicate postoperative rehabilitation. Several studies have addressed the question of MTX safety in the perioperative period. In fact, it is the only DMARD for which we have prospective data regarding perioperative infection risk in patients with RA.

A large, prospective randomized study was undertaken by Grennan et al. [17] to determine whether the risk of surgical complications, including postoperative infections, was increased in patients who continued MTX treatment perioperatively. Three hundred and eighty-eight patients undergoing elective orthopedic surgeries were randomized to either continue or to stop MTX therapy for 2 weeks before surgery and resume 2 weeks postoperatively. The patients were followed for up to 1 year. Patients who continued their MTX had an infection rate of 2%. Patients who held their MTX had an infection rate of 15%. The baseline postoperative infection rate in patients not on MTX at all in this study was 10.5%. There were fewer surgical complications and no postoperative flares in patients who continued their MTX, whereas 8% of patients who discontinued the drug had a flare of their joint disease. An earlier study of 64 patients showed similar results [18]. Only one, much smaller study (including 19 RA patients who discontinued and 13 RA patients who continued MTX) demonstrated an increase in infectious complications in the group remaining on MTX [19]. Thus, the prospective data generally support the practice of continuing MTX use during the perioperative period.

The retrospective data regarding the postoperative infection risk of MTX is consistent with the larger prospective studies. The influence of MTX on surgical complications (both wound infections and healing complications) after elective hand surgery was reviewed in 80 RA cases (129 procedures) over a 5-year period [11]. The mean dose of MTX used by these patients was 10 mg weekly. There was no difference in the infection or complication rate comparing patients taking MTX, MTX plus prednisolone, prednisolone alone, or neither drug. The overall infection rate was 4.7%, with four wound infections (5%) in the MTX group and two infections (4%) in the patients not taking MTX. Diabetes appeared to confer a greater risk for infection in this study population, although the number of cases was small and the use of other DMARDS was not evenly distributed between the four groups. Only one patient (0.8%) developed wound dehiscence; that patient

was in the prednisolone-only group. Another retrospective study of 104 RA patients undergoing foot and ankle surgery observed similar results [20]. The overall complication rate was high in this review, but there was no correlation with MTX therapy.

There is surprisingly little information on the effects of MTX on wound healing. Preclinical studies in animals suggest that this agent may impair wound-healing responses [21–24], but these reports use dosages employed in treatment of malignancies, which are considerably larger than those used by rheumatologists for the treatment of RA. The small amount of clinical data that address wound healing in patients with RA treated with MTX suggests no significant increase in healing complications [11, 17, 18, 25].

In summary, most prospective and retrospective studies have suggested that MTX can be continued in the perioperative period without impairing wound healing or increasing the perioperative infection risk substantially. Moreover, continued disease control without flare as the patient is mobilized for physical therapy is clearly beneficial. However, it is important to realize that the mean dosage of MTX in most of the studies presented here is somewhat low compared with current standard of care. Today, attempts are made to titrate the weekly dosage to a maximum maintenance dose of 20–25 mg weekly or the highest tolerated dose. Regardless, we recommend that MTX be continued perioperatively whenever possible to maintain control of disease activity. This recommendation may be reconsidered in patients who have additional risk factors for developing serious postoperative infectious complications, such as poorly controlled diabetes.

Other DMARDs

There is no published clinical data addressing the perioperative morbidity of RA patients treated with other commonly used antirheumatic drugs, including hydroxychloroquine (Plaquenil™), leflunomide (Arava™), azathiaprine (Imuran™), or sulfasalazine (Azulfidine™). However, hydroxychloroquine has an extremely favorable toxicity profile and is widely considered to be safe to use in the perioperative period as it is not a potent immunosuppressant. Leflunomide, sulfasalazine, and azathiaprine all have immunosuppressive properties and can be toxic at high levels. They generally are held postoperatively until normal bowel and renal function has been restored in patients undergoing arthroplasty. However, the same considerations (i.e., risk of postoperative flare, presence of additional risk factors for infection) discussed concerning MTX likely apply to these agents as well. In addition, leflunomide may potentiate coumadin activity, which is a consideration in arthroplasty patients who will take coumadin for deep venous thrombosis prophylaxis postoperatively [26].

Biologics: TNF-α antagonists

Tumor necrosis factor-α is an inflammatory cytokine that is markedly elevated in the synovial fluid and synovial membrane of RA patients. Many in vitro studies and animal models have shown that this cytokine plays a crucial role in mediating tissue destruction and inflammation (reviewed in [27]). This research led to the development of TNF-α antagonists, which came to market in the late 1990s, and have proven to be very effective in the treatment of RA. There are now three available agents in widespread use (infliximab or Remicade™, etanercept or Enbrel™, and adalimumab or Humira™), often in combination with MTX [28, 29]. The major complication of therapy with TNF-α antagonists is infection [30]. Many case reports exist of various bacterial and opportunistic infections as well as reactivation tuberculosis occurring in the setting of treatment with anti-TNF therapies. However, the risk of infection with more common pathogens is unclear, and little is known about the effect of these medications on perioperative morbidity in humans. Of concern is the potential for Gram-positive infections, as anti-TNF agents were originally developed to treat sepsis; however, when tested in clinical trials, these agents actually increased mortality from Gram-positive sepsis [31].

As one of the TNF-α antagonists (Infliximab) is also widely used to treat IBD, CD patients again can serve as a reasonable surrogate for RA patients. The postoperative course of 40 CD patients undergoing bowel resection who received infliximab was compared with 39 CD patients who were infliximab naïve [32]. Although the infection rate occurring within 10 days of surgery trended up in the patients who had received infliximab, this did not reach statistical significance. Six early infections were reported in the infliximab group versus one early infection in the naïve group ($p = 0.10$). Another study retrospectively reviewed all CD patients undergoing resection, strictureplasty, or intestinal bypass at the Mayo Clinic over a 3-year period, and identified 270 patients [33]. These patients included 107 patients receiving steroids; 105 patients receiving immunosupressives such as MTX, azathiaprine, and 6-mercaptopurine; and 52 patients receiving infliximab. Although the rate of complications occurring within 30 days of surgery was high, and 52% of the 63 (83%) complications were septic, there was no correlation with therapy. Specifically, infliximab treatment within 8 weeks before and 4 weeks after surgery did not increase the risk of early postoperative infections in these CD patients.

Data relating specifically to orthopedic procedures are particularly sparse, but there are two pertinent studies. RA patients undergoing elective foot and ankle surgery who continued all antirheumatic therapy throughout the surgical period were prospectively followed for 12 months after surgery [34]. Group 1 ($n = 16$) patients received TNF-α antagonists, whereas group 2 ($n = 15$) patients did not. The groups were comparable in age, sex, additional DMARD therapies, and steroid use. Group 1 patients had fewer total complications than group 2 patients ($p = 0.033$). This small study offers support for the continuation of anti-TNF therapy in the perioperative period, but how these results relate to total joint arthroplasty is unknown. In contrast to this, a recently published study came to a different conclusion [35]. This study retrospectively identified RA

patients followed at Johns Hopkins who had undergone at least one orthopedic procedure between 1999 and 2004. Charts from 91 patients were reviewed. Ten (11%) of these patients developed a serious postoperative infection (defined as osteomyelitis, septic arthritis, or deep-wound infection requiring a prolonged course of intravenous antibiotics) within 30 days of surgery. Seven of the 10 patients (70%) who developed a serious postoperative infection were on TNF-inhibitor therapy. An increased risk of postoperative serious infection with TNF-inhibitors (odds ratio 5.3, 1.1–24.9) was seen after adjusting for age, gender, disease duration, prednisone use, diabetes, and serum rheumatoid factor. Although the results of this study suggest that patients on TNF inhibitors should discontinue these medications before orthopedic surgeries, the authors acknowledge several limitations to their data. First, the results may have been confounded by indication, as TNF-inhibitor therapy often is prescribed to the sickest patients who may be at greatest risk because of the severity of their disease. Second, there were clear differences between the surgical procedures performed on the group of patients who did and did not develop infection. The group who developed infections were less likely to have undergone primary arthroplasty (0% vs 43% in the infected group, $p = 0.006$), and more likely to have had revision arthroplasty (20% vs 6%, $p = 0.169$), small joint procedures (40% vs 23%, $p = 0.266$), and fusions or resections (40% vs 27%, $p = 0.463$). Although many of these differences were not statistically significant, the numbers of patients being compared were small.

Animal studies have suggested that anti-TNF agents may have the potential to affect the healing response, but it is not clear whether their effects are deleterious or beneficial. Although it may seem more likely that these agents would impair wound healing, a study in rats has suggested that excessive TNF production may inhibit skin wound healing, and that blocking TNF may restore fibroblast growth activity to allow a more normal healing response [36]. Unfortunately, there are no large-scale prospective studies in humans that address the TNF antagonists and surgical wound healing specifically. However, in the previously mentioned study of RA patients undergoing foot and ankle procedures, Bibbo and Goldberg [34] did note that both soft-tissue ($n = 3$) and bone-healing ($n = 3$) complications occurred exclusively in the group of patients who were not receiving anti-TNF therapy (either Enbrel or Remicade). Although these results are reassuring, the presence of other concomitant medical conditions that may influence wound healing (i.e., diabetes or hypoalbuminemia) was not reported in this small study.

Serious infections are a known complication of TNF-inhibitor therapy, and RA patients already are at increased risk of serious infection compared with the general population [37]. Furthermore, patients treated with biological agents historically have been among the most severely affected patients. Although this may be changing as the TNF inhibitors are being used earlier in the disease course, there are no large prospective studies from which recommendations can be drawn. Therefore, at this time, caution dictates holding these agents in the perioperative period, at least one dosage cycle before surgery (1 week for Enbrel, 6–8 weeks for Remicade, and 2 weeks for Humira) until wound healing has progressed to allow for staple/suture removal. However, given the more widespread usage of these medications and the reassuring results from Bibbo and Goldberg [34], prospective investigation into the use of anti-TNF agents in the setting of total arthroplasty should be encouraged.

Biologics: Rituximab

Rituximab (Rituxan™) is a monoclonal antibody directed against CD-20, a cell-surface molecule expressed on a subset of B lymphocytes. The use of this agent to treat RA is a relatively recent development [38], and it is often reserved for those patients who have failed most other available agents, including the anti-TNF medications. However, it has a longer history of use in treating lymphoma, so the majority of the safety data comes from the oncology literature. Originally approved in combination with chemotherapy (the R-CHOP regimen) for the treatment of non-Hodgkin's lymphoma, rituximab depletes B lymphocytes; in a minority of lymphoma patients, there is a measurable decrease in immunoglobulin levels after treatment with this agent. However, there appears to be no increased incidence of infection compared with chemotherapy alone [39]. There are cases reporting reactivation of hepatitis B infection after rituximab treatment in combination with chemotherapy [40–42], but it is not clear if the same risk applies to patients with RA treated with this agent alone. In the clinical trial of rituximab use in RA, 161 patients were randomized to four different treatment groups: MTX alone, rituximab alone, rituximab + MTX, and rituximab + Cytoxan [38]. Rituximab was given in two doses of 1,000 mg given 2 weeks apart. No increase in infectious complications was observed in the rituximab-treated patients, and immunoglobulin levels were only minimally affected despite large decreases in rheumatoid factor. In a prior open-label trial of 22 patients with RA, patients treated with rituximab had mild reductions in total immunoglobulin levels but the levels remained within the normal range. Instead, disproportionate decreases in the levels of autoantibodies were seen in these patients, whereas antipneumococcal and antitetanus toxoid antibody levels remained stable [43].

There are no published preclinical or clinical data or observations regarding surgical complications in patients who have received this therapy. With any drug that perturbs the immune system, the potential exists for side effects impacting wound healing and infectious complication risk; however, there is insufficient data to evaluate the specific effects of rituximab. In patients with RA treated with this medication, a prolonged B-cell depletion occurs, which can last up to 1 year, and should be considered in evaluating an individual patient's risk of postoperative infection. Given this medication's ability to deplete a subset of B cells for prolonged periods of time, we recommend that elective

procedures should probably not be scheduled (if possible) until the B-cell counts ($CD19^+$ cell counts) have returned to normal. In cases where surgery is urgent, or delay of an elective procedure to wait for the B-cell counts would cause undue suffering for the patient, previous treatment with rituximab should not be considered a contraindication to surgery. Instead, the patient should be followed closely postoperatively to ensure that infectious complications are recognized and treated early.

Summary

In summary, with the exception of MTX, there is a lack of data regarding the use of immunosuppressive DMARDs and biologics in RA patients undergoing orthopedic procedures. Studies addressing the perioperative infectious risk of these agents are inadequate, but the data focusing on wound healing is particularly sparse. The small series reviewed here are mostly retrospective and do not adequately answer these questions. However, review of the available literature taken together with the known side effects of these agents can direct sensible decision making. With all of these medications, individualized decisions regarding perioperative use should be guided by the principle of balancing their potential risks with the risk of a postoperative disease flare. Factors to be taken into consideration for each patient include the activity of the disease, use of multiple immunosuppressants, and the presence of other conditions (i.e., other chronic diseases, diabetes, anemia, hypoalbuminemia), which may contribute to postoperative infectious and healing risk. Furthermore, medical control of disease activity should be optimized as much as possible before surgery to enhance rehabilitation and minimize postoperative complications. We have the least data and experience with the biologic agents (i.e., anti-TNFs); thus, a conservative approach should be taken to hold these medications preoperatively and postoperatively until wound healing has taken place. As more prospective data becomes available, recommendations may change appropriately.

Acknowledgement The authors would like to thank C. Ronald MacKenzie, MD, for his editorial assistance in preparation of this manuscript.

References

1. An YH, Friedman RJ (1996) Prevention of sepsis in total joint arthroplasty. J Hosp Infect 33:93–108
2. Schlaghecke R, Kornely E, Santen RT, Ridderskamp P (1992) The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. N Engl J Med 326:226–230
3. McPhee IB, Williams RP, Swanson CE (1998) Factors influencing wound healing after surgery for metastatic disease of the spine. Spine 23:726–732
4. Busti AJ, Hooper JS, Amaya CJ, Kazi S (2005) Effects of perioperative anti-inflammatory and immunomodulating therapy on surgical wound healing. Pharmacotherapy 25:1566–1591
5. Mathis AS, Shah NK, Mulgaonkar S (2004) Stress dose steroids in renal transplant patients undergoing lymphocele surgery. Transplant Proc 36:3042–3045
6. Bromberg JS, Alfrey EJ, Barker CF et al (1991) Adrenal suppression and steroid supplementation in renal transplant recipients. Transplantation 51:385–390
7. Glowniak JV, Loriaux DL (1997) A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery 121:123–129
8. Leopold SS, Casnellie MT, Warme WJ et al (2003) Endogenous cortisol production in response to knee arthroscopy and total knee arthroplasty. J Bone Jt Surg Am Vol 85-A:2163–2167
9. Bruewer M, Utech M, Rijcken EJ et al (2003) Preoperative steroid administration: effect on morbidity among patients undergoing intestinal bowel resection for Crohns disease. World J Surg 27:1306–1310
10. Aberra FN, Lewis JD, Hass D et al (2003) Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. Gastroenterology 125:320–327
11. Jain A, Witbreuk M, Ball C, Nanchahal J (2002) Influence of steroids and methotrexate on wound complications after elective rheumatoid hand and wrist surgery. J Hand Surg [Am] 27:449–455
12. Hanssen AD, Cabanela ME, Michet CJ Jr (1987) Hip arthroplasty in patients with systemic lupus erythematosus. J Bone Jt Surg Am Vol 69:807–814
13. Levitsky J, Te HS, Cohen SM (2003) The safety and outcome of joint replacement surgery in liver transplant recipients. Liver Transplant 9:373–376
14. Cronstein BN (2005) Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacol Rev 57:163–172
15. Choi HK, Hernan MA, Seeger JD et al (2002) Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 359:1173–1177
16. Pincus T, Yazici Y, Sokka T et al (2003) Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol 21:S179–S185
17. Grennan DM, Gray J, Loudon J, Fear S (2001) Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann Rheum Dis 60:214–217
18. Sany J, Anaya JM, Canovas F et al (1993) Influence of methotrexate on the frequency of postoperative infectious complications in patients with rheumatoid arthritis. J Rheumatol 20:1129–1132
19. Carpenter MT, West SG, Vogelgesang SA, Casey Jones DE (1996) Postoperative joint infections in rheumatoid arthritis patients on methotrexate therapy. Orthopedics 19:207–210
20. Bibbo C, Anderson RB, Davis WH, Norton J (2003) The influence of rheumatoid chemotherapy, age, and presence of rheumatoid nodules on postoperative complications in rheumatoid foot and ankle surgery: analysis of 725 procedures in 104 patients. Foot Ankle Int 24:40–44
21. Bland KI, Palin WE, von Fraunhofer JA et al (1984) Experimental and clinical observations of the effects of cytotoxic chemotherapeutic drugs on wound healing. Ann Surg 199:782–790
22. Cohen SC, Gabelnick HL, Johnson RK, Goldin A (1975) Effects of antineoplastic agents on wound healing in mice. Surgery 78:238–244
23. Hernigou P, Thiery JP, Benoit J et al (1989) Methotrexate diffusion from acrylic cement. Local chemotherapy for bone tumours. J Bone Jt Surg Br 71:804–811
24. Shamberger RC, Devereux DF, Brennan MF (1981) The effect of chemotherapeutic agents on wound healing. Int Adv Surg Oncol 4:15–58
25. Kasdan ML, June L (1993) Postoperative results of rheumatoid arthritis patients on methotrexate at the time of reconstructive surgery of the hand. Orthopedics 16:1233–1235
26. Lim V, Pande I (2002) Leflunomide can potentiate the anticoagulant effect of warfarin. BMJ 325:1333,

27. Feldmann MM, Maini RN (2002) Discovery of TNF-α as a therapeutic target in rheumatoid arthritis: preclinical and clinical studies. Joint, Bone, Spine 69:12–18
28. Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH (2003) Comparison of the efficacy of the tumour necrosis factor α blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 62(Suppl 2): ii13–ii16
29. Lipsky PE, van der Heijde DM, St Clair EW et al (2000) Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. NEJM 343:1594–1602
30. Hyrich KL, Silman AJ, Watson KD, Symmons DP (2004) Anti-tumour necrosis factor alpha therapy in rheumatoid arthritis: an update on safety. Ann Rheum Dis 63:1538–1543
31. Fisher CJ, Agosti JM, Opal SM et al (1996) Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. NEJM 334:1697–1702
32. Marchal L, D'Haens G, Van Assche G et al (2004) The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. Aliment Pharmacol Ther 19:749–754
33. Colombel JF, Loftus EV Jr, Tremaine WJ et al (2004) Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol 99:878–883
34. Bibbo C, Goldberg JW (2004) Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot Ankle Int 25:331–335
35. Giles JT, Bartlett SJ, Gelber AC et al (2006) Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in Rheumatoid Arthritis. Arthritis Care Res 55:333–337
36. Kawaguchi HH, Hizuta AA, Tanaka NN, Orita KK (1995) Role of endotoxin in wound healing impairment. Res Commun Mol Pathol Pharmacol 89:317–327
37. Doran MF, Crowson CS, Pond GR et al (2002) Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 46:2287–2293
38. Edwards JC, Szczepanski L, Szechinski J et al (2004) Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. NEJM 350:2572–2581
39. White CA, Weaver RL, Grillo-Lopez AJ (2001) Antibody-targeted immunotherapy for treatment of malignancy. Annu Rev Med 52:125–145
40. Sarrecchia C, Cappelli A, Aiello P (2005) HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HBcAb. J Infect Chemother 11:189–191
41. Law JK, Ho JK, Hoskins PJ et al (2005) Fatal reactivation of hepatitis B post-chemotherapy for lymphoma in a hepatitis B surface antigen-negative, hepatitis B core antibody-positive patient: potential implications for future prophylaxis recommendations. Leuk Lymphoma 46:1085–1089
42. Tsutsumi Y, Kanamori H, Mori A et al (2005) Reactivation of hepatitis B virus with rituximab. Expert Opin Drug Safety 4:599–608
43. Cambridge G, Leandro MJ, Edwards JC et al (2003) Serologic changes following B lymphocyte depletion therapy for rheumatoid arthritis. Arthritis Rheum 48:2146–2154