Review Article

Perioperative immunosuppressive use in patients with rheumatologic diseases

Madonna Michael[1], **Moises Auron**[1,2]

[1]Cleveland Clinic Department of Hospital Medicine, Cleveland, OH, USA; [2]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Madonna Michael, MD. 9500 Euclid Ave., Cleveland, OH 44195, USA. Email: michaem4@ccf.org.

Abstract: Effective and safe perioperative immunosuppressive management for patients with rheumatic diseases is often challenging and complex. Immunosuppressive agents result in decreased immunity, thus increasing the risk of infection, and its anti-inflammatory effect hinders the tissue healing process. The difficulty of the clinical decision-making regarding the safe management of these agents in the perioperative period arises from the need to conciliate several outcomes: ensure adequate clinical control of the underlying rheumatic disease activity, while also aiming to mitigate the risk of perioperative complications, mostly minimizing the risk of impairment of the postoperative tissue healing as well as the risk of postoperative infection. In this review article, we will highlight the peri-operative immunosuppressive management and doses suggested for patients with rheumatic diseases.

Keywords: Immunosuppressants; perioperative; perioperative immunosuppression; rheumatic disease; steroids

Received: 29 January 2018; Accepted: 09 October 2018; Published: 19 October 2018.
doi: 10.21037/jxym.2018.10.01
View this article at: http://dx.doi.org/10.21037/jxym.2018.10.01

Introduction

Effective and safe perioperative immunosuppressive management for patients with rheumatic diseases is often challenging and complex. Immunosuppressive agents result in decreased immunity, thus increasing the risk of infection, and its anti-inflammatory effect hinders the tissue healing process. The difficulty of the clinical decision-making regarding the safe management of these agents in the perioperative period arises from the need to conciliate several outcomes: ensure adequate clinical control of the underlying rheumatic disease activity, while also aiming to mitigate the risk of perioperative complications, mostly minimizing the risk of impairment of the postoperative tissue healing as well as the risk of postoperative infection (1-3).

Several factors play a role in this critical decision, including but not limited to the mechanism of action and half-life of these agents (*Table 1*), the nature and clinical activity of the rheumatic disease, and the type of surgical procedure (4). Available data arising from studies addressing the peri-operative management of immunosuppressant medications remains limited, especially given the continuous evolvement of these medications.

In this review article, we will highlight the peri-operative immunosuppressive management and doses suggested for patients with rheumatic diseases.

Corticosteroids

Corticosteroids remain a fundamental first line therapy in the treatment of autoimmune diseases given its strong anti-inflammatory properties. The corticotrophin-releasing hormone (CRH) secreted by the hypothalamus controls the pituitary release of Adrenocorticotropic hormone (ACTH), which in turn regulates the cortisol release by the adrenal cortex.

Under normal physiologic circumstances, daily production of endogenous glucocorticoids, mainly cortisol, is around 10–12 mg; cortisol levels increase proportionally

Table 1 Commonly used DMARDs used and their half life

Agent	Mechanism of action	Half life
Methotrexate poly-glutamates	Folic acid antagonist	7 days
Etanercept	TNF inhibitor	3.5–5.5 days
Infliximab	TNF inhibitor	9.5 days
Adalimumab	TNF inhibitor	10–20 days
Azathioprine	Purine synthesis inhibitor	5 hours
Rituximab	B cell inhibitor	18–22 days

DMARDs, disease-modifying anti-rheumatic drugs; TNF, tumor necrosis factor.

up to 150 mg per day in relation to the level of stress a person is exposed to. Administration of exogenous steroids, specifically in patients receiving the equivalent of a daily dose of prednisone equal to or more than 20 mg for a minimum of 3 weeks, has the potential to blunt the normal physiological pituitary-adrenal axis, and put these patients at increased risk of acute adrenal insufficiency, especially during physiological stressful conditions such as surgical interventions (1,5). Avoiding perioperative discontinuation of steroids is important to maintain control of inflammatory diseases, prevent flares of inflammatory diseases with subsequent possible organ and/or joint damage, and to eliminate the risk of adrenal insufficiency in patients with chronic steroid use; however, at the same time, exposing patients to higher doses of steroids increase the risk of perioperative complications, specifically infection secondary to immunosuppression and delayed wound healing due to anti-inflammatory effect (1).

During the 1950's, patients considered to be at risk of adrenal insufficiency were administered high doses of steroids around the perioperative period, which was based on case reports of patients developing adrenal crisis in the perioperative period which was clinically diagnosed without formal biochemical confirmation of adrenal insufficiency (6,7). Further studies concluded that although adrenal insufficiency can occur in steroid dependent patients undergoing surgery, its clinical presentation has remained uncommon (8-10).

The aim to identify appropriate peri-procedural stress steroids dosing for chronic steroid users led to several studies. A systematic review of seven cohort studies and 2 randomized controlled trials including 315 patients demonstrated no significant hemodynamic changes when comparing patients receiving the usual daily corticosteroid dose with patients receiving stress dosing. In the cohort studies, the patients who continued their regular steroid dose (prednisone 5–15 mg per day) did not develop perioperative adrenal insufficiency (11). Salem *et al.* conducted an extensive literature review and suggested that steroids requirements vary between patients, considering factors such as surgical procedure intensity, steroid dose and duration. It was determined that the steroid supplementation dose should simulate the normal physiologic response expected with surgery (12). All chronic steroids users should receive their regular daily steroid dose preoperatively. Patients, who receive daily steroid dose equivalent to less than 20 mg of prednisone for rheumatological diseases, undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA), do not require stress dose steroids to minimize the risk of infection (13). For minor surgical procedures (duration less than two hours, i.e., hernia repair), chronic steroid users should receive hydrocortisone 25 mg or equivalent on the day of surgery only. For moderate surgical risk surgeries (i.e., hysterectomy) patients usually receive their home dose preoperatively in addition to hydrocortisone 50–75 mg or equivalent upon induction of anesthesia, followed by a rapid steroid taper, patients can then resume their home doses on postoperative day 1 or 2. Those undergoing major surgical procedures (i.e., cardiac surgery, major spine surgery), should receive hydrocortisone 100–150 mg or equivalent; followed by a rapid steroid taper, for the patients to resume their home doses 2 to 3 days postoperatively. Critically ill patients, and those in shock should receive hydrocortisone 50–100 mg every 6 to 8 hours until shock subsides, followed by a gradual steroid taper (12,14,15).

The risk of acute adrenal insufficiency is most prominent after induction of anesthesia and intraoperative period, given the significant associated hypotension post-induction, as well as the prominent inflammatory response to surgery; therefore when providing supplemental perioperative steroids, the highest dose is recommended prior to induction of anesthesia; perhaps this dose should suffice overall, with continuation of the home steroid dose the next day; however the recommendations are still a gradual taper over 1 or 2 days to minimize the risk of acute adrenal insufficiency; the recommendation for management of perioperative steroids at our institution is found in *Table 2*.

Methotrexate (MTX)

MTX is one of the disease-modifying anti-rheumatic drugs

Table 2 Recommendation for management of perioperative steroids

Preoperative daily steroid dose (Prednisone dose equivalent)	Low risk surgery (e.g., hernia)	Moderate risk surgery (e.g., hysterectomy)	High risk surgery (e.g., cardiac)
Less than 20 mg per day	Continue home dose	Continue home dose	Continue home dose
More than 20 mg per day	Hydrocortisone 25 mg or equivalent on the day of surgery only	Hydrocortisone 50 mg on induction of anesthesia. 25 mg IV every 8 hours × 3 doses. Then resume home dose	Hydrocortisone 100 mg on induction of anesthesia. 50 mg IV every 8 hours × 3 doses. Then 25 mg IV every 8 hours × 3 doses. Then resume home dose
Patients with positive cosyntropin stimulation test. Unknown steroid dose.	Hydrocortisone 25 mg on induction of anesthesia.	Hydrocortisone 50 mg on induction of anesthesia. 25 mg IV every 8 hours × 3 doses. Then resume home dose	Hydrocortisone 100 mg on induction of anesthesia. 50 mg IV every 8 hours × 3 doses. Then 25 mg IV every 8 hours × 3 doses. Then resume home dose

(DMARDs), a class of anti-inflammatory medications. MTX is a folic acid antagonist, which inhibits the synthesis of purines and pyrimidines with subsequently impaired DNA and RNA synthesis and cells proliferation; MTX also has possible direct apoptotic effect on T cells, contributing to the its immunosuppressive and anti-proliferative functions (16). The clinical application of MTX encompasses different scenarios: cancer treatment (certain type of leukemia and breast cancer); inflammatory bowel disease (IBD) (Crohn's disease); autoimmune inflammatory diseases [e.g., rheumatoid arthritis (RA)]. In regards to autoimmune diseases, the studies conducted focused on MTX use in RA patients, in which MTX is administered in oral or subcutaneous weekly doses ranging between 15–25 mg per week (2,4,17). Most studies aiming to determine the safety of continuing MTX in the preoperative period, have shown inconclusive and controversial results (18-20).

Loza *et al.* performed a systematic review of randomized controlled studies and cohort studies including RA patients on MTX undergoing surgeries between the year 1961 and 2007. The authors concluded that it is safe to continue perioperative low doses MTX without increasing the risk of infection or surgical complications (2). A more recent systematic review by Heldmann and Braun echoed the results of the prior study; however, given insufficient data the authors suggested that in patients with high risk of postoperative complications or sepsis (e.g., history of sepsis), MTX can be discontinued 1 week prior to surgery, and restarted after wound healing has established, with close monitoring to signs of disease flare and possible replacement by small dose of corticosteroids to decrease the risk of arthritis flares (17). Another study also suggested discontinuing MTX in cases of postoperative renal insufficiency in an effort to avoid the risk of MTX toxicity (21). Based on the evidence extrapolated from these systematic reviews (almost all studies had a mean MTX dose of less than 15 mg per week), the current recommendation is to continue low dose MTX in the perioperative period, it was also recommended that patients with severe systemic lupus erythematosus (SLE) should discuss with their rheumatologists before deciding to proceed with elective surgeries (2,13,17).

Anti-tumor necrosis factor (TNF) medications

Anti-TNF alpha, are a group of medications that function by inhibiting TNF, which plays a vivid role in the activation of various immune cells and in the inflammatory process required to mount a response to infection; therefore, anti-TNF agents increase the risk of infection.

These agents are mostly used for the treatment of RA, IBD, psoriasis and ankylosing spondylitis (AS) (3). Anti-TNF medications have been linked to serious infections with associated consequent potential increase in morbidity and mortality, especially within the first 6 months of initiating treatment (22). While the respiratory tract is the most common reported site of infection in most of the randomized controlled and meta-analysis studies conducted, yet a wide range of infections ranging from mild to fatal were observed, and the main concern in the perioperative period continues to be the skin and soft tissue infections [i.e., possible surgical site infection (SSI)] (3,23).

A study conducted by Dixon *et al.* suggested that anti-

TNFs are associated with a greater risk of skin and soft tissue infection during the 30-day postoperative period in comparison with other immunosuppressive agents (24). The risk of skin and soft tissue infection is even greater in psoriasis patients because of the higher rate of skin bacterial colonization (3). Den Broeder *et al.* completed a retrospective study of comparing patients who continued versus discontinued anti-TNFs preoperatively; the study included patients with RA; they found no significant difference in the rate of SSI, except in those with history of previous skin or SSI (23). A small, 12-month prospective study, which included RA patients undergoing elective orthopedics surgical interventions, compared sixteen patients on anti-TNFs with fifteen patients on steroids or DMARDs; the anti-TNF medications were discontinued perioperative, and no difference in rate of infection was detected between both groups (25). Additionally, a retrospective analysis performed by Giles *et al.* which included 91 RA patients who underwent orthopedic procedures found that serious postoperative infections occurred in 11% of the patients, which the majority were being treated with anti-TNFs, suggesting a strong association between anti-TNFs and postoperative infections (26).

Most of the studies conducted thus far are retrospective and displayed different data, with no definitive conclusion on whether to continue or discontinue the anti-TNF medications in the postoperative period. Initially it was recommended to discontinue the anti-TNF medications for a period equivalent to three half-lives, recent guidelines suggest that the medication half life does not correlate to the duration of immunosuppression, additionally holding the medication for a dosing cycle was recommended instead for at least 2 weeks post-operatively to allow adequate tissue healing. Ultimately, if there is no clinical evidence of active infection medications can be resumed (13,27,28).

New biologic agents

The same guidelines for anti-TNF inhibitors apply for new biologic agents such as Belimumab (a monoclonal antibody inhibiting B cell proliferation and promoting apoptosis, used for treatment of SLE) and Tofacitinib (a Janus kinase inhibitor used in treatment of RA), where the medications are held for one dosing cycle (4 weeks for Belimumab and 1 week for Tofacitinib) and resumed at least 14 days after surgery if there are no healing complications or active infections (13).

Azathioprine

Azathioprine exerts its mechanism of action by inhibiting the synthesis of purines, which affects DNA synthesis and replication, especially lymphocytes; recent studies suggest that natural killers (NK) and B cells are affected more than T cells (29). It is commonly used as a steroid-sparing maintenance therapy in patients with various rheumatologic diseases (i.e., SLE and RA), IBD and leukemia (30,31). The above-mentioned mechanism of action raises the concern of poor wound healing with perioperative use of Azathioprine.

A retrospective study by Escalante *et al.* reviewed 207 RA patients who underwent a total of 367 various orthopedic surgeries, most common of which were total knee replacements and total hip replacements, 119 and 105 surgeries respectively; the study concluded that perioperative azathioprine use was associated with higher risk of postoperative wound complications when compared to other DMARDs (32). There is limited data focusing on patients with rheumatologic diseases receiving azathioprine, being most studies conducted on IBD patients. Colombel *et al.* retrospectively reviewed a cohort of 270 IBD surgical patients; 64 patients were on azathioprine preoperatively, finding no significant increased risk of postoperative complications among these patients (33). Currently due to the limited data to make a compelling argument to discontinue azathioprine in the perioperative period, clinicians tend to continue azathioprine except in cases of postoperative liver or kidney dysfunction (4).

Rituximab

Rituximab is a monoclonal antibody directed against the B cells, specifically the CD20 antigen, resulting in B cell depletion within 2 to 3 weeks after a dose of rituximab. B cell numbers usually normalize within a year. Patients may experience a significant drop in immunoglobulin levels, which remains for up to six months after initiating rituximab. Rituximab is commonly used in the treatment of rheumatologic diseases (i.e., RA, SLE and vasculitis), oncology (i.e., lymphoma) and in transplant recipients (34).

A retrospective study by Scemla *et al.* compared 38 patients who underwent renal transplant and received rituximab versus 26 renal transplant patients who received other treatments. In total, 55.3% of patients in the rituximab group developed severe bacterial infections compared to 60% of the patients in the control group (35).

There is scant data about the use of rituximab in

the perioperative period. Goodman *et al.* reviewed data regarding immunosuppressants used in perioperative period of elective surgical procedures in patients with rheumatologic diseases; the authors concluded that the risk of increased risk of postoperative infection has not been well established (36). The authors suggested monitoring immunoglobulin levels, specifically IgG levels, at least 100 days after rituximab dose, and if levels normalize, then proceed further with the elective surgery. If levels remain abnormal, then administration of intravenous immunoglobulin (IVIG) is advised prior to surgery (4). Based on systematic reviews and data showing increased risks of infections with rituximab, as well as the limited available data regarding the risks of perioperative use of rituximab, the American College of Rheumatology (ACR) 2017 guidelines, recommended a 6-month wait period after the last rituximab dose, to schedule elective hip or knee surgery (13).

Conclusions

Patients with rheumatic diseases face a plethora of challenges with regards to perioperative immunosuppressive medications management. Limited available data and lack of general consensus poses a challenge for medical decision-making. Changes in immunosuppressive medication doses can result in a flare, which may result in organ damage. Continuing these medications may predispose patients to a greater risk of complications, including but not limited to postoperative infections, and complications related to wound healing. Most of our decisions are evidence based, but in some cases the benefits outweigh the risks. Undoubtedly, we will continue to make tremendous discoveries vital to furthering care for these patients. More research is needed to provide rheumatologic patients with the best quality of life possible.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: The article was commissioned by the editorial office, *Journal of Xiangya Medicine* for the series "Update in Perioperative Medicine". The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2018.10.01). The series "Update in Perioperative Medicine" was commissioned by the editorial office without any funding or sponsorship. MA served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Howe CR, Gardner GC, Kadel NJ. Perioperative medication management for the patient with rheumatoid arthritis. J Am Acad Orthop Surg 2006;14:544-51.
2. Loza E, Martinez-Lopez JA, Carmona L. A systematic review on the optimum management of the use of methotrexate in rheumatoid arthritis patients in the perioperative period to minimize perioperative morbidity and maintain disease control. Clin Exp Rheumatol 2009;27:856-62.
3. Hession MT, Gottlieb AB. Perioperative management of tumor necrosis factor antagonists in patients with psoriasis and other inflammatory disorders. J Dermatolog Treat 2011;22:90-101.
4. Gardner C. Management of medications in patients with rheumatic diseases during the perioperative period. In: Mandell B. editor. Perioperative Management of Patients with Rheumatic Disease. 12th edition. Springer, 2012:71-85.
5. Oelkers W. Adrenal Insufficiency. N Engl J Med 1996;335:1206-12.
6. Fraser CG, Preuss, FS, Bigford WD. Adrenal atrophy and irreversible shock associated with cortisone therapy. J Am Med Assoc 1952;149:1542-3.
7. Lewis, L, Robinson RF, Yee J, et al. Fatal adrenal cortical

insufficiency precipitated by surgery during prolonged continuous cortisone treatment. Ann Intern Med 1953;39:116-26.
8. Knudsen L, Christiansen LA, Lorentzen JE. Hypotension during and after operation in glucocorticoid-treated patients. Br J Anaesth 1981;53:295-301.
9. Bromberg JS, Alfrey EJ, Barker CF, et al. Adrenal suppression and steroid supplementation in renal transplant recipients. Transplantation 1991;51:385-90.
10. Friedman RJ, Schiff CF, Bromberg JS. Use of supplemental steroids in patients having orthopaedic operations. J Bone Joint Surg Am 1995;77:1801-6.
11. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. Arch Surg 2008;143:1222-6.
12. Salem M, Tainsh RE, Bromberg J, et al. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994;219:416-25.
13. 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. J Arthroplasty 2017;32:2628-38.
14. Axelrod L. Perioperative management of patients treated with glucocorticoids. Endocrinol Metab Clin North Am 2003;32:367-83.
15. Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. JAMA 2002;287:236-40.
16. Wessels JAM, Huizinga TWJ, Guchelaar HJ. Recent insights in the pharmacological actions of methotrexate in the treatment of rheumatoid arthritis. Rheumatology (Oxford) 2008;47:249-55.
17. Heldmann F, Braun J. Perioperative use of methotrexate. Clin Exp Rheumatol 2010;28:S110-3.
18. Carpenter MT, West SG, Vogelgesang SA, et al. Postoperative joint infections in rheumatoid arthritis patients on methotrexate therapy. Orthopedics 1996;19:207-10.
19. Sany J, Anaya JM, Canovas F, et al. Influence of methotrexate on the frequency of postoperative infectious complications in patients with rheumatoid arthritis. J Rheumatol 1993;20:1129-32.
20. Murata K, Yasuda T, Ito H, et al. Lack of increase in postoperative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Mod Rheumatol 2006;16:14-9.
21. Rosandich PA, Kelley JT, Conn DL. Perioperative management of patients with rheumatoid arthritis in the era of biologic response modifiers. Curr Opin Rheumatol 2004;16:192-8.
22. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford) 2011;50:124-31.
23. den Broeder AA, Creemers MCW, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol 2007;34:689-95.
24. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:2368-76.
25. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot ankle Int 2004;25:331-5.
26. Giles JT, Bartlett SJ, Gelber AC, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Rheum 2006;55:333-7.
27. Pappas DA, Giles JT. Do antitumor necrosis factor agents increase the risk of postoperative orthopedic infections? Curr Opin Rheumatol 2008;20:450-6.
28. Ding T, Ledingham J, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology (Oxford) 2010;49:2217-9.
29. Lord JD, Shows DM. Thiopurine use associated with reduced B and natural killer cells in inflammatory bowel disease. World J Gastroenterol 2017;23:3240-51.
30. Negrei C, Bojinca V, Balanescua A, et al. Management of rheumatoid arthritis: Impact and risks of various therapeutic approaches. Exp Ther Med 2016;11:1177-83.
31. Abaji R, Krajinovic M. Thiopurine S-methyltransferase polymorphisms in acute lymphoblastic leukemia, inflammatory bowel disease and autoimmune disorders: influence on treatment response. Pharmgenomics Pers Med 2017;10:143-56.

32. Escalante A, Beardmore TD. Risk factors for early wound complications after orthopedic surgery for rheumatoid arthritis. J Rheumatol 1995;22:1844-51.
33. Colombel JF, Loftus E V, Tremaine WJ, et al. Early Postoperative Complications are not Increased in Patients with Crohn's Disease Treated Perioperatively with Infliximab or Immunosuppressive Therapy. Am J Gastroenterol 2004;99:878-83.
34. Christou EAA, Giardino G, Worth A, et al. Risk factors predisposing to the development of hypogammaglobulinemia and infections post-Rituximab. Int Rev Immunol 2017;36:352-9.
35. Scemla A, Loupy A, Candon S, et al. Incidence of infectious complications in highly sensitized renal transplant recipients treated by rituximab: a case-controlled study. Transplantation 2010;90:1180-4.
36. Goodman SM. Rheumatoid arthritis: Perioperative management of biologics and DMARDs. Semin Arthritis Rheum 2015;44:627-32.

doi: 10.21037/jxym.2018.10.01
Cite this article as: Michael M, Auron M. Perioperative immunosuppressive use in patients with rheumatologic diseases. J Xiangya Med 2018;3:38.

