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Perioperative Management of Non-Biological and Biological Therapies in Rheumatic Patients Undergoing Orthopedic Surgery

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1. Introduction

Patients with rheumatoid arthritis (RA) or other inflammatory arthropathies often require orthopedic surgery, and the management of their medical treatments during the perioperative period is an important issue. The two main concerns during this period are the risk of infection and wound healing complications.

These patients receive multidisciplinary care from orthopedic surgeons, rehabilitators and rheumatologists (1). Before orthopedic surgery, the activity of the arthropathy and the non-biological and biological therapies of patients must be taken into consideration for an optimal outcome with no infectious or wound-healing complications. Good clinical and biological control of the disease must be obtained before the surgery, and effective coordination between surgeon and rheumatologist is essential (2).

The management of non-biological (immunosuppressive or immunomodulatory) and biological therapies in orthopedic surgery patients remains controversial. This chapter focuses on disease-modifying anti-rheumatic drugs (DMARDs) and biological therapies (see table 1). Although corticosteroids are immunosuppressants, protocols for their replacement or supplementation are well established in the literature and are not addressed here (3). DMARDs and especially biological therapies are the subject of multiple consultations between rheumatologists and orthopedists or anesthesiologists before surgery. The objective of this chapter is to discuss current protocols for the application of these treatments before and after orthopedic surgery, based on the best available scientific evidence or, in its absence, on accepted recommendations.

2. Disease-modifying anti-rheumatic drugs (DMARDs)

2.1 Methotrexate (MTX)

Until five years ago, there was a tendency to withdraw MTX at around two weeks before surgery, based on reports in various retrospective studies of a higher risk of postoperative complications, especially infections (4). However, a well-designed prospective study by Grennan et al. (5) in 388 patients concluded that the continuation of MTX treatment did not

MODIFYING DRUGS (DMARDS)	BIOLOGICAL THERAPIES
<div><div></div><div>- METHOTREXATE</div><div>- ANTI-MALARIALS</div><div>- LEFLUNOMIDE</div><div>- SULFASALAZINE</div><div>- CYCLOSPORINE A</div><div>- GOLD COMPOUNDS</div><div>- AZATHIOPRINE</div></div>	<div><div></div><div>- INFlixIMAB</div><div>- ETANERCEPT</div><div>- ADALIMUMAB (D2E7)</div><div>- CERTOLIZUMAB</div><div>- GOLIMUMAB</div><div>- ANAKINRA (rHuIL-1Ra)</div><div>- RITUXIMAB</div><div>- ABATACEPT</div><div>- TOCILIZUMAB</div></div>

Table 1. Modifying drugs and biological therapies used in rheumatoid arthritis

increase infection risk or delay wound-healing. Furthermore, patients who had continued with their MTX treatment had fewer postoperative inflammatory outbreaks in comparison to those who had not, and the latter showed a non-significant tendency to a higher frequency of post-surgical complications. Nevertheless, although a rare complication, MTX-associated lymphoproliferative disorders consist of a heterogeneous group of lymphoid proliferations or lymphomas (mainly diffuse large B-cell lymphoma or Hodgkin lymphoma) that develop in patients with autoimmune diseases after prolonged MTX treatment. These lymphoproliferative disorders are often associated with Epstein-Barr virus infection and occasionally regress after the withdrawal of MTX therapy (6).

2.2 Anti-malarials

The anti-malarials used in RA patients are chloroquine and especially hydroxychloroquine, due to its lower ocular toxicity. After their prolonged administration, anti-malarials accumulate in multiple tissues (kidney, spleen, liver, etc). For this reason, despite the absence of well-designed studies, it does not appear appropriate or meaningful to interrupt their administration immediately before surgery. Nevertheless, it should be borne in mind that anti-malarials inhibit platelet aggregation and adhesion (7) and may therefore increase the risk of bleeding.

2.3 Leflunomide (LFN), sulfasalazine, and gold compounds

LFN inhibits pyrimidine synthesis and offers a similar effectiveness to that of MTX but with a greater selectivity, reversibly inhibiting the proliferation of activated autoimmune lymphocytes. Although a low risk of infection was reported in various clinical trials, there appear to be no studies that evaluate this risk or the effects on postoperative wound-healing. However, because LFN can potentiate anticoagulation, the dosage should be adjusted in patients receiving this drug as prophylaxis against deep vein thrombosis (7). With respect to sulfasalazine and gold compounds, no good scientific evidence is available on their perioperative administration. In general, however, the perioperative suspension of their administration is not recommended (8).

2.4 Cyclosporine A and azathioprine

Although there have been no well-designed studies, various publications (7,10) have reported that infections are more frequent after orthopedic surgery in patients receiving azathioprine or cyclosporine A. For this reason, it is recommended to withdraw these drugs one week before and reintroduce them two weeks after this surgery.

3. Biological therapies

Unlike the treatments reported above, biological therapies are designed to specifically block molecules with important pathophysiological roles in AR and other inflammatory arthropies. These molecules include various proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-a), interleukin 6 (IL-6), and interleukin 1 (IL-1), which are responsible for chronic synovitis, bone destruction, and systemic manifestations. Other biological drugs have been developed against cells that participate in the pathogenesis of RA, such as rituximab, directed against CD20 B cells, and abatacept, which prevents activation of T lymphocytes and has shown effectiveness in controlling the disease.

Biological drugs are proteins (monoclonal antibodies or soluble receptors against cytokines, receptors, or cell surface molecules) obtained by biotechnology that block the above-mentioned cytokines or modulate B or T cells in a specific manner. The following are currently available:

- Drugs directed against TNF-a, either monoclonal antibodies (infliximab, adalimumab, certolizumab, or golimumab) or soluble receptors (etanercept). Their administration form and dosage differ according to the pharmacokinetics of these products.
- Abatacept is a fusion protein that blocks the T lymphocyte co-stimulation signal mediated by CD28; it is administered intravenously every 4 weeks.
- Tocilizumab is a humanized monoclonal antibody against IL-6 receptor; it is administered intravenously at an initial dose of 4 mg/kg (USA) or 8 mg/kg (Europe, Japan) every 4 weeks.
- Rituximab is a chimeric monoclonal antibody against the CD20 marker for B lymphocytes; it is administered intravenously at a dose of 500 or 1000 mg on days 0 and 15 and repeated every 6-12 months according to the disease activity.
- Anakinra is a recombinant human antagonist of IL-1 receptor; it is administered subcutaneously every day.

These drugs block cytokines or modulate cells involved in the cell immune response to infections. Hence, in theory, they should be withdrawn before surgery, despite the absence of clinical studies to support this decision. No clinical trial has addressed complications after orthopedic surgery in RA patients receiving biological treatments, but there have been some retrospective studies. Bibbo et al. (11) investigated the influence of infliximab and etanercept in orthopedic surgery and concluded that they could be administered safely in the perioperative period without increasing the risk of infectious or wound-healing complications. However, the pathologic study of the wounds is not reported, and the authors do not describe how they assessed wound-healing delay or bone-healing complications, two key variables in their study. A more recent retrospective study on clinical factors related to infliximab-treated RA patients undergoing orthopedic surgery (12) concludes that infliximab does not increase the risk of surgical or infectious complications at one year post-surgery. We did not observe any wound healing complications after hand surgery in fourteen rheumatoid patients treated with etanercept or infliximab (Fig. 1 and 2). Experimental results of TNF-a administration in murine models of wound-healing complications have not been consistent. Although TNF-a inhibition could theoretically have a negative impact on wound-healing (13), studies by our group and other authors suggest that it may improve collagenization of the wound (14), supporting its continuation during the perioperative period (Fig 3 and 4).



Fig. 1. Metacarpophalangeal deformity and arthritis in right hand of woman with rheumatoid arthritis and under treatment with etanercept. Surgical wound for implantation of metacarpophalangeal prosthesis. Treatment was not suspended during the perioperative period. Surgical wound healing was excellent.

No data are available on the effect of rituximab on surgical complications in RA patients. Its administration produces a prolonged (6 months–1 year) depletion of CD-19B lymphocytes and may therefore increase the risk of perioperative infection. Its effects on wound-healing are less clear. It therefore appears prudent to suspend treatment and delay surgery until the CD-19 lymphocyte B count of the patient is normalized (15). Nevertheless, experience with the administration of rituximab to lymphoma patients undergoing surgery suggests that it can be continued when surgery is essential and that its administration should not be a contraindication for surgery.

Tocilizumab blocks IL-6, inducing hepatic synthesis of C-reactive protein (CRP), which may mask signs and symptoms of post-surgical infectious complications, such as fever or elevated CRP (16, 17). The effects of IL-6 inhibition on wound-healing, by interfering with the initial inflammatory phase of the surgical wound, are not known.



Fig. 2. Ulnar deformity and metacarpophalangeal arthritis in right hand of man with rheumatoid arthritis under treatment with infliximab and that underwent metacarpophalangeal prosthesis. Treatment was not suspended during the perioperative period. Wound-healing was satisfactory, with no complications.

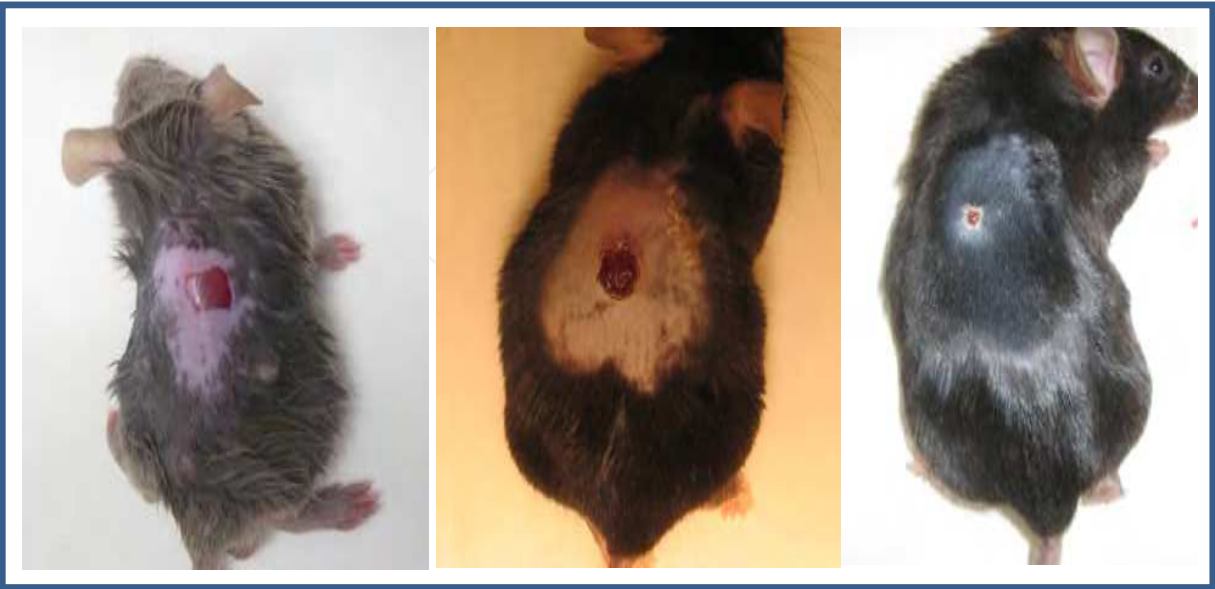


Fig. 3. Skin wound-healing during a 3-week period in etanercept-treated. DAB1J mice with collagen-induced arthritis

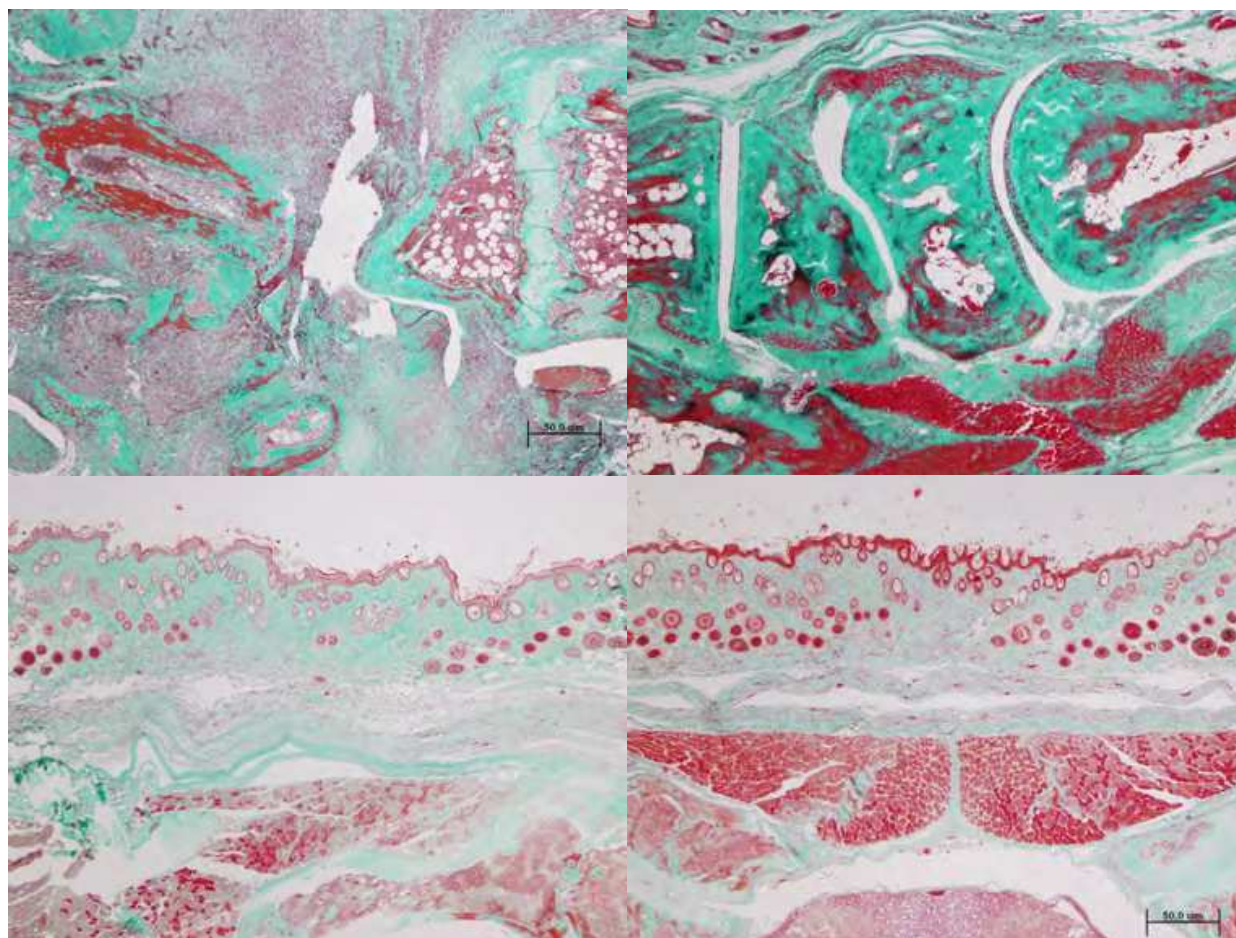


Fig. 4. Severe osteoarticular lesions in DAB1J mice with collagen-induced arthritis at day 15 (upper-left image). Absence of osteoarticular lesions in etanercept-treated mice (upper-right image). Skin wound-healing in DAB1J mice with collagen-induced arthritis at day 15. Note complete re-epithelization and skin appendages recovery in control (lower left image) and etanercept-treated (lower right image) mice [original magnification 4x, Masson Trichrome stain].

We could find no study on the effect of abatacept on surgical complications or wound healing. However, no associated postoperative complications were described in case reports on infections in patients who underwent surgery while receiving this drug (18).

Given the above data, and until new scientific evidence becomes available, it appears sensible to suspend these treatments before surgery, determining the pre-surgical interval according to the drug's half-life, only reintroducing them when the wound has healed with no complications. We propose the following recommendations (summarized in Table 2) for each drug.

- Infliximab: suspend treatment 6 weeks before surgery.
- Adalimumab: suspend treatment 2 weeks before surgery.
- Golimumab/Certolizumab: suspend treatment 4 weeks before surgery.
- Etanercept: suspend treatment 1 week before surgery.
- Anakinra: suspend treatment 24-48 hours before surgery.
- Rituximab: suspend treatment and delay surgery until serum levels of CD-19 B lymphocytes normalize (usually 3-6 months after last dose). Nevertheless, if urgent

- surgery is required or cannot be delayed due to the patient’s condition, surgery can be performed without normalization of these serum levels.
- Tocilizumab: suspend treatment 4 weeks before surgery but take into account that patients with infectious complications may not present with elevated CRP levels or fever.
 - Abatacept: suspend treatment 4 weeks before surgery.

BIOLOGICAL THERAPY	TIMING OF SUSPENSION BEFORE SURGERY
INFLIXIMAB	6 WEEKS
ETANERCEPT	1 WEEK
ADALIMUMAB (D2E7)	2 WEEKS
CERTOLIZUMAB	4 WEEKS
GOLIMUMAB	4 WEEKS
ANAKINRA (rHuIL-1Ra)	24-48 HOURS
RITUXIMAB	AFTER NORMALIZATION OF SERUM LEVELS OF CD-19 B LYMPHOCYTES (3-6 MONTHS)
ABATACEPT	4 WEEKS
TOCILIZUMAB	4 WEEKS

Table 2. Biological therapies and recommended timing of their suspension before surgery

Future therapies

Considerable clinical and experimental evidence suggests that various endogenous neuropeptides play a major role in educating our immune system to be self-tolerant. The fact that neuropeptides regulate various layers involved in the maintenance of tolerance, including regulation of the balance between pro-inflammatory and anti-inflammatory responses and between self-reactive Th1/Th17 cells and regulatory T cells, makes them attractive candidates for the development of novel therapies to treat autoimmune disorders such as RA. Vasoactive intestinal peptide is the paradigmatic immunomodulatory neuropeptide, but other neuropeptides possess similar properties, including melanocyte-stimulating hormone, urocortin, adrenomedullin, neuropeptide Y, cortistatin, and ghrelin (19). All have demonstrated marked beneficial effects in animal models of collagen-induced arthritis without affecting wound healing (20-23).

4. Conclusions

In the majority of cases, there are no well-designed studies to support clear recommendations on the perioperative management of patients with inflammatories arthropies receiving anti-rheumatic treatment, especially the new biological therapies. Available evidence suggests that methotrexate, anti-malarials, and gold compounds can be continued during surgery. However, leflunomide, sulfasalazine, azathioprine, and cyclosporine A should be withdrawn due to the increased risk of infection associated with

their use. With regard to the new biological therapies, it should be borne in mind that they inhibit cytokines and modulate cells that participate in the physiological response against infections and in wound-healing. Until data from well-designed prospective studies become available, it therefore appears prudent to withdraw these drugs before surgery for a time interval based on their pharmacokinetics.

5. Key points

1. In patients with inflammatory arthropies requiring orthopedic surgery, good clinical and biological control of the disease must be obtained before the intervention; therefore, coordination between orthopedic surgeon and rheumatologist is essential.
2. We must know the biological and non-biological therapies received by our patients for their perioperative management, thereby reducing the risk of infection and surgical wound-healing complications.
3. Methotrexate can be maintained during the perioperative period, but leflunomide, sulfasalazine, azathioprine, and cyclosporine A should be suspended, because available studies suggest their association with a higher infection risk.
4. T and B cells and cytokines (tumor necrosis factor-alpha, interleukin 6, and interleukin 1) are involved in anti-infection defense and surgical wound-healing and are modulated or blocked by biological therapies administered to patients with inflammatory arthropies.
5. There have been no clinical trials on surgical complications in patients with inflammatory arthropies receiving biological therapies; therefore, recommendations are based on retrospective and animal studies.
6. Retrospective studies suggest that infliximab and etanercept can be safely administered during the perioperative period to patients undergoing orthopedic surgery without increasing their risk of infection or wound-healing complications.
7. Murine studies suggest that collagenization of the surgical wound is improved by the inhibition of tumor necrosis factor-alpha with etanercept.
8. In patients under treatment with rituximab, it is recommendable to program the surgery once the serum count of CD-19 B lymphocytes has normalized; however, if this is not possible, its administration should not be considered a contraindication for the surgery.
9. Tocilizumab blocks IL-6, inducing the hepatic synthesis of C-reactive protein (CRP), which can mask the signs and symptoms of infectious post-surgical complications such as fever or elevated CRP.
10. Given the absence of high-quality scientific evidence, we recommend suspending biological therapies before the surgery in accordance with their half-life and not reintroducing them until the surgical wound has healed.

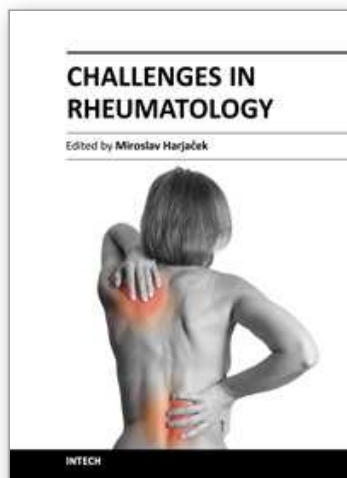
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Challenges in Rheumatology

Edited by Dr. Miroslav Harjacek

ISBN 978-953-307-848-9

Hard cover, 190 pages

Publisher InTech

Published online 22, December, 2011

Published in print edition December, 2011

Rheumatology is a subspecialty of medicine that focuses on the biology, cause, diagnosis and the treatment of a variety of musculoskeletal and other systemic diseases. The field of rheumatology is expanding rapidly and several very exciting developments have occurred during the recent years. Firstly, there has been a new dramatic understanding of the nature of inflammation and the possibility of specifically regulating the aberrant immune inflammatory response. Secondly, an understanding of pathogenesis has lead to the development of new, more targeted therapies. Challenges in Rheumatology has assembled an impressive group of international experts who have studied specific aspects of certain rheumatic diseases and have extensive experience either in pathophysiology, or with the in-depth diagnosis and/or management of rheumatic patients. They communicate their knowledge and experience to the reader in chapters that are conveniently organized as pathophysiology, clinical manifestations and diagnosis of selected rheumatic diseases, medical and perioperative orthopedic management, and the economic impact of rheumatic diseases. We hope that this book will help trainees become better physicians and scientists, and that it will help practicing rheumatologists to provide better care, and ultimately, improve the quality of life of our patients.

How to reference

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Juan Salvatierra Ossorio, Magdalena Peregrina-Palomares, Francisco O´Valle Ravassa and Pedro Hernandez-Cortes (2011). Perioperative Management of Non-Biological and Biological Therapies in Rheumatic Patients Undergoing Orthopedic Surgery, Challenges in Rheumatology, Dr. Miroslav Harjacek (Ed.), ISBN: 978-953-307-848-9, InTech, Available from: <http://www.intechopen.com/books/challenges-in-rheumatology/perioperative-management-of-non-biological-and-biological-therapies-in-rheumatic-patients-undergoing>

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