

Perioperative management of disease-modifying antirheumatic drugs and other immunomodulators

Moreira PM¹, Correia AM², Cerqueira M², Gil MF¹

¹ Anesthesiology, Hospital de Braga

² Rheumatology, Hospital de Braga

Correspondence to

Pedro Moreira (ORCID: 0000-0002-6227-9583)

E-mail: pedromoreiramf@gmail.com

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Abstract

Objectives: We aim to summarize the relevant evidence and provide guidance for perioperative management of disease-modifying antirheumatic drugs (DMARDs) and other immunomodulators used in the treatment of the various inflammatory rheumatic diseases in patients submitted to elective surgery.

Methods: This is a review article directed towards clinical practice, based on recent literature available in PubMed database, as well as guidelines published by Rheumatology Societies.

Results: Treatment with conventional DMARDs (methotrexate, hydroxychloroquine, sulfasalazine and leflunomide) can be continued perioperatively; targeted synthetic DMARDs should be suspended at least 3 to 7 days before surgery, depending on the drug, and restarted 3-5 days after the procedure, while biologic DMARDs should be withheld a dosing cycle prior to surgery and resumed at least 14 days after the procedure, with evidence of complete wound healing. In the case of Systemic Lupus Erythematosus (SLE), one should consider the severity of the condition to make the decision about discontinuing immunomodulators (mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus) as these should be continued in severe SLE because of the increased risk of life-threatening flares. The usual dose of glucocorticoids should be continued perioperatively; however, elective procedures with high-risk surgical site infection should be postponed in patients under ≥ 20 mg/day prednisone or equivalent until the inflammatory process is controlled with the minimum effective dose.

Conclusions: The perioperative management of patients with rheumatic disease under DMARDs or other immunomodulators is challenging but vital for achieving the best outcome possible. A multidisciplinary approach agreed upon by the anesthesiologist, surgeon and rheumatologist is the best strategy for success.

Keywords: Biological therapies; Immunosuppressants; Surgery ; Infectious and arthritis; DMARDs.

INTRODUCTION

Patients with inflammatory rheumatic disease are often considered for elective surgery, particularly orthopedic surgery. They may incur in high risk of perioperative complications because decompensation of the inflammatory condition can arise from surgical insult as well as from thoughtless suspension of immunosuppressive therapy. In the other hand, maintenance of immunosuppressive therapy carries a higher risk of surgical site infection and incomplete wound healing. In the case of orthopedic surgery, rehabilitation may be delayed and the final outcome compromised, hence close cooperation between the anesthesiologist, the surgeon and the rheumatologist is essential to outline the best strategy for any given patient, and any given procedure.¹⁻³

The core drug therapy of inflammatory rheumatic diseases is disease-modifying antirheumatic drugs (DMARDs), which distinguish themselves into three categories: conventional synthetic, biologic, and targeted synthetic DMARDs. They all earn the denomination of DMARD by exerting a beneficial impact on the course of the condition for at least one year through a reduction in joint inflammation, preventing articular structural damage and a sustained improvement in patient function.

Conventional synthetic DMARDs include methotrexate (MTX), leflunomide, sulfasalazine, and hydroxychloroquine. These drugs are used in the treatment of conditions such as Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), other spondyloarthritis, connective tissue diseases and as glucocorticoid (GC) sparing therapies. They suppress the inflammatory cascade and modulate the immune system through different mechanisms; this carries a possible increased risk of infection due to immunosuppression.^{1,4}

Other drugs with immunosuppressive action - immunomodulators - are employed mostly in inflammatory myopathies and connective tissue diseases, such as Systemic Lupus Erythematosus (SLE), as induction and as maintenance therapy. Mycophenolate mofetil (MMF), azathioprine, cyclosporine, and tacrolimus main action is through immune system modulation and consequent immunosuppression.

Biologic DMARDs are used in various rheumatic conditions such as RA, PsA, or other spondyloarthritis, and SLE. They are for the most part monoclonal antibodies that act at the molecular level against specific targets in the immunologic cascade.^{1,5} As they were only recently introduced in medical practice, literature regarding their use in the perioperative period is scant and in most of the cases, related to non-surgical patients.

Corticotherapy is especially effective initially in the course of the disease and periods of clinical exacerbation due to its rapid onset anti-inflammatory action. For this reason, glucocorticoids are frequently used in the various inflammatory rheumatic conditions.

The literature review presented aims to assist the management of DMARDs and other immunomodulators used in the treatment of the various rheumatic diseases in patients who will be submitted to surgery.

MATERIAL AND METHODS

A literature review was conducted to encompass the available evidence and latest guidelines about the perioperative management of DMARDs and other immunomodulators.

The search terms “perioperative management of antirheumatic”, “perioperative management of DMARDs” and “perioperative management of rheumatic disease” were used to screen the relevant literature in PubMed; entries were filtered by most recent (<10 years) and by language (Portuguese, Spanish or English). The presented filters were selected to include only publications that incorporate the latest evidence and that were understandable to the authors in their original writing. All the articles analyzed were literature reviews, guidelines, or recommendations from renowned international rheumatology societies, such as the American College of Rheumatology (ACR), the British Society of Rheumatology, and the German Society for Rheumatology. Most of the data presented in these publications resulted from studies conducted in patients with inflammatory rheumatic diseases, being rheumatoid arthritis the most mentioned one. The original articles were reviewed and referenced. Besides the PubMed search, a book edited by the Portuguese Rheumatology Society about the use and management of biological anti-rheumatic drugs was also consulted.

RESULTS

Corticotherapy

A retrospective study conducted in 10923 RA patients undergoing elective knee or hip replacement showed that the risk of infections leading to hospitalization within 30 days postoperatively was significantly higher in patients receiving 5–10 mg prednisone equivalent/day (odds ratio [OR] 1.32) and >10 mg/day (OR 2.10) compared to patients not receiving GC therapy.⁶⁻⁸ Another study showed that GC doses exceeding the 15 mg/day were

associated with an increased risk of any post-arthroplasty infection (OR 21.0). GC stress dosing is not recommended if corticotherapy is directed for the rheumatic condition and if the daily dose is ≤ 15 mg of prednisone or equivalent, as it doesn't seem to impact hemodynamic stability.^{2, 3, 7, 9-14}

Conventional synthetic DMARDs and other immunomodulators

In a randomized control trial (RCT) that included 388 patients with RA undergoing orthopedic surgery, patients were randomized to 3 groups: group A - continued MTX,; group B - withheld MTX and group C - never on the drug. Fewer infections and surgical complications were observed in patients who continued MTX (2%), and in the group of patients that stopped MTX 15% of complications were registered and 10 % in the group who never had taken MTX; six weeks after surgery there were no flares in group A, six flares in group B (8%), and six flares in group C (2.6%). This evidence demonstrates low infection risk and prevention of flares with continued therapy.^{7, 10, 15, 16}

Regarding the other csDMARDs studies are very limited with no RCTs evaluating the infection risk in the peri-operative period; nonetheless, ACR guidelines suggest continuing these medications through surgery.²

Evidence about MMF, azathioprine, cyclosporine, and tacrolimus is uncertain and mostly derived from transplant patients under immunosuppressive therapy. One Medicare study of 3339 solid organ transplant patients undergoing arthroplasty who were frequently treated with one or more immunosuppressors had a greater risk of pneumonia, sepsis and periprosthetic infection compared to controls (2.4% vs 1.0%), but the specific contribution of immunosuppression to this risk could not be determined.^{7, 11, 17}

We wish to highlight the recommendations for management of immunosuppression in SLE patients because this is a very challenging and complex disease with a multiplicity of manifestations that may be severe and therefore require a specific guided treatment. According to the 2017 ACR guidelines for perioperative management of antirheumatic medication, severe SLE is defined as the presence of severe organ involvement, such as lupus nephritis, central nervous system lupus, severe hemolytic anemia (Hb < 9.9 g/dL), thrombocytopenia (platelets <50,000/mL), vasculitis (other than mild cutaneous vasculitis) including pulmonary hemorrhage, myocarditis, lupus pneumonitis, severe myositis (with muscle weakness and not just increased muscle enzymes), lupus enteritis, lupus pancreatitis, cholecystitis, lupus hepatitis, protein-losing

enteropathy, malabsorption, myositis/orbital inflammation, severe keratitis, severe posterior uveitis/retinal vasculitis, severe scleritis, optic neuritis, anterior ischemic optic neuropathy, under induction or maintenance treatment.²

The ACR in their guidelines suggest that the risk of a life-threatening flare in a patient with severe SLE may be higher and more dangerous than a postoperative infection. In non-severe SLE, suspension of therapy should be considered 1 week before surgery and restarted 3 to 5 days after the procedure, in the absence of signs of infection or other surgical site complications. Evidence, albeit scarce, reports an increased risk of infection associated with this immunosuppressive therapy whilst an increased risk of flare with the suspension of therapy is not established. Accordingly, the morbidity associated with a surgical infection may be more important than a possible flare.^{1-3, 7, 10, 13}

The data regarding maintenance or suspension of immunosuppressors like MMF, azathioprine, cyclosporine, and tacrolimus during the perioperative period in other inflammatory rheumatic diseases other than SLE is scarce. Some authors recommend continuing these drugs before an elective surgery independently of the severity of the disease^{1, 15}; others recommend to withhold them between one week to 1-2 days before surgery in patients with mild disease.^{6, 7}

Biologic and targeted synthetic DMARDs

ACR Guidelines summarize the results of multiple studies that showed an increased risk of infection with biologic DMARDs use (OR ~1.5), including serious opportunistic infections, as expected due to its significant immunosuppressive effect, but without showing any differences between the various medications in this class.² Besides that, there are studies conducted in patients with RA under treatment with an anti-tumor necrosis factor (TNF) who underwent an orthopedical procedure that showed an increased infection risk in the peri-operative period with relative risks 2 to 21 times greater than patients who weren't under anti-TNF treatment^{6, 7, 15} To complement this data, there are also studies that highlight the benefit of suspending anti-TNF drugs before elective surgery, by showing a significant decreased risk of perioperative infections (OR 0.62).^{6, 18} Regarding flares in the post-operative period, a study with 120 patients with RA submitted to total knee or hip arthroplasty, where 51% were under biologic therapy, at 6 weeks post-surgery 63% had flared. The authors verified that patients who flared had a significantly higher disease activity at baseline and that numerically more patients who had a flare were under biologic DMARDs. Yet, stopping biologic DMARDs did not predict flares while a higher baseline disease activity predicted flaring by 6 weeks (OR 2.12, $p = 0.02$).^{19, 20}

The equivalent of two half-lives of the drug was previously recommended as the suspension period before surgery, even though the immunosuppressive effect of each drug is not comparable to its half-life. Because of that, guidelines now recommend a stopping time of one dosing cycle and that surgery should be scheduled at the end of a treatment cycle. Longer periods of suspension are not recommended because they don't further decrease the risk of infection and can trigger a flare requiring GC therapy.^{2, 3, 7, 11, 21}

Rituximab is an anti-CD20 monoclonal antibody with a particularly high risk of infection associated with its use due to hypogammaglobulinemia. Studies conducted in nonsurgical patients with RA and SLE showed a relative risk of serious infections with rituximab around 0.66 to 0.73, and a relative risk of all serious adverse events from 0.85 to 0.89, making rheumatology societies recommend to stop rituximab treatment 3 to 6 months before surgery and to schedule the surgery in month 7 after the last infusion, as ACR advocate.^{2, 6, 21}

Guselkumab and risankizumab are IL-23 inhibitors mostly used in the treatment of psoriasis and recently approved for PsA. In the case of guselkumab, the German Society for Rheumatology recommends a withholding period of 8 weeks before elective surgery.⁶ For risankizumab there is no data on the ideal timing for surgery but, according to its usual dosing schedule, procedures should be planned for at least 12 weeks after the last treatment.

Targeted synthetic DMARDs are recently developed drugs that inhibit small molecules involved in cellular signal transduction of hematopoietic, inflammatory and immunologic cascades. These include the Janus-kinase (JAK) inhibitors tofacitinib, baricitinib and upadacitinib, all approved for use in inflammatory rheumatic diseases.

Evidence indicates a particularly high risk of infection with tofacitinib use despite its short half-life, showing an increased infection risk among non-surgical patients who were taking the drug (OR 5.7 for all type of infections),²² whereby guidelines suggest withholding tofacitinib 7 days before surgery, restarting 3 to 5 days after the procedure.^{2, 7, 21} Evidence regarding upadacitinib and baricitinib is vacant; the recently updated recommendations of the German Society of Rheumatology suggests nonetheless stopping these drugs 3 to 4 days before surgery.⁶

DISCUSSION

Corticotherapy

Data on GC suggest that its use is associated with a higher risk of infection in total arthroplasties in a dose-dependent manner, whereby added dosing should be actively avoided. In patients with inflammatory rheumatic diseases under corticotherapy planned for elective surgery, the usual dose of GC should be maintained in the perioperative period. Elective surgeries with a high risk of infection, particularly those involving prosthesis implantation, in patients under ≥ 20 mg daily of prednisone or equivalent should be postponed until the inflammatory process is controlled with the minimum possible dose.

Conventional synthetic DMARDs and other immunomodulators

The literature about perioperative use of conventional synthetic DMARDs states that infection risk is not increased when treatment is maintained as usual and may be in fact decreased. The data obtained with MTX showed that patients who continued the drug during the perioperative period did not have an increased risk of infection, and that patients who discontinued MTX had an increased number of flares, showing that continuing the drug limits disease flares without compromising safety. For the remaining conventional synthetic DMARDs (leflunomide, hydroxychloroquine and sulfasalazine) there are no similar studies, however, and according to current recommendations, we conclude that these conventional DMARDs should be continued during the perioperative period.

We therefore recommend for most procedures that conventional synthetic DMARDs should be continued, with no dose reduction (Table I).

Evidence suggests that in severe SLE the risk of a life-threatening flare may be higher and more dangerous than a postoperative infection, and so immunosuppressive therapy should be continued. In the other hand, in non-severe SLE the morbidity associated with a surgical infection may be more important than a possible flare, thus we recommend that in that case immunomodulators should be withheld (Table II).

For patients with other rheumatic diseases who are receiving MMF, azathioprine, cyclosporine or tacrolimus, we suggest that management in the perioperative period may be analogous to the rule applied to SLE patients, suspending therapeutic in cases of non-severe disease manifestations.

In the event of an urgent or emergent procedure in a patient under conventional synthetic DMARDs, therapy should generally be continued, always in agreement with surgeon, rheumatologist and anesthesiologist and considering each patient and each procedure.

Biologic and targeted synthetic DMARDs

About biologic DMARDs, available studies have shown a general increased risk of infection associated with their use in the perioperative period. Despite the increase in the number of flares in patients who discontinued biological therapy prior to surgery, there was no association between the risk of flare and drug withdrawal, and it was found that the high activity of the disease in the preoperative period was the main determinant factor for the occurrence of a flare of rheumatic disease. In light of this evidence and guidelines available, biologic DMARDs should be withheld during one dosing cycle of each drug and restarted after indication of complete wound healing, at least 14 days after the procedure. For the targeted synthetic DMARDs, there isn't a general rule to drive the decision, with studies suggesting a longer period of suspension prior to surgery for tofacitinib (7 days) in comparison with the other JAK inhibitors concerning its infection risk.

In Table III we identify the distinct biologic and targeted synthetic DMARDs in use and the optimal timing for scheduling surgery.

Therapy with biologic DMARDs should be resumed at least 14 days after surgery, after the removal of sutures/staples and other foreign material, and in the absence of local or systemic infection, confirmed or suspected.^{2, 10, 21}

In case of urgent or emergent surgery in a patient under biologic or targeted synthetic DMARDs therapy one should assume a high risk of infection and withheld treatment immediately; therapy may be restarted when the same conditions for elective surgery are met.³

The potential benefit of suspending DMARD therapy is mostly due to an expected decrease of the risk of surgical site infection. By reason, that benefit may be questionable in procedures with negligible risk of infection. The decision should therefore be discussed and take into account aspects such as ongoing inflammatory activity and patient factors that increase the risk of infection.^{7, 9, 21} Modifiable risk factors for perioperative infection should also be addressed, such as glycemic and body temperature control, avoidance of blood transfusion, and smoking to improve outcome.¹¹ Reducing GC exposure in the preceding months of surgery has the best evidence for a beneficial impact on surgical outcome, hence the importance of planning surgery with the rheumatologist, as elective procedures should be scheduled when inflammatory activity is in remission and therapy is optimized.^{3, 9}

Management of anti-rheumatic medications in patients who undergo an elective surgery is a current theme and a part of the daily clinical practice, therefore of crucial importance to discuss. This review presents a recap of the most recent recommendations from the international rheumatology societies and the data presented in those guidelines about the studies conducted in rheumatic patients receiving conventional or biologic DMARDs in the peri-operative period. With this review we propose the adoption of similar attitudes or suspension times when indicated by clinicians of different specialties in order to standardize the care provided to patients with rheumatic diseases, minimizing the infection risk and the disease flares through surgery. We emphasize that there are only few studies regarding management of anti-rheumatic drugs during peri-operative time and RCTs are needed to clarify the scientific knowledge in this area. It is important to include in those studies patients with various rheumatic diseases beyond RA, to expand the type of surgeries not limiting to the orthopedical ones and to compare data about infection risk in patients who suspend and who continue all types of DMARDs, including the more recent ones. It is also essential to do this comparison taking into account other factors that may impact infection risk as disease activity, tobacco exposure, obesity and co-morbidities such as diabetes. The evidence is generally lacking, of low quality and, in some cases, is indirect, so the adopted strategy should ultimately be personalized and discussed with the rheumatologist, the anesthesiologist and the surgeon.

CONCLUSION

The perioperative management of patients with rheumatic disease is challenging but essential for the best surgical outcome. Therapy adjustment has the main goal of reducing the concerning higher risk of surgical site infection these drugs induce, so a standard approach regarding the suspension of therapy and the scheduling of the procedure is suggested according to the available literature. A multidisciplinary deliberation is well-considered with open communication between rheumatologist, anesthesiologist, and surgeon. In the absence of high-quality evidence, we advise a personalized approach for any given patient and procedure.

Tables and Figures

Table I. Conventional synthetic DMARDs

Conventional synthetic DMARDs	Dosing	Continue/Suspend
Methotrexate (Ledertrexato [®] , Metex [®] , Nordimet [®])	Weekly	CONTINUE
Leflunomide (Arava [®])	Daily	CONTINUE
Hydroxychloroquine (Plaquinol [®])	Daily	CONTINUE
Sulfasalazine (Salazopirina [®])	Daily or twice daily	CONTINUE

DMARDs: disease-modifying antirheumatic drugs

Table II. Immunosuppressors used in the treatment of SLE

Severe SLE	Dosing	Continue/Suspend
Mycophenolate mofetil (CellCept [®])	Daily or twice daily	CONTINUE
Azathioprine (Imuran [®])	Twice to thrice daily	CONTINUE
Cyclosporine (Sandimmun [®])	Twice daily	CONTINUE
Tacrolimus (Advagraf [®])	Twice daily	CONTINUE
Non-severe SLE	Dosing	Continue/Suspend
Mycophenolate mofetil (CellCept [®])	Twice daily	SUSPEND one week before surgery
Azathioprine (Imuran [®])	Twice to thrice daily	SUSPEND one week before surgery
Cyclosporine (Sandimmun [®])	Twice daily	SUSPEND one week before surgery
Tacrolimus (Advagraf [®])	Twice daily	SUSPEND one week before surgery

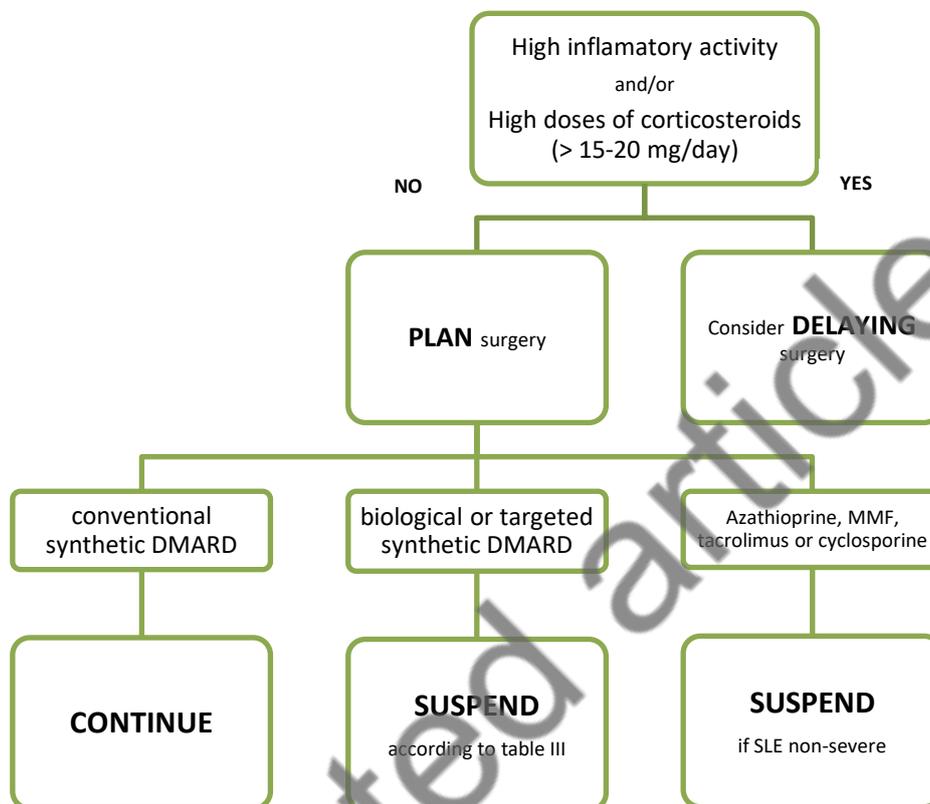
Table III. Biologic and targeted synthetic DMARDs

Biologic DMARDs	Dosing	Schedule surgery to (from last administration):
Adalimumab (Humira [®] , Idacio [®])	Every 2 weeks	Week 3
Etanercept (Enbrel [®])	Weekly or every 2 weeks	Week 2
Golimumab (Simponi [®])	Every 4 weeks (SC) or every 8 weeks (EV)	Week 5 (SC) or week 9 (EV)
Infliximab (Remicade [®] , Inflectra [®])	Every 4, 6 or 8 weeks	Week 5, 7 or 9
Abatacept (Orencia [®])	Monthly (EV) or weekly (SC)	Week 5 (EV) or week 2 (SC)
Certolizumab (Cimzia [®])	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Truxima [®] , MabThera [®])	2 doses 15 days apart every 4 to 6 months	Month 7
Tocilizumab (Roactemra [®])	Weekly (SC) or every 4 weeks (EV)	Week 2/3 (SC) or week 5 (EV)
Anakinra (Kineret [®])	Daily	Day 2
Secukinumab (Cosentyx [®])	Every 4 weeks	Week 5
Ixekisumab (Taltz [®])	Every 4 weeks	Week 5
Ustekinumab (Stelara [®])	Every 12 weeks	Week 13
Guselkumab (Tremfya [®])	2 doses 4 weeks apart, then every 8 weeks	Week 9
Risankizumab (Skyrizi [®])	2 doses 4 weeks apart, then every 12 weeks	*
Belimumab (Benlysta [®])	Every 4 weeks	Week 5
Targeted synthetic DMARDs	Dosing	Schedule surgery to:
Tofacitinib (Xeljanz [®])	Daily to twice daily	7 days after last dose
Upadacitinib (Rinvoq [®])	Daily	3/4 days after last dose
Baricitinib (Olumiant [®])	Daily	3/4 days after last dose

DMARDs: disease-modifying antirheumatic drugs

* No data yet on optimal timing of suspension before elective surgery.

Figure 1. Proposed algorithm of approach to rheumatic patient under DMARD's indicated for elective surgery.



DMARD: Disease-modifying Antirheumatic Drugs; SLE: Systemic Lupus Erythematosus;
MMF: Mycophenolate Mofetil

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