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A narrative review of the perioperative management of DMARDs

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INTRODUCTION

Disease-modifying antirheumatic drugs (DMARDs) have been used in clinical practice since the 1950s, when hydroxychloroquine, azathioprine and methotrexate were made widely available for clinical use.[1] Since the late 1990s, so called 'non-conventional DMARDs' have emerged, including biologic DMARDs such as tumour necrosis factor inhibitors (TNFi) and monoclonal antibodies, as well as targeted synthetic agents such as Janus kinase inhibitors (JAKi). The development of these agents was driven largely by the identification of key molecular mediators that drive autoimmune inflammatory conditions encountered in the fields of rheumatology, gastroenterology, dermatology and neurology.[2,3] Although collectively referred to as 'anti-rheumatic drugs', these medications have transformed the management of these autoimmune conditions.[4,5] Examples of therapeutic effects of these drugs include reduction of disease activity and structural joint damage in rheumatoid arthritis,[2,6] remission in patients with active ulcerative colitis,[7] and disease regression in psoriasis.[3] Common conditions for the use of DMARDs are presented in Table 1. Biologic agents now dominate the Australian Pharmaceutical Benefit Scheme charts for highest overall cost, and represent a significant proportion of the fastest growing drug costs.[8]

Table 1. Common conditions

Gastroenterology	Crohn's disease Ulcerative colitis
Dermatology	Psoriasis Cutaneous sarcoidosis
Neurology	Multiple sclerosis Myasthenia gravis
Rheumatology	Rheumatoid arthritis Systemic lupus erythematosus Ankylosing spondylitis Psoriatic arthritis Juvenile idiopathic arthritis

Increasing numbers of patients are presenting for both elective and emergency surgery taking conventional and non-conventional DMARDs. These operations can be related to their autoimmune condition, such as joint replacement in inflammatory arthropathies,[9] or abdominal procedures in inflammatory bowel disease,[10] but many patients present for surgery for unrelated conditions.

Perioperative management of patients receiving this diverse group of agents must navigate both consideration of the underlying disease and complications that may result from the actions of the medications themselves. There has long been a mechanistic concern that the immunosuppressive nature of DMARDs may increase the risk of postoperative complications, including infection and poor wound healing. However, temporary cessation of these medications in the preoperative period could lead to a disease flare, which might also increase perioperative complications and lead to worse outcomes overall.

Most international guidelines mainly cover the evidence for use of DMARDs in the context of managing the specific autoimmune conditions, with only a small section dedicated to perioperative considerations and recommendations. The limited guidelines which have focused on the perioperative management of DMARDs only cover specific conditions or surgical procedures.

We aim to present a narrative review of the existing guideline literature on the perioperative management of DMARDs, highlight discrepancies between guidelines, and identify controversies in the recommendations. Evidence will be summarised by the three major drug groups: i) conventional DMARDs, ii) biologic DMARDs, and iii) targeted synthetic DMARDs, with consideration given to the underlying pathologies and potential surgical interventions.

EXISTING GUIDELINES

A total of 25 international guidelines were identified from a search of Ovid Medline, Google Scholar, and Guidelines International Network between 2010 and 2023 (Table 2). While corticosteroids are a mainstay treatment for many autoimmune conditions, this review will focus exclusively on DMARDs. Additionally, this review will not cover the use of biologic agents as they apply to the treatment of cancer. Guideline recommendations on the perioperative management of this group of medications are summarised below.

Table 2. Guidelines

YEAR	TITLE & PROFESSIONAL ASSOCIATION
Gastroenterology	
2023	Korean clinical practice guidelines on biologics and small molecules for moderate-to-severe ulcerative colitis *Korean Association for the Study of Intestinal Diseases*
2021	Preoperative Management of Gastrointestinal and Pulmonary Medications *Society for Perioperative Assessment and Quality Improvement*
2020	ECCO Guidelines on Therapeutics in Crohn's Disease: Surgical Treatment *European Crohn's and Colitis Organisation*
2019	ACG Clinical Guideline: Ulcerative Colitis in Adults *American College of Gastroenterology*
2019	British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults *British Society of Gastroenterology*
Dermatology	
2020	British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update *British Association of Dermatologists*
2019	Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics *American Academy of Dermatology, National Psoriasis Foundation*
2016	From the Medical Board of the National Psoriasis Foundation: Perioperative management of systemic immunomodulatory agents in patients with psoriasis and psoriatic arthritis *National Psoriasis Foundation*
2016	British Association of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016 *British Association of Dermatologists*
Neurology	
2022	Preoperative Management of Medications for Neurologic Diseases *Society for Perioperative Assessment and Quality Improvement*
Rheumatology	
2023	An Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis *Australia & New Zealand Musculoskeletal Clinical Trials Network, The Australian Rheumatology Association, Cochrane Musculoskeletal*
2023	Perioperative management of patients with inflammatory rheumatic disease. Updated recommendations of the German Society for Rheumatology *German Society for Rheumatology*
2022	Preoperative Management of Medications for Rheumatologic and HIV Diseases *Society for Perioperative Assessment and Quality Improvement*
2022	Preoperative evaluation and perioperative management of patients with rheumatic diseases *UpToDate®*
2022	2022 American College of Rheumatology/ American Association of Hip and Knee Surgeons Guidelines for the Perioperative Management of Antirheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroscopy *American College of Rheumatology, American Association of Hip and Knee Surgeons*
2022	Perioperative management of disease-modifying antirheumatic drugs and other immunomodulators *Portuguese Society of Rheumatology*
2021	Recommendations for psoriatic arthritis management: A joint position paper of the Taiwan Rheumatology Association and the Taiwanese Association for Psoriasis and Skin Immunology *Taiwan Rheumatology Association, Taiwanese Association for Psoriasis and Skin Immunology*
2019	Clinical Practice Guidelines. Management of Rheumatoid Arthritis *Malaysian Society of Rheumatology, Ministry of Health, Academy of Medicine Malaysia*
2019	The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis *The British Society for Rheumatology*
2019	2018 update of the APLAR recommendations for treatment of rheumatoid arthritis *Asia-Pacific League of Associations for Rheumatology*
2017	BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs *The British Society for Rheumatology, British Health Professionals in Rheumatology*
2017	2016 updated Thai Rheumatism Association Recommendations for the use of biologic and targeted synthetic disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis *Thai Rheumatism Association*
2015	2014 Update of the Consensus Statement of the Spanish Society of Rheumatology on the Use of Biological Therapies in Rheumatoid Arthritis *Spanish Society of Rheumatology*
2013	Recommendations for using TNFα antagonists and French Clinical Practice Guidelines endorsed by the French National Authority for Health *French National Authority for Health*
2012	Canadian Rheumatology Association Recommendations for the Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs: Part II Safety *Canadian Rheumatology Association*

ECCO: European Crohn's and Colitis Organisation; ACG: American College of Gastroenterology; AAD: American Academy of Dermatology; NPF: National Psoriasis Foundation; HIV: human immunodeficiency virus; DMARD: disease-modifying antirheumatic drugs; APLAR: Asia-Pacific League of Associations for Rheumatology; BSR: British Society for Rheumatology; BHPR: British Health Professionals in Rheumatology; TNFα; tumour necrosis factor alpha.

CONVENTIONAL DMARDS

Conventional DMARDs exert their effects on the inflammatory cascade through a range of mechanisms, leading to a broad array of anti-inflammatory and immunomodulatory effects. Table 3 presents mechanistic-focused categories of current DMARDs and specific medications within each group.

Table 3. Categories of conventional DMARDs

Antimetabolites	methotrexate, 6-mercaptopurine, azathioprine, thioguanine, mycophenolate, leflunomide
Antimalarials	hydroxychloroquine
Aminosalicylates	sulfasalazine, mesalazine
Calcineurin inhibitors	ciclosporin, voclosporin, tacrolimus

DMARDs: disease-modifying antirheumatic drugs.

Methotrexate and other antimetabolites

Antimetabolites exert their effect by preventing cell replication, though the exact mechanisms by which these agents dampen the autoimmune response is still unclear.[11] Methotrexate and the thiopurines (azathioprine, 6-mercaptopurine, and thioguanine) are the main antimetabolites used in clinical practice for autoimmune disease. These medications act to inhibit nucleotide synthesis by enzyme inhibition, and some, like the thiopurines, also inhibit lymphocytes.[12]

Antimetabolite DMARDs are used for a wide range of autoimmune diseases including rheumatoid arthritis and inflammatory bowel disease.

Of the 25 reviewed guidelines, 14 discuss the use of methotrexate in the perioperative period. All 14 guidelines recommend continuing methotrexate in the perioperative period,[9,10,13-24] as studies have demonstrated no increase in postoperative complications following abdominal or orthopaedic surgery with continuation, noting that most published data is for patients taking low dose methotrexate (<15 mg/week).[25-35] Six of the 14 guidelines recommend temporary cessation for patients at risk of poor wound healing, however this recommendation appears to be based on expert opinion.[9,14-18] The German Society for Rheumatology recommend that patients taking high dose methotrexate (>20 mg/week) be given a temporary dose reduction perioperatively, given the limited evidence of safety in these patients.[18]

Five guidelines recommend perioperative continuation of thiopurines,[10,15,23,24,36] as studies have shown no increased risk of postoperative infection,[37,38] though two rheumatology guidelines recommend withholding thiopurines for 1-2 days prior to surgery based primarily on expert opinion.[18,39]

Despite conflicting data regarding risk of postoperative infection with continuation of leflunomide in the perioperative period,[40-43] guidelines still recommend its continuation in this period.[9,15,18-22] In patients where there is concern for increased risk of postoperative infection, such as prior prosthetic joint infection, washout procedures to facilitate accelerated drug elimination, or withholding the medication prior to elective surgery may be considered.[9,15,18,20]

Hydroxychloroquine

Hydroxychloroquine inhibits the activation of Toll-like receptors on the surface of endosomes, suppressing production of tumour necrosis factor and reducing the release of pro-inflammatory cytokines.[44] It is a first-line treatment for systemic lupus erythematosus (SLE) and is also used in rheumatoid arthritis and antiphospholipid syndrome. Seven of the reviewed guidelines explored the perioperative management hydroxychloroquine, and whilst there is little safety data on perioperative continuation of hydroxychloroquine, all guidelines recommend continuation, especially given its half-life of 45-50 days, except where there is a history of severe or recurrent infection, or QT interval prolongation.[9,15,18-22]

Sulfasalazine

The mechanism of action of sulfasalazine and other aminosalicylates is not known, but is thought to involve inhibition of cytokine synthesis and T-lymphocyte proliferation, as well as inhibition of leukotriene and prostaglandin synthesis through cyclooxygenase and lipoxygenase.[45]

Aminosalicylates are used in inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Guidelines recommend that aminosalicylates are continued perioperatively.[15,18]

Cyclosporine and tacrolimus

Cyclosporine and tacrolimus are calcineurin inhibitors and used mainly in solid organ transplantation. Their use in autoimmune disease is limited to being a third- or fourth-line agent, due to the risk of nephrotoxicity with long-term use. Calcineurin inhibitors impair the transcription of cytokines, in particular interleukin-2 (IL-2) and tumour necrosis factor (TNF).

Guidelines recommend perioperative continuation based on safety data from the gastroenterology and neurology populations.[13,15,17,22,45]

Patients with systemic lupus erythematosus

Perioperative management of people with SLE is complex. The American College of Rheumatology (ACR) and American Association of Hip and Knee Surgeons (AAHKS), UpToDate® and Society for Perioperative Assessment and Quality Improvement (SPAQI) recommend differential medication management based on disease severity. For people with non-severe SLE (based on an absence and low risk of clinical and/or serological flares), guidelines recommend withholding SLE medications for 1 week preoperatively including mycophenolate mofetil, mycophenolic acid, cyclosporine, mizoribine, azathioprine and tacrolimus.[9,19,22] In practice however, if a patient's disease is difficult to control, specialists may elect to continue these medications. For people with severe SLE (e.g. frequent flares, haemolytic anaemia, vasculitis, severe organ impairment, or multiorgan involvement), guidelines recommend continuation of these medications.[9,19,22,23]. However, patients at high risk of postoperative infection (e.g. history of recurrent or severe infection, such as prosthetic joint infections or sepsis), and with stable disease for more than six months, sometimes have medications withheld. Even in these high risk situations though, hydroxychloroquine and methotrexate are often continued.[9] Due to the wide range of disease severity and often complex decision-making required in this cohort, consultation with a rheumatologist is mandatory.

BIOLOGIC DMARDS

Biological products are isolated from living cells or tissues in humans, animals, or microorganisms.[46,47] Biologic DMARDs are currently used to modulate the immune system through three main mechanisms[48]:

1. Inhibition of cytokine function
2. Inhibition or depletion of lymphocytes
3. Inhibition of the complement system

Biologic DMARDs work through a variety of inhibitory pathways. These medications are collated by their general and specific pathways and targets, in Table 4.

Table 4. Categories of biologic DMARDs

Mechanism of action	Example medications
Inhibition of cytokine function	
TNF inhibitors	adalimumab, certolizumab, etanercept, golimumab, infliximab
BlyS-specific inhibitor	belimumab
IL-1 inhibitors	anakinra, canakinumab, rilonacept
IL-6 inhibitors	tocilizumab, sarilumab, satralizumab
IL-17 inhibitors	brodalumab, ixekizumab, secukinumab
IL-23 inhibitors	guselkumab, risankizumab, tildrakizumab, ustekinumab (IL-12/IL-23 inhibitor)
IFNAR1 inhibitor	anifrolumab
Inhibition or depletion of lymphocytes	
CD20 inhibitors	rituximab, ocrelizumab, ofatumumab, ublituximab
CD19 inhibitor	inebilizumab
CD52 inhibitor	alemtuzumab
CD80/86 inhibitor	abatacept
Integrin inhibitors	vedolizumab, natalizumab
Inhibition of the complement system	
C5 inhibitor	eculizumab

DMARDs: disease-modifying antirheumatic drugs; TNF: tumour necrosis factor; BlyS: B-lymphocyte stimulator; IL: interleukin; IFNAR1: interferon alpha and beta receptor subunit 1.

Inhibitors of cytokine function

Cytokines are small proteins released from a variety of cells and form an integral part of cell signalling and the immune response. Examples of cytokines relevant to biologic DMARDs are tumour necrosis factor (TNF), B-lymphocyte stimulator (BlyS), interleukins (IL), and interferons. Anti-cytokine medications are commonly the first biologic DMARD class used for many rheumatological, gastrointestinal and dermatological conditions, and they function to reduce the autoimmune-mediated inflammatory response that characterise these conditions.

Infliximab is a TNF inhibitor (TNFi) and was the first biologic DMARD approved for use by the United States of America (US) Food and Drug Administration (FDA) in 1998[49] and in Australia by the TGA in 2000.[50] Since then, four additional TNFi have been developed. Infliximab, adalimumab, certolizumab, and golimumab are monoclonal antibodies against TNF, and etanercept is a fusion protein of IgG and TNF receptor fragments.[51] TNFi agents exert their effect by neutralising TNF, a key proinflammatory cytokine released by white blood cells. TNFi are used in inflammatory bowel disease, rheumatoid arthritis, and psoriasis. Additionally, belimumab is a BlyS, belongs to the TNF superfamily and is an inhibitor used in SLE to try and target the B-cell dysfunction commonly observed with the disease.

IL inhibitors such as anakinra (first approved by the FDA in 2001) inhibit ILs or IL receptors. These are used in rheumatoid arthritis, giant cell arteritis, systemic sclerosis, psoriasis, and inflammatory bowel disease.

Finally, in the last two years, the US and Australia have both approved anifrolumab, an interferon receptor inhibitor for the treatment of moderate to severe SLE.

There is mainly low quality, conflicting evidence regarding whether cytokine inhibitors should be continued perioperatively. As a result, international organisations have produced different recommendations assessing similar evidence. When organisations recommend perioperative cessation, they generally recommend that surgery be scheduled at or after the next dose of biologic was to be given, or after 3-5 half-lives, to allow sufficient time for washout of the biologic agent prior to surgery. Dosing cycles are dependent on the drug, indication, and patient.

Gastroenterology

The European Crohn's and Colitis Organisation (ECCO) recommends that TNFi and IL inhibitors be continued in patients with Crohn's disease undergoing abdominal surgery, even with primary anastomosis.[36] This recommendation is based on a multicentre prospective cohort study and meta-analysis demonstrating no increase in surgical site infection or anastomotic leak.[52,53]

Conversely, the British Society of Gastroenterology recommend that TNFi be discontinued, where possible, prior to elective surgery, and ask that clinicians consider the presence of fistulae, abscesses, anaemia, low albumin and corticosteroid use when deciding[10]. These recommendations are based on six positive meta-analyses and systematic reviews (versus one negative review[54]) showing greater risk of infectious complications with biologic continuation.[37,55-59] The SPAQI also recommend withholding TNFi for at least one dosing interval before surgery (more so for patients with Crohn's disease[10,60]), but base their recommendations on the American College of Rheumatology (ACR) guidelines.[23]

Similarly, Korean guidelines recommend that patients with moderate-to-severe ulcerative colitis continue TNFi[61] based on previously cited studies, and other retrospective data demonstrating no increase in postoperative complications.[58,62-66]

Dermatology

The British Association of Dermatologists (BAD) recommend perioperative cessation of biologic agents[67] to reduce the risk of postoperative infection, while American and Taiwanese guidelines recommend an approach based on surgical invasiveness, with cessation for moderate-to-high risk procedures, but continuation for low risk procedures.[13,17,68] It is important to note however, that most of the studies relied upon in dermatology were underpowered and recommendations ultimately relied on expert opinion and concern for disease flare. Consideration of commencement of methotrexate or cyclosporin in the perioperative period has also been suggested to prevent disease flare when biologics are withheld.[13,17]

Rheumatology

All rheumatology guidelines recommend that TNFi be withheld perioperatively in patients with inflammatory arthritis[9,16,18,19,21,22,39,69-73] with the exception of one.[20] This latter guideline recommends considering temporary cessation only if individuals are at a high risk of infection, or if the impact of infection would be severe. As with dermatology, most studies used to form the guidelines have been of low quality, without adjustment for known confounders, and have unsurprisingly produced conflicting results. Several studies and meta-analyses demonstrate an increase in risk of infections if continued in the perioperative period.[74-81] Others have demonstrated no significant association with postoperative complications.[29,82-89] Studies of length of cessation prior to surgery have failed to show any outcome differences.[90,91]

There is limited evidence regarding the perioperative management of IL inhibitors. Registry data has demonstrated no association between biologic washout time and postoperative complcations,[92] yet nine guidelines recommend that IL inhibitors be withheld.[9,18,22,23,39,69,70,73,93]

The ACR and AAHKS guidelines state that if disease is difficult to control, and that symptomatic relief from the surgery outweighs the risk of postoperative infection, rheumatologists may elect to continue TNFi and IL inhibitors.[9]

Inhibition or depletion of lymphocytes

These biologic agents inhibit or deplete the number of lymphocytes by using inhibitors of lymphocyte surface antigens, which are labelled according to cluster of differentiation (CD) such as CD20, or the integrin transmembrane receptors.

Rituximab is a monoclonal antibody against CD20 that was first approved for use by the FDA in non-Hodgkin's lymphoma in 1997, and later for rheumatoid arthritis in 2006. CD20 inhibitors are now used in rheumatoid arthritis, some forms of vasculitis, SLE, antiphospholipid syndrome, multiple sclerosis and myasthenia gravis. There are a number of other lymphocyte antigenic targets used for drugs in current use including CD19 (inebilizumab), CD52 (alemtuzumab) and CD80/86 (abatacept). The first two are used primarily for neurological disorders while abatacept is used for rheumatoid and psoriatic arthritis.

Integrin, the transmembrane receptor, provides another fruitful target for inhibition. Vedolizumab and natalizumab are receptor antagonists used for inflammatory bowel disease and multiple sclerosis.

Rheumatology

For patients with inflammatory arthritis, guidelines have generally recommended perioperative cessation of biologics including rituximab and abatacept for at least one dosing interval prior to elective surgery,[9,19,21,22,39,70,73] with the caveat that rheumatologists may elect to continue biologics if the risk of disease flare outweighs the risk of postoperative infection.[9]

Given the paucity of quality data, and long rituximab dosing interval of 4-12 months, other guidelines recommend just scheduling surgery 3-4 months following the last infusion, but at least four weeks prior to the next infusion.[18,20,22] One guideline also suggests to consider measuring and treating preoperative immunoglobulin levels if required, particularly in patient populations with a high risk of infection or history of recurrent infections, as low immunoglobulin levels increase the risk of infection.[93]

Neurology

Rituximab, ocrelizumab and ofatumumab are used in multiple sclerosis (MS) and myasthenia gravis, and alemtuzumab is used in MS. SPAQI recommend continuing these perioperatively,[24] but do concede that the recommendation is based on expert opinion due to limited available evidence.

On the other hand, a few studies have demonstrated an increased risk of MS relapse within 6 months of natalizumab discontinuation[94,95] so SPAQI recommend continuing natalizumab perioperatively with input from the prescribing neurologist.[24]

Gastroenterology

Perioperative continuation of vedolizumab did not increase postoperative infectious complications following colectomy in UC patients in smaller studies,[96-98] so ECCO recommend continuation,[36] but larger studies are needed to validate this. SPAQI recommend withholding vedolizumab and natalizumab for at least one dosing interval prior to surgery, however this recommendation was based on the ACR recommendations on ustekinumab.[23]

SLE

Patients with well controlled, non-severe SLE are sometimes permitted to cease biologic treatments such as belimumab, with close monitoring for disease flare, but for patients with poorly controlled or severe SLE, it is often recommended to continue biologic treatment, in consultation with the patient's rheumatologist.[9,22,39]

Should rituximab be withheld in patients who have severe SLE, there are concerns regarding risk of disease flare and organ damage, particularly as the medication has a long dosing interval. Therefore, rituximab should not be withheld in patients with severe SLE, and instead, surgery should be scheduled towards the end of the dosing cycle in month five or six.[9,22]

Inhibition of the complement system

Finally, eculizumab, an inhibitor of complement protein C5 is used in neuromyelitis optica and some variants of myasthenia gravis.

SPAQI recommend continuing eculizumab perioperatively,[24] based mostly on expert opinion.

TARGETED SYNTHETIC DMARDS

The third category of DMARDs are targeted synthetic drugs which inhibit intracellular enzymes that form part of the transduction pathway for the proinflammatory response, in particular the cytokine inflammatory response. While fewer in number than the biologic agents, categories of synthetic DMARDs are presented below, in Table 5.

Table 5. Categories of targeted synthetic DMARDs

JAK inhibitors	baracitinib, tofacitinib, upadacitinib, deucravacitinib
PDE4 inhibitor	apremilast

DMARDs: disease-modifying antirheumatic drugs; JAK: Janus kinase; PDE4: phosphodiesterase-4.

JAK inhibitors

Janus kinases (JAK) are intracellular tyrosine kinases that act as second messengers from the cell surface cytokine receptors. JAK inhibitors (JAKi) are simple chemical structures with highly specific targets, effectively acting as inhibitors of cytokine pathways and, unlike biologics, can be given orally. They have relatively quick onset times and short half-lives, meaning they are often taken once or twice daily. JAK inhibitors are used in patients with rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, ulcerative colitis and atopic dermatitis.

Guidelines suggest ceasing JAK inhibitors at least three days prior to surgery to allow for washout[9,17-19,22,73] Previously, guidelines recommended withholding tofacitinib for seven days prior to surgery due to concerns about the long duration of immunosuppression, despite its short serum half-life[21,39,99]. However, recent evidence has shown a more rapid reversal of tofacitinib's immunosuppressive effects following interruption of therapy, resulting in a change in recommendation.[100] If JAK inhibitors are not withheld, these agents may diminish or eliminate the acute phase response, so it is important to closely monitor for infection, even if inflammatory markers remain within normal limits.

PDE4 inhibitors

Apremilast is a phosphodiesterase-4 (PDE4) inhibitor that leads to an increase in intracellular cyclic adenosine monophosphate (cAMP), and subsequent decrease in both immune cell activation and proinflammatory cytokines. It is used in patients with psoriatic arthritis, plaque psoriasis and oral ulcers associated with Behcet's disease.

Of the 25 reviewed guidelines, five discuss the perioperative management of apremilast. One guideline is not able to make any firm recommendations,[17] stating there is insufficient evidence. The remaining four guidelines recommend continuation of apremilast perioperatively, unless the patient's past history indicates an increased risk of postoperative infection.[9,18,19,22]

RECOMMENCEMENT OF THERAPY

Following surgery, all guidelines are conservative in recommencing biologic and JAK inhibitor therapy. For example, the American College of Rheumatology recommends that biologics should only be restarted "once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days after surgery".[9] These recommendations are however, based on low quality studies and expert opinion.

While there is likely an optimal duration of interruption to therapy that provides a balance between a lower risk of infection, good wound healing, and reducing the risk of disease flare, the current literature provides insufficient evidence to make definitive recommendations.

CONTROVERSIES

Research into the optimal perioperative management of biologic and targeted synthetic DMARDs significantly lags against the pace of their rapid development and widespread therapeutic adoption. The knowledge gap is reflected by the paucity of available evidence and the varied recommendations seen between guidelines and indications.

For example, the American College of Rheumatology recommends that patients with conditions other than SLE, undergoing total hip or knee replacement surgery, should have surgery scheduled at the end of a biologic DMARD dosing cycle, with the next dose of the biologic withheld. This recommendation is based on low quality studies and expert opinion.

However, the European Crohn's and Colitis Organisation (ECCO) guidelines do not recommend cessation of biologic DMARDs for patients with Crohn's disease having abdominal surgery, based on a meta-analysis of 18 non-randomised studies and a prospective cohort study.[52]

These guidelines are both disease-specific and surgery-specific. It remains unclear whether the patient taking infliximab for rheumatoid arthritis having abdominal surgery should follow the rheumatology advice to stop infliximab, or the gastroenterology advice to continue infliximab, or conversely, which guideline the patient taking infliximab for Crohn's disease having a joint replacement should follow. Since both guidelines are based on low quality evidence, it is difficult for the perioperative medicine practitioner to make much sense of the current evidence base.

Management of these patient cohorts have not featured prominently in the emerging field of perioperative medicine. This is likely due to a combination of factors, including the perceived complexity of these patients, lack of familiarity with novel immune medications, and perhaps because other comorbidities (such as cardiovascular issues) command more attention. Regardless of the reasons, raising the profile of these patient groups is important to ensure that the perioperative risks they face can be minimised through individualised perioperative management and promotion of new research to investigate best practice.

SURGICAL PROCEDURES

The risk of infection and poor wound healing varies with the surgical procedure being undertaken. There is a clear difference in risk between a patient undergoing a gastroscopy or small bowel biopsy, compared to a patient having an oesophagectomy or bowel resection. Yet, most guidelines that advocate for perioperative cessation of DMARDs, do not clearly outline which surgical procedures constitute major surgery with a substantial risk of postoperative infection and/or wound breakdown. There is certainly no high-quality evidence to guide these decisions. Three guidelines have attempted to define high surgical risk with statements such as “surgical procedures during which the respiratory, gastrointestinal, or genitourinary tract is entered” or where “there is a major break in sterile technique, pillage from the gastrointestinal tract, or an active infection or devitalised tissue”.[15,17,68] One guideline recommends the consideration of prophylactic antibiotics should the patient undergo high-risk or emergency surgery.[71] Another guideline recommends prophylactic antibiotics in oral surgery due to the increased risk of bacterial contamination.[18] However, mitigation strategies against postoperative infection when immunomodulatory drugs are continued (such as prolonged antibiotic use, using an alternative surgical approach, or selectively improving the immune response to infection) have not been investigated, to our knowledge.

The guidelines discuss patients who are generally at an increased risk of infection, however, do not further stratify against specific factors such as age, active disease, tobacco exposure, obesity, nutritional statues, diabetes, vascular disease, or other comorbidities. These factors also need to be taken into consideration when deciding whether to continue or withhold their DMARDs.

PATIENT-CENTRED, MULTIDISCIPLINARY, PERIOPERATIVE MANAGEMENT

Given the uncertainty about best practice in DMARD management, and the potential significance of outcomes relating to underlying disease control or surgical risk, it is important that perioperative decision-making involves the patient and their treating specialists. Patients taking these medications may have experienced life-altering changes in their chronic and often debilitating disease and are likely to be motivated and engaged with their healthcare providers.

Decisions should consider the severity of their underlying disease and any comorbidities that may increase the risk of infection or wound breakdown including diabetes, vascular disease, obesity, and tobacco exposure. Informed consent should consider the potential risk of disease flare, postoperative infection and poor wound healing, as well as a presentation of the limited evidence base and expert opinions about optimal medication management and timing of surgery. Patients and practitioners may benefit from the use of tools such as a likelihood-consequence matrix to develop a shared understanding, not only of technical risks, but outcomes that each party considers important.

The specific input of treating specialists for the underlying disease should be sought, especially for complex patients, as they likely have unique knowledge of the individual patient, their disease course over an extended period, and likely have experience managing similar patients in the perioperative period. These discussions are best had early in the perioperative journey, ideally at the time that surgery is first contemplated, providing sufficient time to optimise, plan and consider the implications of changes to the management of these complex chronic conditions, including timing of surgery in relation to drug administration cycles.

CONCLUSION

In summary, **conventional** DMARDs can be continued perioperatively for most patients, with a small number of exceptions (e.g. a history of poor wound healing). For **targeted** synthetic DMARDs, apremilast can be continued in the perioperative period for most patients, whilst JAK inhibitors should be ceased three days prior to surgery, for most patients.

Perioperative management of **biologic** DMARDs remains an area with large knowledge gaps and significant disagreement between expert groups. Rheumatology and dermatology guidelines lean towards withholding biologics perioperatively, neurology guidelines advise continuation, and gastroenterology guidelines are conflicting.

As we have highlighted, the conflicting advice between guidelines can be attributed to the heterogeneity of patient populations, wide variety of therapeutics being studied, range of surgical procedures being studied, and the paucity of high-quality data to guideline decision making. In this context, individualised decisions made in consultation with treating specialists that consider the unique circumstances of the patient, the severity of their underlying condition and the specifics of the surgical intervention will remain paramount.

Additional studies are needed to investigate the optimal management of biologic DMARDs in the perioperative period, however, we acknowledge the challenges of conducting research on this heterogeneous group of drugs, patients and pathologies. While existing guidelines typically reflect the interests of specific cohorts of patients with unique disease pathologies, it is hoped that accumulated observational and trial data will create the opportunity to undertake a more systematic review and develop broader multidisciplinary consensus guidelines to inform the perspective of the perioperative medicine practitioner.

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