Management of Disease Modifying Anti-Rheumatic Drugs in the Peri-Operative Period

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Summary and Key Recommendations

Over the past 2 decades, new drug development for autoimmune inflammatory diseases including rheumatoid arthritis and related conditions, psoriasis and inflammatory bowel disease has been rapid. Many of these drugs, in particular biologic and targeted synthetic DMARDs, are associated with an increased risk of infection although whether this extends to post-operative infections including prosthetic joint infections is less clear. Data to support evidence-based decision making regarding the peri-operative management of DMARDs are limited and largely of low quality.

- It is advised to ensure a full drug history, including hospital prescribed injections and infusions, is taken from all patients as most new biologic DMARDs will not appear on GP prescription records. This should include all drugs received in the past 6 months where possible.
- It is currently recommended that patients can continue conventional DMARDs throughout surgery but should pause all biologic DMARDs at least 1 dosing interval prior to surgery. For some drugs this can be up to 3-6 months although most are dosed more frequently.
- Patients receiving new JAK inhibitors, a daily targeted synthetic DMARD, should hold this medication at least 1 week prior to surgery.
- Biologic DMARDs and JAK inhibitors can be restarted a minimum of 14 days after surgery once it is confirmed that there are no issues with wound healing and staples and sutures have been removed. They should NOT be administered in the setting of infection.
1. Introduction

Disease modifying anti-rheumatic drugs [DMARDS] are now the standard of care for many autoimmune inflammatory diseases such as rheumatoid arthritis [RA] and other inflammatory arthritides, connective tissue diseases including systemic lupus erythematosus [SLE], psoriasis and inflammatory bowel disease. Most patients with inflammatory arthritis will start DMARDs soon after diagnosis and will likely remain on these for the rest of their lives. Therefore, it is probable that patients with these conditions who require surgery will be receiving these drugs at the time surgery is planned. Many DMARDs are immunosuppressive and thus there is a concern whether continued DMARDs through the peri-operative period may increase the risk of post-operative infections, and particularly for patients undergoing orthopaedic procedures, prosthetic joint infections.

The aim of this chapter is to review the use of common DMARDs in the peri-operative period. Most of the evidence about DMARD use and surgical risk is based on studies in patients with RA undergoing elective orthopaedic procedures, the most common procedure in this patient group, and will be the focus of this chapter. It is not certain but is likely that the evidence from elective orthopaedic surgery can also be applied to other elective procedures and other conditions. The evidence in this chapter is not meant to represent specific treatment guidelines but will reference clinical guidelines where these exist. In all patients, individualised risk and decision making should take preference over strict guidelines. Management of DMARDs in non-planned or urgent surgeries will be discussed briefly towards the end of the chapter.

2. What are DMARDs?

The goal of treating RA is remission or low disease activity and DMARDs play an integral role in this treatment. DMARDs themselves represent a heterogenous group of medications which have the common feature of having been shown in clinical trials to slow or stop radiological damage. Successful treatment results in reduction in symptoms and joint inflammation as well as inhibition of bone and joint damage. In recent years, a treat-to-target approach, with the target being remission, has been adopted by the rheumatology community, whereby DMARDs are started as soon as possible after disease onset and escalated until disease control is achieved [1]. Once disease control is achieved, the DMARD is either maintained or in some patients, the dose may be tapered, but rarely discontinued unless adverse effects are experienced. DMARDs are now classed into 3 broad sub-categories: conventional synthetic [cs], biological [b] and targeted synthetic (ts) DMARDs (Table 1).

Conventional synthetic DMARDs include the commonly used drugs methotrexate (MTX), sulfasalazine, hydroxychloroquine and leflunomide. Methotrexate is recommended as the first line treatment for RA by the European League Against Rheumatism (EULAR) [1] and is one of the recommended first line treatments by the National Institute for Health and Care Excellence (NICE) [2]. Other drugs in this category used more often in other autoimmune inflammatory diseases included ciclosporin (psoriasis), 5-ASA/mesalamine (inflammatory bowel disease) and mycophenolate mofetil and azathioprine [connective tissue diseases]. The mechanism of action of these drugs in RA and related conditions is not always known, with many being repurposed from other conditions, but all are thought to be immunomodulatory and immunosuppressive to variable degrees.

In the early 2000s, the management of autoimmune inflammatory diseases such as RA underwent a revolution with the introduction of bDMARDs. Unlike csDMARDs, most bDMARDs have been developed specifically for RA and other autoimmune inflammatory diseases. They are protein-based compounds, largely monoclonal antibodies or recombinant receptor proteins, with specific cellular (such as CD20 on B-cells) or cytokine targets (such as tumour necrosis factor (TNF) and interleukin (IL-6)). They must be administered by subcutaneous or intravenous routes.
The first of these was infliximab, an anti-tumour necrosis factor (TNF) monoclonal antibody. Over the past 20 years we have seen an exponential growth in bDMARDs across indications, with >20 new biologic drugs targeted against several different cytokine and cell types (Table 1). The majority of these are licensed for rheumatoid arthritis, but over the last few years we have seen biologics specifically developed for ankylosing spondylitis [e.g. anti-IL17], psoriasis (e.g. anti-IL12/23) including psoriatic arthritis, inflammatory bowel disease [e.g. anti-α4β7 integrin] and SLE (e.g. anti-B-lymphocyte stimulator (BLys)). Unlike most csDMARDs, bDMARDs are classed as high-cost drugs and their use is regulated in the UK by NICE [3].

Table 1 Common Disease Modifying Anti-Rheumatic Drugs Used in the Management of Rheumatoid Arthritis and Other Autoimmune Inflammatory Diseases*

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Usual maintenance dose, route</th>
</tr>
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<tbody>
<tr>
<td><strong>csDMARDs</strong></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>15-25 mg weekly, PO or SC</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200-400 mg daily, PO</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>2 g daily, PO</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>20 mg daily, PO</td>
</tr>
<tr>
<td><strong>bDMARDs</strong></td>
<td></td>
</tr>
<tr>
<td>Tumour necrosis factor inhibitors</td>
<td></td>
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<tr>
<td>Adalimumab</td>
<td>40 mg weekly, SC</td>
</tr>
<tr>
<td>Etanercept</td>
<td>50 mg weekly, SC</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3 mg/kg 8 weekly, IV</td>
</tr>
<tr>
<td>Certolizumab-pegol</td>
<td>200 mg every 2 weeks, SC</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50 mg once monthly, SC</td>
</tr>
<tr>
<td><strong>Anti-B cell therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Rituximab [anti-CD20]</td>
<td>2*1000mg 2 weeks apart, every 6+ months</td>
</tr>
<tr>
<td>Belimumab [anti-BLyS]</td>
<td>Weight based dose once monthly, IV or 200mg once monthly, SC</td>
</tr>
<tr>
<td><strong>Anti-IL17</strong></td>
<td></td>
</tr>
<tr>
<td>Secukinumab</td>
<td>150-300mg monthly, SC</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>80 mg every 4 weeks, SC</td>
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<tr>
<td>Brodalumab</td>
<td>210 mg every 2 weeks, SC</td>
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<tr>
<td><strong>Anti-IL12/23</strong></td>
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<tr>
<td>Ustekinumab</td>
<td>45 mg every 12 weeks, SC</td>
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<tr>
<td><strong>Anti-IL23</strong></td>
<td></td>
</tr>
<tr>
<td>Guselkumab</td>
<td>100 mg every 8 weeks, SC</td>
</tr>
<tr>
<td><strong>Anti-IL6</strong></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>162 mg once weekly, SC or 8 mg/kg once monthly, IV</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>200 mg every 2 weeks, SC</td>
</tr>
<tr>
<td><strong>Anti-CTLA4</strong></td>
<td></td>
</tr>
<tr>
<td>Abatacept</td>
<td>125 mg once weekly, SC or weight based dose once monthly IV</td>
</tr>
<tr>
<td><strong>Anti-α4β7 integrin</strong></td>
<td></td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>108 mg every 2 weeks, SC or 300mg every 8 weeks, IV</td>
</tr>
<tr>
<td><strong>tsDMARDs</strong></td>
<td></td>
</tr>
<tr>
<td>Baricitinib</td>
<td>2-4 mg daily, PO</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>5 mg BD, PO</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>5mg-20mg daily P</td>
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This list is not exhaustive and drug development for autoimmune inflammatory diseases has been rapid over the past 10 years. A full medication list, including hospital prescribed injections or infusions, should be confirmed with the patient.

Most recently, tsDMARDS, have been approved, initially for RA but also now used in psoriatic arthritis and inflammatory bowel disease. Unlike bDMARDs, tsDMARDS are targeted oral medications. The current licensed therapies, baricitinib and tofacitinib, inhibit janus kinase [JAK inhibitors] and differ from bDMARDs in their daily oral formulation. Like bDMARDs, they are high-cost drugs and their use is regulated by NICE.

In 2018, NICE published updated guidelines for the management of RA [2]. These state that all patients with new RA should be treated initially with csDMARDs. Although there is a range of medications in this category, the majority of patients are started on MTX with a smaller proportion started on sulphasalazine [4]. Some patient, particularly those deemed to have risk factors for more severe disease, are started on a combination of csDMARDs, usually MTX plus hydroxychloroquine or less commonly MTX plus sulfasalazine. If the first csDMARD [or combination] is not effective or not tolerated, a second csDMARD will be substituted or added. For patients whose disease has not been brought under control with two csDMARDs, most will move onto a bDMARD. Biologic DMARDs are often used in combination with csDMARDs but never in combination with another bDMARD or tsDMARD, due to a concern about heightened infection risk [5]. Patients who do not respond to their first b/tsDMARD will tend to cycle through these two classes of DMARDs until disease control can be optimised.

Currently the majority of DMARDs are initiated by hospital specialists. Some csDMARDs, such as MTX maybe be prescribed subsequently in primary care under a shared care agreement with the hospital but b/tsDMARDs are exclusively prescribed by hospital doctors and as such will not usually appear on GP records in the UK or on repeat prescription lists; therefore all patients with an autoimmune inflammatory disease should be asked specifically for a full list of their medications from all sources. A special note should be made for the drug, rituximab. An anti-CD20 monoclonal antibody administered by intravenous infusion, this treatment temporarily but profoundly depletes a patient’s B-cells. The B-cell depletion is rapid, but the length of depletion is variable. The drug is usually administered at intervals no less frequent than 6-monthly, although some patients can go as long as a year before further rituximab is required due to prolonged effects. As the gap between infusions can be long in some patients, they may not consider it as one of their regular medications and should be directly asked.

In addition to DMARDs, it has been estimated that over 50% of patients with RA will also receive treatment with glucocorticoids [6]. Although the edict to try and minimise exposure to steroids remains true for RA, many patients will receive intermittent courses of steroids, often administered intramuscularly or intra-articularly for management of early disease activity until the effects of csDMARDs are realised or for treatment of disease flare.

3. Peri-operative risk of DMARDs

The main risks of joint arthroplasty include bleeding and infection, including surgical site infections [SSI] and other immediate post-operative complications such as catheter-related urinary tract infections; however the most feared risk is prosthetic joint infections, primarily due to Staphylococcus aureus. Although the absolute risk of prosthetic joint infection following joint arthroplasty is low, estimated to affect <2% of joint replacements [7] , numerically this still represents a significant burden for the health care system. The impact of prosthetic joint infections is profound and infected prosthetics often require removal of the hardware, prolonged IV antibiotics, resulting in significant functional decline and high mortality. It also comes at an
incredible expense to the health system. The risk of prosthetic joint infections is estimated to be significantly higher among patients with RA compared to those undergoing the procedure for the more common osteoarthritis [7,8].

Patients with rheumatoid arthritis already have an increased risk of infection more generally, including native joint infections [9]. Infection has long been recognised as an important cause of morbidity and mortality in RA where it has been shown that even prior to the advent of biologic DMARDs, patients with RA had a 2-fold increase in a risk of hospitalised infection and a 22-fold increased risk of septic arthritis. The introduction of bDMARDs has increased this risk further, with many large national drug registries showing a small but further increased risk of serious infection with bDMARDs [10,11], including joint infections [12]. The risk appears to be highest in the first 6 months of therapy but decreases as inflammation comes under control. Following ineffectiveness, infection is the leading cause for TNFi discontinuation [13]. The reasons for this increased infection risk are complex and not solely related to DMARD treatment. Other risk factors include active inflammation, poor mobility, comorbidities including more frequent pulmonary disease and the widespread use of glucocorticoids [14].

Given that there is a known association between DMARDs and infection even outside of the peri-operative period, careful management of DMARDs around the time of surgery to minimise this risk further is therefore critical; however, stopping DMARDs prior to surgery increases the risk of disease flare and subsequent further glucocorticoid use, both of which will also increase the risk of infection in the peri-operative period and interfere with rehabilitation following joint replacement. Thus, any decision around management of DMARDs in the peri-operative period is a careful balance between reducing the risk of post-operative infection but also preventing a disease flare.

Understanding the role DMARDs play in the risk of prosthetic joint infections and other surgical complications has been challenging due to the absence of high-quality controlled trials. Most of the evidence to help guide treatment decisions have been based on case series or observational research. These study designs suffer from bias and confounding, such that patients deemed to be higher risk for infections may be asked to discontinue their treatment preferentially to others. The complexity or nature of the surgery may also influence treatment decisions. Both factors will also be risk factors for adverse surgical outcomes and thus any conclusions may be confounded.

There is also a challenge of measurement error and exposure misclassification using large observational datasets, an increasingly common approach, which may not accurately capture short pauses in therapies. Patients who are no longer receiving DMARD treatment may differ significant from those whose disease is under control on treatment but who temporarily pause treatment prior to surgery. Therefore, identifying appropriate and relevant comparison groups is also challenging. The next section explores data related to individual DMARDS and peri-operative risk.

3.1 Conventional Synthetic DMARDs

a. Methotrexate

Methotrexate remains the best studied csDMARD. The best evidence regarding MTX and surgical risk comes from a 2001 unblinded clinical trial [15] which randomised 88 patients receiving MTX to continue their therapy and 72 patients to discontinue MTX 2 weeks prior to surgery, restarting it 2 weeks later. Overall, adverse outcomes were uncommon in both groups but a combined outcome of infectious and surgical complications was less common among the group who continued their MTX compared to those who stopped [2 versus 15%, p<0.003]; however, 8% if patients who stopped their MTX flared in the 6-week post-op period compared to no patients who continued their MTX [p=0.04]. The conclusions of this trial were that patients should continue their MTX through the peri-operative period.
Results from other studies have been mixed, although overall, the quality of these studies has been
low. A small unblinded study which randomized 64 patients [1:1] to either continue or interrupt
MTX 1 week prior to orthopaedic surgery observed no post-operative infections in either group [16].
It should be noted that the average dose of MTX in this study was 10mg/week which is much lower
than current doses, which range from 15-25mg/week.

A 1996 case series observed 32 patients [13 of whom were assigned to interrupt their MTX 1 week
prior to surgery and 19 who were not] and found a higher rate of infections among patients who
continued their MTX, including 2 infected prostheses, 1 infected joint fusion, and 1 deep wound
infection compared to no infections among those who interrupted their therapy [p=0.03] [17]. This
compares to a 2006 Japanese study which looked at outcomes in 48 patients (77 procedures) who
continued their MTX prior to surgery and 12 (21 procedures) who discontinued MTX at least 1 week
prior to surgery with no difference in rates of infection but higher rates of post-operative flare and
poorer wound healing among those who stopped [18].

b. Non-Methotrexate csDMARDs
Unfortunately, the information we have regarding other csDMARDs is very limited. An observational
study found no difference in short term outcomes among 41 patients who continued leflunomide
compared to 41 patients who had stopped leflunomide at least 4 weeks prior to surgery [19].
Notably there were no serious or deep infections in either group. For other commonly used drugs in
this class, particularly hydroxychloroquine and sulphasalazine, there are very limited data although
these drugs are not felt to have significant immunosuppressive effect. A 1996 retrospective study of
204 patients undergoing various orthopaedic procedures did not identify any csDMARD as a risk
factor for early wound complications in a multivariable model [20].

Based on these very limited data, both the 2017 American College of Rheumatology [ACR]/American
Association of Hip and Knee Surgeons (AAHKS) Guidelines for the Peri-operative Management of
DMARDs in patients undergoing elective knee and hip surgery [21] and the 2017 British Society for
Rheumatology [BSR] guidelines for the prescription and monitoring of csDMARDs [22] state that
csDMARDs can be continued over the perioperative period. It should be noted however that due to
the prolonged clinical effects of many csDMARDs, the likelihood of a flare in the very short term is
overall very low, such that missing a few days of treatment is unlikely to have a major effect in most
patients. For example, omitting the dose on the morning of surgery in a fasting patient should not
have any detrimental effects on disease activity and therefore, decisions should be made on a case
by case basis.

Special attention should be paid in those patients receiving methotrexate who do develop infection
due to the known drug interaction between MTX and trimethoprim [23], which increases the risk of
pancytopenia. For all csDMARDs, it is advised that they are temporarily discontinued in all patients
receiving any antibiotics until the course of antibiotics is complete [22].

3.2 Biologic and Targeted Synthetic DMARDs

There have been more publications regarding the safety of peri-operative outcomes in patients
receiving bDMARDs, but there have been no randomised trials on this topic. As such, all guidance is
based on observational data and expert opinion.

a. TNF Inhibitors
Like csDMARDs, most data on bDMARDS in the peri-operative period have focused on orthopaedic
procedures with most studies focusing on TNF inhibitors, the oldest and most used bDMARD. Again,
balancing between the risk of post-operative infections and disease flare remains an important
issue, especially as the effects of bDMARDs are quicker than most csDMARDs and flare of disease
after drug discontinuation may occur sooner. A 2020 systematic review of studies looking at TNF inhibitor discontinuation found that 62% of patients who were previously in remission will flare once the treatment has stopped [24] although the timing of this can be highly variable. A small observational study of 31 patients with RA undergoing elective foot or ankle surgery who were all advised to continue their usual DMARDs found no difference in the rates of infectious complications between the 15 patients who were receiving TNF inhibitors compared to the 16 who were not [25]. Den Broeder et al undertook a large retrospective analysis of outcomes, with a focus on SSI, following 1219 elective orthopaedic procedures in patients with RA [26]. They compared outcomes between those who had not received TNF inhibitors, those who had stopped TNF inhibitors at least 4 half-lives prior to surgery and those who received the drug within this window. They found no difference in the risk of SSI (Odds Ratio (OR) 1.5 (95% Confidence interval (CI) 0.4, 5.2) between those who had received TNF inhibitors and had either stopped or continued their drug. The strongest risk factor for SSI was a history of previous SSI or skin infection. It should be noted however that a local protocol to advise patients to stop their TNF inhibitor 2 weeks prior to surgery was in place although practice varied and adherence to this protocol was not recorded.

Infliximab is a TNF inhibitor which is given by intravenous infusion every 8 weeks and as such, dates of doses are recorded accurately in administrative databases. George et al [27] undertook an analysis which studied the association between the timing of the most recent infusion of infliximab and the date of orthopaedic surgery, with the reference group being those who received their last dose between 8-12 weeks prior to date of procedure. They found no difference in the rates of serious infection within 30 days or prosthetic joint infection over 1 year between the reference group and other groups who had received the drug either within 4 weeks, 4-8 weeks, 12-16 weeks or >16 weeks prior to surgery. Although this study did allow for patient differences in their statistical model, infliximab is now one of the less commonly used TNFi in rheumatology, with patients [and hospitals] favouring self-injection at home.

Despite these reassuring studies, not all studies have been consistent in these findings. A 2016 meta-analysis of 5 observational studies looking at the risk of TNF inhibitors and post-operative complications included 2743 patients, of whom approximately 50% of patients continued their TNF inhibitors throughout the operative period [28]. It found that SSI infections were less common among patients who discontinued their therapy [3% versus 6%, OR 0.6 [95% CI 0.4-0.9]] but with a higher rate of flares among patients who discontinued compared to those who continued (20% versus 3%, OR 5.0 (95% CI 1.1-24.8)). This analysis did not look specifically at prosthetic joint infections.

b. Non-TNF Inhibiting bDMARDs

Data regarding the peri-operative risk of non-TNF inhibitors is very limited. A large analysis by George et al [29] compared the risk of serious infection within 30 days and prosthetic joint infections within 1 year among 10923 procedures in 9911 patients receiving various bDMARDs. They found that compared to abatacept, an anti-CTLA4 receptor antagonist, the risks were similar with TNF Inhibitors, tocilizumab and rituximab, although the sample size of patients receiving the latter 2 drugs was small.

The French AIR Rituximab registry [30] reported on surgical outcomes among 133 patients who had undergone 140 surgical procedures, including 94 orthopaedic procedures, following rituximab. Overall, complications were rare with 9 patients experiencing 12 complications, including 8 SSI. The mean time between the most recent rituximab infusion and the date of surgery was 6.4 months [interquartile range 4.3– 8.7 months] and there was no difference between patients with and without complications.

The retrospective observational 2013 Tocilizumab in the Peri-operative Period (ToPP) study reported on 166 procedures [31]. Overall post-operative infections, delayed wound healing and flares were
experienced in 3, 20 and 36 cases respectively. There was no control group and no analysis of time on/off tocilizumab and occurrence of adverse events, although adverse events were slightly higher among patients undergoing foot or spinal surgery. Finally, analysis of the French REGATE (Tocilizumab) registry [32] identified 167 patients who underwent 175 surgical procedures including 103 orthopaedic surgeries (58.9%). Most patients in the study received intravenous tocilizumab which was dosed every 4 weeks. The mean delay between the most recent tocilizumab and the date of surgery was approximately 5 weeks and did not differ significantly between patients with and without complications. There were 10 severe infections including 5 SSIs. The strongest risk factor for post-operative infection was a history of diabetes mellitus.

Tocilizumab is a powerful suppressor of the acute phase response which may persist beyond the usual dosing period. A small study by Hirao et al which compared 22 patients receiving tocilizumab and 22 patients receiving csDMARDs found that on post-operative days 1, 2, and 3, patients receiving tocilizumab had a lower mean daily temperature compared to those receiving csDMARDs only [33]. No increase in CRP was observed in patients receiving tocilizumab. Thus, the acute phase response in the setting of infection in the post-operative period may be suppressed in patients receiving tocilizumab and thus close monitoring and high suspicion for infection is warranted.

c. Targeted Synthetic DMARDS
There have not been any studies reporting on the risk of tsDMARD use in the peri-operative period although like TNF inhibitors and other bDMARDs, they have been shown to increase the risk of infections in patients with RA [34]. Importantly there is evidence to suggest that JAK inhibitors may increase the risk of venous thromboembolism [35] and appropriate VTE prophylactic measures should be in place for patients with current or recent exposure to these medications.

4. Guidance on the use of b/ts DMARDs in the Peri-operative Period

In the absence of high-quality research in this area and with the mixed findings across studies, coupled with the known general increased risk of infection in relation to b/ts DMARDs, both the 2017 ACR/AAHKS [21] and the 2019 BSR bDMARD Safety Guidelines [36] recommend that patients receiving b/tsDMARDs stop their b/tsDMARD therapy prior to surgery. This was based on consensus and expert opinion, including the opinion of patients who, as stated in the ACR/AAHKS Guidelines, weighed the risk of infection as more concerning than the risk of disease flare.

The safest length of time that a patient should stop their drugs prior to surgery to manage the balance between infection risk and disease flare is unknown and has varied in past guidelines to include specific dosing intervals as well as multiples of drug half-lives. Both guidelines now state that patients should stop their b/tsDMARD at least 1 dosing interval prior to surgery, with the principle being that the effect of the drug will be at its nadir at the end of the dosing cycle. For rituximab this means surgery should be planned for 6 months after the last dose.

In cases of doubt, consultation with the patient’s rheumatologist is warranted, as it is possible to check a patient’s CD19 lymphocyte counts which can indicate if B-cell reconstitution has occurred post-rituximab. The BSR guidelines highlight 2 exceptions to this general b/tsDMARD guideline: for higher risk procedures [not defined], the BSR guidelines state that a longer period of time, such as 3-5 half-lives of the drug, should be considered. For some drugs, however, this may be a very long period and therefore, may be difficult to implement in practice. They also suggest a slightly longer interval for subcutaneous tocilizumab of 2 weeks compared to the usual dosing interval of 1 week due to the observed suppression of fever and CRP following treatment [33]. The safest dosing gap for patients receiving tsDMARDS is unknown. Currently available therapies are daily oral doses and both ACR/AAHKS and the BSR guidelines recommend patients interrupt their therapy for at least 1 week.
There is no evidence to guide the optimal time to restart DMARDs following surgery. In all cases, it is suggested that treatment should be resumed a minimum of 14 days after surgery once it is confirmed that there is no issues with wound healing, SSI or systemic infection and staples and sutures have been removed.

Attention should be paid to recent use of glucocorticoids and where possible, ensuring the patient is on as low a dose as possible is warranted. A 2019 study [29] found that compared to patients who have not received steroids within 90 days of surgery, patients receiving 10 mg or more per day had higher incidence of hospitalised infection and higher incidence of prosthetic joint infection. This was not a randomised study and it is known that patients receiving chronic glucocorticoids may also have more severe underlying disease. Chronic steroid use will also impair wound healing, increase the viability of skin and superficial blood vessels, and increase the risk of diabetes, osteoporosis and fracture.

5. Peri-operative use of DMARDS in patients undergoing unplanned surgery

In the case of patients undergoing urgent or unplanned surgery, it will not be possible to interrupt DMARD or glucocorticoid therapy prior to surgery. In these cases, it is crucial to ascertain an accurate drug history and for patients receiving b/ts DMARDS, discontinuation of these therapies in the post-operative period until effective wound healing is observed [minimum 14 days] would be recommended in line with guidelines for elective surgery. Careful attention to post-operative infections is warranted.

6. Consultation with the DMARD prescriber

Optimally, there should be a dialogue between the rheumatologist or other hospital doctor who has prescribed the DMARD and the surgical team. Although guidelines exist for management of DMARDS in the peri-operative period, individual risk assessment based on the patient and the procedure should take place. For some patients with severe underlying rheumatic diseases, such as SLE or vasculitis, the risk of organ-threatening damage when DMARDs are discontinued may outweigh the risk of post-operative complications and therefore, personalised treatment protocols may need to be put in place [21].

7. Conclusions

Unfortunately, despite the widespread use of DMARDs in the management of rheumatic diseases and other inflammatory conditions, information to inform their use in the peri-operative period is of generally poor quality. Guidelines based on expert opinion and observational data suggest that csDMARDs can be continued through the peri-operative period but that b/tsDMARDS should be discontinued at least one dosing interval prior to surgery. In all cases, an individualised risk assessment should take place based on the patient and the planned procedure and where possible, consultation with the DMARD prescriber is indicated.
References


3. National Institute for Health and Care Excellence. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDS or after conventional DMARDs only have failed [Internet]. 2016 [cited 2020 Sep 1]. Available from: https://www.nice.org.uk/guidance/ta375


### Appendix: Supplementary biological agents

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<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Dosing Details</th>
<th>Note</th>
</tr>
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<tr>
<td>Ibrutinib</td>
<td>Tyrosine kinase inhibitor</td>
<td>420mg od</td>
<td>Withold for 1 week prior</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Proteosome inhibitor</td>
<td>2.3mg - 4mg weekly</td>
<td>Time surgery 1 week after dose</td>
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<tr>
<td>Ruxolitinib</td>
<td>JAK 1 &amp; 2 inhibitor</td>
<td>5mg-20mg od</td>
<td>Withold for 1 week prior</td>
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