



## Facilitating the translation of evidence into best practice: Optimising the pharmacological management of inflammatory arthritis

### Summary of key living recommendations

1. Rheumatologists should use a treat-to-target approach for all patients with rheumatoid arthritis, irrespective of the choice of initial treatment regimen.
2. Rheumatology departments, in conjunction with Medicines Governance Committees<sup>1</sup>, should develop and implement local protocols around choice of DMARD in people with rheumatoid arthritis who have not responded to TNFi.
3. Rheumatology departments should develop and implement local protocols (and supporting materials for prescribers and consumers) that facilitate down-titration of biological/targeted synthetic disease-modifying antirheumatic drugs for rheumatoid arthritis and axial spondyloarthritis, where appropriate.
4. Health service organisations should develop and implement local programs to optimise opioid therapy for the treatment of pain in inflammatory arthritis.
5. Rheumatology departments should develop and implement local programs to optimise use of glucocorticoids for the treatment of rheumatoid arthritis.
6. Health service organisations should develop and implement local guidance for the perioperative use of DMARDs in people with inflammatory arthritis.

### Background

Living guidelines present up-to-date and state-of-the-art knowledge and guidance to practitioners. They use continuous evidence surveillance and rapid response pathways to incorporate new relevant evidence into systematic reviews and clinical practice guideline recommendations as soon as it becomes available.(1) For further information on living evidence see <https://livingevidence.org.au/about-living-evidence>.

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<sup>1</sup> Examples of medicines governance committees include drug and therapeutics committees, medicines advisory committees or equivalent, medication safety committees.

As part of the ViP bDMARDs Program, the 'Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis' ([mskguidelines.org](http://mskguidelines.org)) was developed to present the best available, current scientific evidence for pharmacological management of the most common forms of inflammatory arthritis, namely rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (SpA), including choice of disease-modifying antirheumatic drug (DMARD), switching, combination therapy and down-titration of treatment.

## Purpose

CATAG has developed this document to facilitate and support the translation of best available evidence into practice for the management of inflammatory arthritis. This will assist good governance and decision-making for health service organisations, medicines governance committees and health professionals.

These recommendations will be updated as further recommendations from the Australian Living Guidelines are released.

## Scope

This guidance applies to the care of those patients who have been diagnosed with RA, PsA and SpA and adapts the Living Guidelines for consideration by medicines governance committees. It can be used in conjunction with formulary decisions and recommendations.

## LIVING RECOMMENDATIONS

### **1. Rheumatologists should use a treat-to-target approach for all patients with RA, irrespective of the choice of initial treatment regimen.**

Methotrexate (MTX) is considered first-line therapy for RA. The Living Guideline panel considered the **choice of MTX monotherapy versus MTX combination therapy** as the initial choice of treatment in people with RA who have not previously received any DMARDs.

A network meta-analysis that compared MTX monotherapy to MTX-based combination therapies was used as the primary evidence source for this recommendation(2) and two subsequent RCTs of MTX monotherapy versus MTX in combination with JAK inhibitors were used. (3,4) Based on data from the network meta-analysis, the probability of achieving an ACR50 response with MTX monotherapy is about 41%; this increases to 56-67% with the use of initial combination therapy (either triple therapy or MTX plus most b/tsDMARDs). Triple therapy is defined as methotrexate plus sulfasalazine plus hydroxychloroquine. Combination therapy was also shown to have similar tolerability and safety compared to MTX monotherapy and consumers in general were not averse to combination therapy. It did not show a difference in efficacy between 'triple therapy' (MTX, sulfasalazine and hydroxychloroquine) and any b/tsDMARD in combination with MTX.(2) It is important to note that b/tsDMARDs are more expensive and are not subsidised for initial therapy in Australia.

The Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis recommends:

- Consider using methotrexate in combination with other DMARDs as initial therapy in people with RA. For most people this implies triple therapy (methotrexate + sulfasalazine + hydroxychloroquine). While the combination of methotrexate and most b/tsDMARDs is also effective, this is currently not a feasible option for most people.

The Living Guideline panel also considered evidence that **compared oral MTX with MTX injections** (via either the subcutaneous or intramuscular route) in people with RA. The rationale for considering parenteral (injected) MTX in preference to oral administration is that MTX may not be fully absorbed when taken orally (particularly at doses greater than 15mg/5), and therefore injection offers a higher effective dose, which may improve efficacy. Furthermore, it has been postulated that by avoiding the gastrointestinal tract, injectable MTX may avoid or reduce some of the gastrointestinal adverse effects that are commonly experienced by MTX users.

In total, there was at best low certainty evidence that suggested that parenteral MTX may result in slightly greater efficacy than oral MTX at the same dose, with little difference in safety or tolerability. Subcutaneous MTX may result in slightly greater improvements in pain and function compared with oral MTX.(6,7)

The panel considered that the evidence for a potential difference in efficacy favouring parenteral MTX may be sufficient to warrant consideration of a switch to the subcutaneous route in those who have not achieved their treatment goals with oral MTZ in preference to abandoning MTX altogether.(8)

Consider the following factors when making a decision about using subcutaneous rather than oral MTX in an individual with RA:

- Individual preferences and treatment goals
- Prior experience with oral methotrexate, including the balance of benefits and adverse effects
- Current disease activity, prognosis, and impact
- Comorbidities (e.g., malabsorption)
- Concurrent medications (e.g. other injected medications)
- The ability to either self-administer or access weekly injections.

It is important that any decision regarding the choice of disease-modifying therapy should be made within a shared decision-making framework following a clear discussion of potential benefits and harms, tailored to the individual's circumstances.

The Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis recommends:

- We conditionally recommend oral administration for people with RA who are commencing treatment with methotrexate.

In people who have had an inadequate response or who have been intolerant of oral methotrexate, consider a trial of subcutaneous methotrexate.

## Resources

From the Australian Rheumatology Association:

- An [information sheet](#) on self-injection of methotrexate
- A [video guide](#) to self-injection of methotrexate
- [Guidance](#) on the safe disposal of medical sharps

**2. Rheumatology departments, in conjunction with Medicines Governance Committees, should develop and implement local protocols around choice of DMARD in people with rheumatoid arthritis who have not responded to TNFi.**

The Living Guideline panel considered evidence from a living network meta-analysis (NMA) of DMARDs in people with RA who have had an inadequate response or intolerance to a TNF inhibitor (TNFi). None of the effective interventions were found to differ from any other in any of the efficacy or safety outcomes measured in the network meta-analysis.(8) There was general agreement that the NMA data demonstrated that in people with RA who have had an inadequate response to a TNFi, switching to a different therapy (either another TNFi or a b/tsDMARD with a different mechanism of action) was superior to continuation of the current therapy, or discontinuation of b/tsDMARD therapy altogether. The panel also agreed that there is likely to be little difference in efficacy between the various b/tsDMARD options, including TNFi, abatacept, IL-6 inhibitors, rituximab and the JAK inhibitors (JAKi).(8) The choice of b/tsDMARD would be determined by individual factors, including values, preferences and clinical circumstances, and also by an evaluation of potential harms.(8)

- On average, all available b/tsDMARDs are likely to be similar in terms of their effectiveness in people who have had an inadequate response to a TNFi. The choice of subsequent therapy is therefore likely to depend on an individual assessment of potential risks and other contextual factors:
  - Risk considerations specific to different classes of b/tsDMARDs may include:
    - JAKi - cardiovascular disease, thrombosis, cancer, thromboembolism, herpes zoster
    - Rituximab - severe COVID-19, other infections, progressive multifocal leukoencephalopathy, reduced response to vaccination
    - Tocilizumab - intestinal perforation in those at risk (e.g., diverticular disease)
    - Abatacept - reduced response to vaccination
    - TNFi - infections, including tuberculosis
  - Other factors that may be important in the choice of subsequent DMARD therapy may include:
    - Individual preferences and treatment goals
    - Preferred route and frequency of administration of DMARDs
    - Prior experience with DMARDs, including adverse effects
    - Current disease activity and prognosis
    - Comorbidities
    - Pregnancy planning
    - Concurrent medications
    - Impact of RA on daily activities, work and other life roles

**3. Rheumatology departments should develop and implement local protocols (and supporting materials for prescribers and consumers) that facilitate down-titration of b/tsDMARDs for rheumatoid arthritis and axial spondyloarthritis, where appropriate.**

The decision to down-titrate bDMARDs is a shared decision between the patient and treating clinician.

The aim for treatment of people with inflammatory arthritis conditions is to achieve either disease remission or low disease activity using the lowest possible dose of biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs). Benefits of reducing the dose include fewer injections or

infusions, the convenience of taking less medicines and reduced cost. Limited data from clinical trials suggest there is little difference in safety or tolerability of b/tsDMARDs if the dose is reduced.(8) These benefits must be weighed against the risk of losing disease control, experiencing more pain, inflammation and joint damage, experiencing a flare or being unable to undertake usual daily activities. Nevertheless, most people are able to regain good control by returning to the previous dose.(8)

The Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis recommends:

- In people with RA or SpA who have been in sustained low disease activity or remission for at least 6 months, consider stepwise reduction in the dose of b/tsDMARD. Continue dose reduction until cessation is achieved or the lowest effective b/tsDMARD dose is identified, as long as the treatment target is maintained.
- Do not routinely reduce the dose of b/tsDMARDs in patients with psoriatic arthritis who are in low disease activity or remission.
- Abrupt cessation of b/tsDMARDs is not recommended for patients with RA, SpA or PsA.

The Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis recommend the following practical information:

- Following dose reduction, patients should undergo a clinical review at least every 3 months, including measurement of disease activity.
- Patients should be provided with a plan to follow if there is a symptomatic flare following dose reduction, including a mechanism for patients to contact their prescriber between visits if necessary.
- In the event of loss of disease control (e.g., persistent increase in composite disease activity measure or new symptoms that are unacceptable to the patient), it is possible to reintroduce of the previous effective dose of b/tsDMARD.
- During b/tsDMARD dose reduction, concurrent csDMARDs should be continued at a stable dose.

## Resources

- [b/tsDMARDs down-titration algorithm for rheumatoid arthritis](#)
- [bDMARDs down-titration strategies used in clinical trials](#)
- [bDMARDs down-titration patient decision aid](#)
- [Down-titration factsheet](#)

## 4. Health service organisations should develop and implement local programs to optimise opioid therapy for the treatment of pain in inflammatory arthritis

Pain, for both people with inflammatory arthritis and their clinicians is a significant issue, with pain management a high priority.(9) The pain is often due to inflammation, but may also be as a result of joint damage or destruction and peripheral and central sensitization.(10) This pain may not be controlled by DMARDs and non-steroidal anti-inflammatory drugs (NSAIDs) and additional pain relief may be required. The use of opioids may provide short-term improvement in pain, however, there is potential for significant adverse effects, such as risk of dependence, misuse or overdose. There is no

data on the benefits of long-term use of opioids, but the potential for long-term harms of opioid use for chronic non-cancer pain is widely accepted. Any decision to initiate the use of opioids should take place within a clear shared decision-making framework, tailored to the individual's circumstances (including comorbidities and concomitant medications).(8)

The Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis recommends:

- Do not routinely use opioids for the treatment of pain in RA, SpA or PsA.
- A brief course of a short-acting opioid may be considered for severe pain associated with RA only, and only when other analgesic options have failed.

### Resources

- [NPS MedicineWise opioids program](#)
- [NSW TAG Preventing and managing problems with opioid prescribing for chronic non-cancer pain](#)
- [Clinical practice guideline for deprescribing opioid analgesics: summary of recommendations](#)
- [Opioid Analgesic Stewardship in Acute Pain Clinical Care Standard](#)

## 5. Rheumatology departments should develop and implement local programs to optimise use of glucocorticoids for the treatment of rheumatoid arthritis.

Glucocorticoids (most commonly prednisone or prednisolone) play a role in the treatment of RA, with approximately 50% of patients estimated to receive glucocorticoids in varying doses, for varying durations, at varying stages of their disease(11), however it has been identified that they have the potential for adverse effects, particularly with high doses or long-term use. These include osteoporotic fractures, infection, skin thinning, easy bruising, weight gain, diabetes, hypertension and cataracts(12).

For management of disease flares (i.e. loss of low disease activity state, or increase in disease activity) in patients with recent onset or established disease, short-term glucocorticoid treatment is a common strategy to rapidly decrease inflammation and alleviate symptoms.(8)

Long term use of low-dose glucocorticoids has been used in patients with established disease, who have not been able to reach low-disease activity or remission with DMARDs. The evidence suggests that any potential benefits of long-term glucocorticoids in RA are likely to be of negligible clinical importance. shared decision-making framework that takes into account all of these factors is of paramount importance.(8)

The use of glucocorticoids in RA should aim for the lowest dose and shortest duration that achieves the individual patient's treatment goals, and should include a plan to monitor for and attempt to mitigate long-term harmful effects.(8)

The Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis recommends:

- Consider using short-term glucocorticoids for the treatment of RA flare in people with previously well-controlled disease, via either a systemic (oral, intramuscular or intravenous) or intra-articular route, in the lowest possible dose for the shortest possible time.

Any flare should prompt consideration of the need for adjustment of the DMARD regimen.

- Do not routinely use glucocorticoids as a long-term (>6 months) adjunct to DMARDs for the treatment of RA.

## Resources

- [NPS Practice review -Rheumatoid arthritis](#)
- [Webinar recording: Corticosteroids: Indications guide optimal use](#)
- [Podcast: The contemporary role of methotrexate and glucocorticoids in RA](#)

## 6. Health service organisations should develop and implement local guidance for the perioperative use of DMARDs in people with inflammatory arthritis

A large proportion of people with inflammatory arthritis will undergo orthopaedic surgery over the course of their illness, and it is estimated that over 80% of such patients take conventional or biologic DMARDs at the time of their orthopaedic surgery.(13) Two options exist with regards to stopping these medicines- stopping therapy, which increases the risk for post-operative disease flare or continuing therapy, which carries a risk of infection.

The evidence regarding csDMARDs was sufficient to warrant a conditional recommendation in favour of continuing these drugs without interruption in most individuals undergoing elective surgery, although some patients may elect to hold treatment based on an individual assessment of risks and benefits.

bDMARDs are potent immunomodulators that are associated with an increased risk of infection in general, and therefore the lowest-risk approach may be to temporarily discontinue these drugs in the perioperative period. However it was also noted that the current body of observational evidence does not suggest that continuation of therapy is associated with an important risk of infection, and it remains unknown whether interruption of treatment for an arbitrary period either reduces the risk of infection or has a net beneficial effect versus the risk of disease flare. It is thought that disease flare in the perioperative period is unlikely to be benign, particularly if there is an impact on rehabilitation from surgery or if it results in rescue therapy with glucocorticoids.(8)

There is a current lack of evidence for tsDMARDs, the potential impact on the risk of infection and other perioperative complications (including the possibility of blunting of the acute phase response in the setting of infection and a theoretical increase in the risk of thrombosis), the panel agreed on a conditional recommendation to temporarily discontinue tsDMARDs perioperatively.(8)

The Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis recommends:

- Do not routinely discontinue csDMARDs in the perioperative period.
- Do not routinely discontinue bDMARDs in the perioperative period; consider temporary discontinuation in individuals with a high risk of infection or where the impact of infection would be severe.
- Consider temporary discontinuation of tsDMARDs in the perioperative period.

The Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis recommend the following practical information.

Consider the potential risks and benefits of temporary discontinuation of DMARDs in the perioperative period based on the following factors:

- Type and urgency of surgery
- Risk factors for infection
- Potential impact of infection or flare
- Other risk factors for infection
- The patient's preferences and goals.

For patients planning to withhold DMARDs perioperatively, consider the following schedule as a guide:

- For most bDMARDs, withhold for one dosing cycle prior to surgery.
  - i.e., plan surgery at approximately the time of the subsequent dose (e.g., for a monthly injection, aim for surgery in the 5th week after the last injection)
- For rituximab, aim for surgery at least 3 months after the most recent dose.
- For JAK inhibitors, stop treatment approximately 7 days before surgery.
- For methotrexate, withhold for one dosing cycle prior to surgery (i.e. plan surgery 1-2 weeks after the most recent dose).
- For leflunomide, stop treatment approximately 7 days before surgery.

Aim to recommence DMARDs when surgical sutures have been removed, adequate wound healing has occurred and there are no other symptoms or signs of infection.

Be aware that some b/tsDMARDs (e.g., tocilizumab and JAK inhibitors) may diminish or eliminate the acute phase response, particularly if the drug is discontinued or recommenced close to the time of surgery, and therefore the practitioner should be vigilant for the possibility of infection even in those with normal inflammatory markers.

## Further information

- Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis [mskguidelines.org](http://mskguidelines.org)
- [CATAG bDMARDS project](#)
- NPS bDMARDS program <https://www.nps.org.au/bdmards>

## Appendices

### Appendix 1: Glossary

<b>Term</b>	<b>Definition</b>
b/tsDMARD	Biological/targeted synthetic disease-modifying antirheumatic drug
csDMARDs	Conventional synthetic disease-modifying antirheumatic drug
DMARD	disease-modifying antirheumatic drug
Down-titration	The stepwise reduction in dose, by either reducing the dose or increasing the dosing interval
JAKi	Janus kinase (JAK) inhibitors
Medicines governance committees	the group assigned responsibility for governance of the medication management system, and for ensuring the safe and effective use of medicines in the health service organisation.(14) These may also be known as a medicines advisory committee, pharmacy and therapeutics committee, drug committee, drug and therapeutics advisory committee, formulary committee or quality use of medicines committee.
MTX	methotrexate
NMA	network meta-analysis
PsA	psoriatic arthritis
RA	Rheumatoid arthritis
SpA	axial spondyloarthritis
TNFi	Tumour Necrosis Factor (TNF) inhibitor
tsDMARD	targeted synthetic disease-modifying antirheumatic drug

## Appendix 2: How this guidance was developed

This guidance was developed in consultation with the CATAG member organisations listed below:

- ACT Health
- NSW Therapeutic Advisory Group (NSW TAG)
- Northern Territory Drug and Therapeutics Committee
- Queensland Health Medicines Advisory Committee (QHMAC)
- South Australian Medicines Advisory Committee (SAMAC)
- Tasmanian Medicines Access and Advisory Committee (TMACC)
- Victorian Therapeutics Advisory Group (Vic TAG)
- Western Australian Therapeutics Advisory Group (WATAG)

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#### **+ TARGETED THERAPIES ALLIANCE**

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