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ARTICLE

Managing the drug treatment of rheumatoid arthritis

SUMMARY

Rheumatoid arthritis is an inflammatory condition affecting synovial joints. Without treatment, the underlying inflammatory process leads to joint destruction, pain, deformity, disability and accelerated cardiovascular disease.

Disease-modifying antirheumatic drugs will attenuate the inflammation. Their benefits are seen at all stages of the disease, however the best outcomes are achieved when they are used shortly after the onset. Patients with suspected rheumatoid arthritis should be referred promptly.

Disease-modifying antirheumatic drugs are often used in combination and can have serious adverse effects. Their safe use requires ongoing monitoring to identify potential adverse events.

The risk of infection is increased and vaccination is best given before starting disease-modifying antirheumatic drugs.

Tom D Wilsdon
Clinical pharmacology registrar[1]
Associate lecturer[2]

Catherine L Hill
Consultant rheumatologist[3,4]
Clinical professor[5]

[1] Department of Clinical Pharmacology
Flinders Medical Centre
[2] School of Medicine
Nursing and Health Sciences
Flinders University
[3] Department of Rheumatology
The Queen Elizabeth Hospital
[4] Department of Rheumatology
Royal Adelaide Hospital
[5] School of Medicine
Faculty of Health Sciences
University of Adelaide
Adelaide

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Introduction

Rheumatoid arthritis is a chronic autoimmune condition that classically presents as a symmetrical polyarthritis of proximal small synovial joints. It has a prevalence of 0.46% in the Australasian region, and affects women more frequently than men.[1] The onset is usually between 35 and 60 years, however the majority of the disease burden in Australia is in people over 65 years.[2]

The cause of rheumatoid arthritis remains unknown, although our understanding of the pathological processes has advanced greatly in the last 20 years. Many pro-inflammatory cytokines are involved and some of these are therapeutic targets for the development of new drugs.[3]

Optimal management of rheumatoid arthritis requires an understanding of the therapeutic goals, the options available to attain them and the associated potential complications. Drugs are only one part of the management of the patient.

The significance of inflammation

The cytokine milieu in rheumatoid arthritis influences a multitude of physiological processes. These include promoting the influx of immune effector cells into the joint synovium, and activation of osteoclasts, chondrocytes and fibroblasts.[3] There is a positive feedback loop that reinforces the inflammatory process. Unabated, this process results in joint pain and destruction, ultimately causing deformity and disability.

Chronic inflammation also contributes to an increased risk of myocardial infarction, stroke and death. A Canadian population-based prospective cohort study reported an absolute increase in cardiovascular events of 5.7 per 1000 person-years (95% confidence interval 4.9–6.4) in patients with rheumatoid arthritis compared to those without.[4] The use of disease-modifying antirheumatic drugs (DMARDs) to attenuate the inflammatory process has been shown to prevent joint erosions and reduce pain, cardiovascular morbidity and mortality.[3,5]

Nomenclature

The development of targeted monoclonal antibodies and small-molecule kinase inhibitors has widened the therapeutic options in rheumatoid arthritis. Each drug has a proven ability to modify the disease process to varying extents. However, the increase in drugs has thwarted our simple terminology of DMARDs, as the term no longer refers solely to synthetic chemical entities. A new nomenclature has been proposed[6] and applied to the drugs registered in Australia for the treatment of rheumatoid arthritis (see Box).

A systematic review and meta-analysis found that corticosteroids reduce demonstrated radiographic erosions.[7] While this effect defines corticosteroids as DMARDs, their toxicity profile makes routine long-term use undesirable. Other infrequently used DMARD therapies include azathioprine, ciclosporine and gold salts.

Box **Disease-modifying antirheumatic drugs**

Synthetic DMARDs

Conventional

- methotrexate
- sulfasalazine
- leflunomide
- hydroxychloroquine
- corticosteroids

Targeted

- Janus kinase inhibitors
  - tofacitinib

Biologic DMARDs

Tumour necrosis factor antagonists

- adalimumab
- golimumab
- certolizumab pegol
- infliximab*
- etanercept

IL-1 receptor antagonist

- anakinra

IL-6 receptor antagonist

- tocilizumab

Anti-CD20 monoclonal antibody

- rituximab

CTLA-4-Ig fusion protein

- abatacept

DMARDs disease-modifying anti-rheumatic drugs
IL interleukin
CTLA cytotoxic lymphocyte-associated antigen
* also available as a biosimilar

The importance of early treatment

Remission is unlikely to occur without intervention.[8] Bone erosions are detectable in 25% of people within three months of onset[9] and in 70% by three years.[10] Delaying treatment beyond three months causes more joint destruction and a higher chance of requiring persistent DMARDs to maintain remission.[11] Early DMARD therapy during this 'window of opportunity' (that is within three months of onset) will more readily induce remission and delay progression.[9]

Methotrexate monotherapy

Methotrexate is the backbone of rheumatoid arthritis treatment. Monotherapy consistently reduces radiographic progression and improves quality of life.[12] Approximately 40% of patients will respond to monotherapy.[13] Limited comparative data suggest that other conventional DMARD monotherapies are as effective as methotrexate.[14] However, its demonstrated long-term benefits, cost, acceptable safety profile and synergy with other DMARDs make methotrexate the recommended first choice for monotherapy in the guidelines of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[15,16]

Combination therapies

Combining DMARDs is frequently used as a first-line strategy, particularly for those with poor prognostic factors. A systematic review and network meta-analysis compared methotrexate monotherapy to methotrexate in combination with other DMARDs for patients with rheumatoid arthritis who were treatment-naïve or had an inadequate response to methotrexate alone.[13] The combination of methotrexate with sulfasalazine and hydroxychloroquine, so called 'triple therapy', has greater efficacy than monotherapy in both early rheumatoid arthritis and non-responders, but higher toxicity.[13] Combining methotrexate with biologic DMARDs has also demonstrated superior outcomes compared to methotrexate monotherapy in those with an inadequate response.[13]

The optimal combination of DMARDs and timing of combination therapy is debated. Unless methotrexate is poorly tolerated it should always be continued when starting other DMARDs.

Choosing the right treatment

The choice of treatment for a patient is influenced by the duration and severity of disease, previous treatments and regulatory restrictions. There are also patient-specific factors such as comorbidities, patient preference, family planning, and financial and social circumstances.

Pre-treatment evaluation

Before starting DMARDs, all patients should have baseline blood tests including full blood examination, serum creatinine and liver enzymes. Abnormalities may alter the choice of therapy and dosing (e.g. methotrexate is renally excreted). All patients should be screened for hepatitis B virus, hepatitis C virus and tuberculosis as there is a risk of reactivation of latent infections or worsening of active infection.

Other important considerations include congestive heart failure, malignancy, lymphoproliferative disease, multiple sclerosis, chronic obstructive pulmonary disease, bronchiectasis and interstitial lung disease. Further evaluation is required before treatment.

Pregnancy, contraception and lactation

The management of rheumatoid arthritis before, during and after pregnancy can be challenging. Although many women will have an improvement in

disease activity during pregnancy, remission is rare.[17] Poor pregnancy outcomes occur more commonly with high disease activity and include miscarriage, prematurity and pre-eclampsia.[17] With the exception of sulfasalazine and hydroxychloroquine, all DMARDs are considered either unsafe or of uncertain safety during pregnancy.[18] Counselling on effective methods of contraception is essential to prevent unplanned pregnancy while taking teratogenic drugs.[17] Planned pregnancy is preferable and allows time for appropriate treatment changes to be made while optimising disease control. Certain DMARDs (e.g. leflunomide, methotrexate) must be stopped at least 3–6 months before conception.[18]

During lactation the immunosuppressive effects of some DMARDs may affect the infant because of drug excretion into breast milk. Information on drugs and lactation can be found at the United States National Institute of Health Lactmed website (https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) or via local medicines information services.

Treating to target

The aim for every patient is to achieve a target of remission or low disease activity, as this leads to better outcomes.[16] Disease activity is quantified by validated tools, such as the disease activity score based on a 28-joint count (DAS28), the clinical disease activity index (CDAI) and the simplified disease activity index (SDAI).[16] A score is calculated from patient-reported pain and function, serum markers of inflammation (e.g. C-reactive protein or erythrocyte sedimentation rate) and physical joint examination. A score of moderate to high disease activity is an indication for more intense therapy with combination DMARDs until the target score (or lower) is achieved. While the optimal scores for defining low disease activity and remission continue to be refined, the treat-to-target approach is recommended by the ACR and EULAR guidelines.[15,16] These provide a practical summary of evidence-based treatment algorithms, although they do not completely reflect the Australian regulatory restrictions. The Australian restrictions can be reviewed at the Australian Government Department of Human Services website (www.humanservices.gov.au/health-professionals/enablers/rheumatoid-arthritis).

Monitoring

Monitoring treatment with DMARDs is important to ensure their safe and effective use. The potential adverse effects of methotrexate include mouth ulcers, gastrointestinal discomfort, hepatotoxicity, myelosuppression, reversible alopecia and pneumonitis. The development of adverse drug reactions should prompt review for incorrect dosing, drug interactions or new renal impairment. Supplementation with folic acid can improve the gastrointestinal symptoms and reduce the risk of liver function abnormalities.[19] Although an optimal folic acid regimen has not been identified, 5–10 mg orally once a week, preferably not on the same day as methotrexate, is generally recommended.

Details regarding adverse drug reactions and the monitoring of DMARDs can be found in the Table,[20,21] or in previous *Australian Prescriber* articles.[22-27] Patient medicine information handouts are also available from the Australian Rheumatology Association website (www.rheumatology.org.au).

Infection

Patients with rheumatoid arthritis have an increased incidence of infection compared to the general population, in particular those with higher disease severity, corticosteroid use and other comorbidities.[28] Combination DMARD regimens, especially those that include a biologic drug, are associated with a markedly increased risk of serious infections.[29] This risk is highest in the first six months of therapy.[29] These infections are of concern, in particular reactivation of tuberculosis.[30] The risk of reactivation of latent tuberculosis is high with DMARD use, particularly with biologic DMARDs and tofacitinib.[15] Vigilance for infection is important, as its signs and symptoms may be atypical in immunosuppressed patients. In particular the febrile response may be blunted due to cytokine blockade. Patients should be advised to seek medical attention if they have localising symptoms of infection, an unexplained illness or a fever.

The management of minor infection requires ongoing clinical review until it resolves, with early consideration of antimicrobial therapy. Herpes zoster is more common in people taking tofacitinib and biologic drugs and may have multi-dermatomal presentations.[31] Early antiviral treatment is required. The continuation of DMARDs with recurrent minor infections should be discussed with the treating rheumatologist.

Serious infections requiring hospitalisation or intravenous antibiotics usually lead to the discontinuation of most DMARDs, especially tumour necrosis factor antagonists. Long-term corticosteroids, if part of the current therapy, should be continued and possibly increased during infection due to the likelihood of adrenal suppression and the risk of an Addisonian crisis if they are stopped. Resumption of other DMARDs may be

considered after recovery, but must be done with informed consent and close monitoring. Repeated infections, irrespective of severity, may also lead to DMARD discontinuation.

Disease flares

The definition of a 'flare' in rheumatoid arthritis poses a challenge, as patient and physician reports of flare do not always correlate with an increase in disease activity.[32] Flares defined by increased disease activity are associated with increased pain, functional deterioration and radiographic progression.[33] These flares often occur when the dose of DMARD is reduced.

Objective assessment of disease activity is essential to determine if treatment intensification is required. This should include a joint assessment, a patient- and physician-reported disease severity measure, and measures of inflammation such as C-reactive protein or erythrocyte sedimentation rate. Increases in disease activity should trigger an urgent review by a rheumatologist.

Pain may be managed with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs). Opioid analgesia may cause adverse drug reactions without additional benefit and is best avoided.[34]

Glucocorticoids may be considered for disease flares. They are given either orally at low dose (e.g. prednisolone 10–15 mg daily), intramuscularly or intra-articularly. Intramuscular injections (e.g. methylprednisolone acetate) have the benefit of sustained activity without the inconvenience of daily oral dosing or a requirement for tapering the dose.

Vaccination

When indicated, vaccination for pneumococcus, influenza, hepatitis A and B and human papillomavirus is recommended irrespective of DMARD choice.[15] Live vaccines should be avoided in people taking DMARDs, although varicella zoster may be considered in those who are not on biologic DMARDs.[15] Vaccines may be given any time during therapy, however the best time is before treatment as DMARDs may attenuate the immune response. We recommend consulting the Australian Immunisation Handbook for further details.[35]

Complementary medicines

Despite widespread use of complementary medicines there remains a lack of evidence of their benefit. No complementary medicines have demonstrated disease-modifying effects. Meta-analyses of the published data suggest that omega-3 polyunsaturated fatty acids are effective at improving pain and reducing NSAID use. The optimal dose is yet to be determined (reported range 1.7–9.6 g daily).[36] Evening primrose oil, borage seed oil, *Tripterygium wilfordii* Hook F (thunder god vine) and blackcurrant seed oil may improve some symptoms of rheumatoid arthritis.[36,37] Adverse effects have been reported, making the harm–benefit profile unfavourable.[37]

The advent of biosimilars

A biosimilar is a biologic drug that is similar, but not identical, to a registered original biologic drug. The differences may theoretically result in altered efficacy and increased immunogenicity, therefore strict regulation is essential. The Australian Therapeutic Goods Administration requires multiple criteria to be fulfilled before a biosimilar can be registered.[38] Considering the current expense of biologic drugs for rheumatoid arthritis in Australia, a cheaper and effective biosimilar is an attractive option. Even if it is deemed to be equivalent to the original product, the safety and efficacy of switching between products is uncertain.

Conclusion

The advances in rheumatoid arthritis therapy over the last 20 years have markedly changed the way the disease is managed and have improved outcomes. Understanding the therapeutic goals and the options available to achieve them, pre-treatment evaluation, and the ongoing monitoring for complications of the disease and its treatment, will ensure the best outcomes for patients. Further advances in biotechnology are likely to lead to even more changes in the therapeutic landscape of rheumatoid arthritis. ≺

Tom Wilsdon attended Editorial Executive Committee meetings as the clinical pharmacology registrar for Australian Prescriber *in 2016. He is a member of the South Australian Formulary Committee.*

Catherine Hill is currently the Honorary Secretary of the Australian Rheumatology Association, Chair of the South Australian Medicines Evaluation Panel, member of the South Australian Medicines Advisory Committee, member of the Drug Utilisation Subcommittee of the Pharmaceutical Benefits Advisory Committee, and previous member of the Australian Committee for Prescription Medicine for the Therapeutic Goods Administration. She has been the principal local investigator for drug trials with GSK, Servier, Axsome and Merck, and has been involved in drug trials by UCB, Roche and Abbvie. Catherine has received airfares and accommodation costs from Abbvie and Bristol-Myers Squibb to attend meetings internationally and interstate.

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Table **Disease-modifying antirheumatic drugs and monitoring in rheumatoid arthritis**

Drug	Adverse drug reaction	Monitoring	Action
For all DMARDs	Myelosuppression Hepatotoxicity	Routine unless otherwise specified: FBE, EUC, LFTs at baseline, 2–4 weekly for 3–6 months and every 6–12 weeks thereafter. This regimen is influenced by comorbidities and changes to therapy.	Abnormalities in blood monitoring may lead to dose adjustments, treatment interruption or cessation.
	Malignancy	Age-related cancer screening programs and self-reported symptoms	
	Infection	Self-reported fever (>38 °C), localising symptoms or unexplained illness. Fever may not always be present due to DMARD-induced alterations in cytokine profile. Maintain a high index of suspicion, particularly for reactivation of latent tuberculosis or hepatitis B infection.	
Methotrexate	Alopecia	Self-reported hair loss	Usually reversible after stopping drug
	Mouth ulcers	Self-reported mouth ulcers Inspection of oral mucosa	Folic acid supplementation (not on day of methotrexate)
	Pneumonitis	Symptoms of cough or dyspnoea Routine respiratory examination	CXR, PFTs and urgent specialist review
	Abnormal LFTs Cirrhosis	LFTs as per routine for all DMARDs	Continue folic acid supplementation. If AST or ALT <2 x ULN, repeat LFTs in a month. If normalising, continue. If persistent elevation, reduce dose. If AST or ALT >2 x ULN, interrupt treatment and discuss with rheumatologist.
Sulfasalazine	Haemolytic anaemia	Symptoms of anaemia	Stop treatment and seek specialist advice.
	Abnormal LFTs	LFTs as per routine for all DMARDs	If AST or ALT <2 x ULN, repeat LFTs in a month. If normalising, continue. If persistent elevation, reduce dose. If AST or ALT >2 x ULN, interrupt treatment and discuss with rheumatologist.
Corticosteroids	Adrenal suppression (more likely with courses >3 weeks and prednisolone doses ≥7.5 mg)	No specific monitoring required	Do not stop abruptly. Consider increasing the dose during intercurrent acute illness.
	Diabetes	Blood glucose and HbA1c monitoring	If continued use is necessary, consider escalation of hypoglycaemic treatment.
	Hypertension	Blood pressure checks each visit	If continued use is necessary, consider antihypertensive drugs.
	Osteoporosis (when used at doses of prednisolone ≥7.5 mg for ≥3 months)	Bone mineral density assessment at baseline, repeat at 3 months Self-reported skeletal pain suggesting fracture	If continued use is necessary, strongly consider starting a bisphosphonate.
	Psychosis Mania Delirium Depression Insomnia	Vigilance for new or worsened mental health or sleep disturbance	Cease, or use the lowest possible dose. Seek specialist advice. Discuss with rheumatologist.

Table **Disease-modifying antirheumatic drugs and monitoring in rheumatoid arthritis (continued)**

Drug	Adverse drug reaction	Monitoring	Action
Hydroxychloroquine	Photosensitivity	Self-reported sensitivity	Sun protection strategies
	Haemolytic anaemia	Symptoms of anaemia	Stop treatment and seek specialist advice.
	Blue–grey skin discolouration	Self-reported skin discolouration and examination of sun-exposed sites	Stop treatment immediately and seek specialist advice. Sun protection strategies
	Corneal deposits Retinal toxicity	Baseline ophthalmological assessment, then repeat at 5 years with annual review thereafter if therapy ongoing.[20] Annual review is recommended from initiation of therapy in high-risk patients (age >70 years, macular disease, renal disease, liver disease, higher than recommended dose).[20] Self-reported visual disturbance	Stop drug and seek specialist advice.
Leflunomide	Alopecia	Self-reported hair loss	Usually reversible. Reduce dose or stop drug.
	Hypertension	Blood pressure assessment on each visit	Reduce dose and/or add antihypertensive.
	Pneumonitis	Symptoms of cough or dyspnoea Routine respiratory examination	CXR, PFTs and seek specialist review.
	Peripheral neuropathy	Self-reported paraesthesia or weakness	Stop drug, consider NCS and EMG if not resolving, seek specialist advice.
	Hepatotoxicity	LFTs every 2–4 weeks for 3 months, then every 3 months ongoing	If AST or ALT <2 x ULN, continue and repeat LFTs in a month. If AST or ALT 2–3 x ULN, reduce dose and repeat LFTs in 2–4 weeks. Continue if normalising. If persistent elevation, discuss with rheumatologist. If AST or ALT >3 x ULN, stop drug and repeat LFTs in 2–4 weeks. If elevated, discontinue, consider washout and discuss with rheumatologist. **Note:** For any severe reactions to leflunomide consider cholestyramine washout (8 g 3 times a day for 11 days)
Tofacitinib	Abnormal LFTs	LFT frequency determined by other DMARDs used	If AST or ALT 1–2 x ULN, seek specialist advice. If AST or ALT >2 x ULN, seek urgent advice.
	Myelosuppression	FBE after 3–4 weeks, then every 3 months	Seek specialist advice, stop drug if severe.
	Dyslipidaemia	Lipid profile 8 weeks after starting and then guided by results	Modify lifestyle and diet, consider lipid-lowering therapy.
	Reactivated tuberculosis	Ideally detected pre-treatment, but may present during treatment as pulmonary or disseminated disease	Stop treatment immediately and seek specialist advice.
	Herpes zoster	Patient-reported rash or pain	Start antiviral treatment within 72 hours of rash onset. If recurrent, discuss with rheumatologist.
Abatacept	COPD exacerbation	Symptoms of COPD exacerbation	Treat exacerbation and discuss with rheumatologist.
	Hypertension	Blood pressure	Modify lifestyle, consider antihypertensive.
	Injection site reactions	Visualisation of injection site	Rotation of injection sites, antihistamines, topical cold packs, topical corticosteroids
	Anaphylaxis	–	See *Australian Prescriber* wallchart[21]
Rituximab	Infusion reactions	–	Stop or slow the rate of infusion, treat symptoms.
	Anaphylaxis	–	See *Australian Prescriber* wallchart[21]
	Myelosuppression	FBE before each treatment	If severe, delay treatment.

Table **Disease-modifying antirheumatic drugs and monitoring in rheumatoid arthritis (continued)**

Drug	Adverse drug reaction	Monitoring	Action
Anakinra	Myelosuppression (especially neutropaenia)	FBE frequency determined by other DMARDs used. Neutropaenia may be delayed and prolonged.	Discontinue and discuss with rheumatologist.
	Injection site reactions	Visualisation of injection sites	Rotation of injection sites, antihistamines, topical cold packs, topical corticosteroids
	Infection	As per routine monitoring for all DMARDs	Arrange follow-up visit, consider antimicrobial, remain vigilant for deterioration and the need for hospitalisation, stop if serious infection.
	Anaphylaxis	–	See *Australian Prescriber* wallchart[21]
TNF inhibitors	Injection site reactions	Visualisation of injection sites	Rotation of injection sites, antihistamines, topical cold packs, topical corticosteroids
	Drug-induced lupus	Self-reported rash, fever or arthralgia	Assess urine for evidence of glomerulonephritis. Assess serum lupus antibody profile and complement levels. Seek urgent advice from rheumatologist.
	Demyelinating syndrome	Self-reported neurological symptoms	Consider MRI, seek specialist advice.
	Malignancy	Participation in age-appropriate screening programs	Stop treatment immediately and seek specialist advice.
	Infection	As per routine monitoring for all DMARDs	Arrange follow-up visit, consider antimicrobial, remain vigilant for deterioration and the need for hospitalisation, stop if serious infection.
	Reactivated tuberculosis	Ideally detected pre-treatment, but may present during as pulmonary or disseminated disease without fever	Stop treatment immediately and seek specialist advice.
	Herpes zoster	Self-reported rash or pain	Start antiviral treatment within 72 hours of rash onset. If recurrent, discuss with rheumatologist.
Tocilizumab	Hypertension	Blood pressure checks each visit	Modify lifestyle modification, consider antihypertensive.
	Myelosuppression	FBE at baseline, then every 4–8 weeks	Interrupt treatment and discuss with rheumatologist.
	Dyslipidaemia	Lipid profile at baseline. Repeat after 4–8 weeks of treatment, then as per relevant guidelines	Modify lifestyle modification, consider lipid-lowering therapy.
	Gastrointestinal perforation	Self-reported abdominal pain	Stop therapy and discuss with rheumatologist.
	Infection	As per routine monitoring for all DMARDs **Note:** CRP is an unreliable marker for infection during tocilizumab therapy due to IL-6 blockade	Minor infection – interrupt treatment until recovered. Serious infection – stop treatment.
	Abnormal LFTs	LFTs at baseline and every 4–8 weeks for 6 months, then every 3 months	If AST or ALT >1–3 x ULN, reduce dose, or stop until normal. If AST or ALT >3 x ULN, stop until >1–3 x ULN then reduce dose. If AST or ALT >5 x ULN, discontinue treatment.

ALT	alanine aminotransferase	EMG	electromyography	MRI	magnetic resonance imaging
AST	aspartate aminotransferase	EUC	electrolytes, urea, creatinine	NCS	nerve conduction study
COPD	chronic obstructive pulmonary disease	FBE	full blood examination	PFTs	pulmonary function tests
CRP	C-reactive protein	HbA1c	glycated haemoglobin	TNF	tumour necrosis factor
CXR	chest x-ray	IL-6	Interleukin-6	ULN	upper limit of normal
DMARDs	disease-modifying antirheumatic drugs	LFTs	liver function tests		

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