bpacnz
PRIMARY CARE
UPDATE SERIES

02

RHEUMATOID ARTHRITIS:

A COLLABORATIVE APPROACH TO MANAGEMENT

Welcome to the bpac[nz] primary care update series. For the next topic in our musculoskeletal theme, we're going to be reviewing rheumatoid arthritis, with guest commentary from **Associate Professor Simon Stebbings**, a consultant rheumatologist from the Southern DHB. Although most patients with rheumatoid arthritis are initially managed in secondary care, best patient outcomes are achieved when secondary and primary care clinicians work collaboratively to promptly diagnose, initiate treatment and monitor disease progression and adverse effects of medicines.

NOVEMBER 2020
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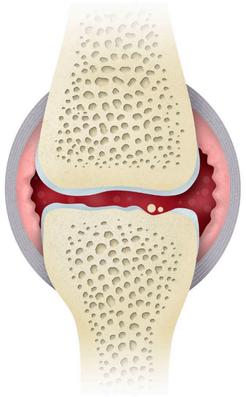
Rheumatoid arthritis (RA)



A **systemic autoimmune response that targets the synovium of joints**, causing inflammation, pain, swelling, stiffness and joint damage

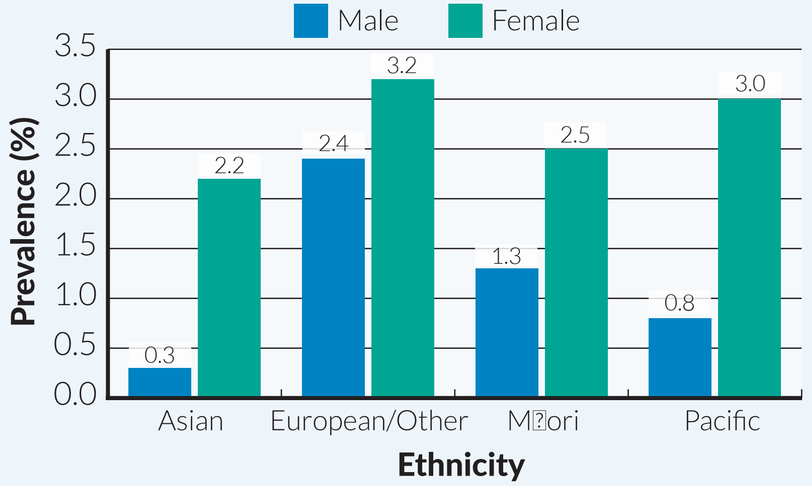
- Extra-articular manifestations may also occur
  e.g. in the lungs, skin, eye mucosa and salivary glands

Risk factors include female sex, genetics and smoking

- Although RA can affect people of any age, there is a bi-modal pattern of onset

Younger onset	Later onset
• Fewer erosions at onset • Mostly seropositive • Predominantly affects women	• More erosions at onset • Not always seropositive • More equal gender distribution

RA Prevalence in New Zealand, 2019



Ministry of Health. New Zealand Health Survey: Annual Update of Key Results 2018/19. Available at: https://www.health.govt.nz/publication/annual-update-key-results-2018-19-new-zealand-health-survey (Accessed Aug, 2020).

1. Aletaha D, Smolen JS. JAMA. 2018;320:1360–72; 2. Innala L, Berglin E, Möller B, *et al.* Arthritis Res Ther. 2014;16:R94; 3. Simon TA, Kawabata H, Ray N, et al. Adv Ther. 2017;34:2481–90.

The main diagnostic features

- Synovitis (joint tenderness, warmth and erythema, joint swelling, reduced ROM)
  - Often symmetrical and affecting multiple small joints
  - Other differential diagnoses have been excluded
  - Morning stiffness that lasts more than 30 min
  - Pain during squeeze test
- Symptoms longer than six weeks*
- RF-positive **and/or** anti-CCP-positive
- Elevated CRP **and/or** ESR†

Other tests to request:**
FBC, creatinine, LFTs, ANA, urinalysis

Patients with RA are more likely to have other autoimmune diseases

X-rays are often recommended as part of the diagnostic work-up, and are important to assess damage and progression, but are not required to make a diagnosis in early-stage RA

** **See the practice tool for more specific information on identifying patients with RA in primary care**

* Earlier if there is a strong family history; † Suspicion of rheumatoid arthritis needs to be documented on the request form in order for an ESR test to be performed at community laboratories.

ANA, antinuclear antibody; Anti-CCP, anti-cyclic citrullinated peptide/protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; LFT, liver function test; RF, rheumatoid factor; ROM, range of motion. 1. Aletaha D, Smolen JS. JAMA. 2018;320:1360–72.

Once RA is suspected, early referral and/or consultation with secondary care is key

Prompt initiation of DMARD treatment is associated with improved long-term outcomes

- DMARDs target critical pathways in the patient's inflammatory response to limit disease progression

One meta-analysis demonstrated that **patients with RA treated within 1 year of symptom onset have 33% less joint damage** compared with those starting DMARD treatment after >1 year of symptoms (median follow-up 3 years)

Demoruelle MK, Deane KD. Curr Rheumatol Rep. 2012; 14:472–80.

The decision to initiate a DMARD often is made by the rheumatologist following confirmation of the patient's diagnosis

…**However**, while the patient is waiting for an initial rheumatology appointment and before DMARDs take effect, **medicines for symptomatic relief are usually required** (see next slide)

DMARD, disease modifying anti-rheumatic drug; RA, rheumatoid arthritis.

1. Drug treatment for rheumatoid arthritis. National Institute for Health and Care Excellence (NICE). Available at: http://pathways.nice.org.uk/pathways/rheumatoid-arthritis (Accessed Oct, 2020).

Medicines for managing acute RA symptoms

Medicines to acutely manage pain and inflammation are often given when DMARDs are being initiated ("**bridging**") or when flares occur

- Use for the **shortest period of time** possible

NSAIDs alone may be sufficient in patients with mild disease activity

- ✓ NSAIDs can be **co-prescribed with methotrexate** in most patients with RA (see next slide)
- ✓ Paracetamol can also be used for additional pain relief, if required
- ✗ **Avoid opioids** as an analgesic

Corticosteroids can be used for patients with more severe disease activity, or who do not respond sufficiently to NSAIDs alone

- **Oral dosing** is usually preferred
- A **one-off intra-muscular injection** can sometimes be considered for acute symptoms
- **Intermittent intra-articular injections** may be useful if one or two joints are affected, or for "problematic" joints

DMARD, disease modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis.

1. Singh JA, Saag KG, Bridges S, et al. Arthritis Care Res. 2016;68:1–25; 2. Drug treatment for rheumatoid arthritis. National Institute for Health and Care Excellence (NICE). Available at: http://pathways.nice.org.uk/pathways/rheumatoid-arthritis (Accessed Oct, 2020); 3. Colebatch AN, Marks JL, van der Heijde DM, Edwards CJ. J Rheumatol 2012; 90: 62-73.

Methotrexate – the first-line DMARD for patients with RA

Once weekly dosing

- Ensure the patient understands their dosing regimen and adverse effects to look out for
- Dose increased as tolerated, usually with guidance from the rheumatologist

	Monitoring (for adverse effects of methotrexate)	**Frequency**	**What to look for**	**Action**
Laboratory tests	Full blood count ←	Baseline; every 2–4 weeks initially until the dose of methotrexate is stable; then every month to three months thereafter	WBC count <3.5×10⁹/L; neutrophils <2.0×10⁹/L; platelets <150×10⁹/L	Discuss with rheumatologist
			MCV >105 fL	Check vitamin B12, folate and TSH
	Liver function tests ←		AST, ALT >2× the upper limit of normal	Withhold until discussed with rheumatologist. Also: • Re-check alcohol intake (up to 1–2 standard drinks once or twice a week is acceptable) • Review NSAID use; may cause liver dysfunction • Review other medicine use
			Unexplained decrease in albumin (in absence of active disease)	
	Serum creatinine ←		Moderate renal function deterioration	Reduce methotrexate dose and address possible causes
			Significant renal function deterioration	Withhold until discussed *with* or referred to rheumatologist
Symptoms/signs	Rash or oral ulceration		**Warn the patient that they need to report any of these symptoms immediately if they occur**	Withhold until discussed with rheumatologist. Oral folinic acid or folinic acid mouthwash may help with mucositis
	Nausea and vomiting, diarrhoea			Discuss with rheumatologist about giving oral methotrexate in three divided doses over 36 hours once a week or giving methotrexate by subcutaneous injection to avoid nausea
	New or increasing dyspnoea or dry cough (pneumonitis)	Baseline chest x-ray and respiratory function tests recommended		Withhold and discuss URGENTLY with rheumatologist. Arrange chest x-ray and respiratory function tests
	Severe sore throat or abnormal bruising			Immediate FBC and withhold until results available. Discuss any unusual results with rheumatologist

AST, aspartate aminotransferase; ALT, aspartate transaminase; DMARD, disease modifying antirheumatic drug; FBC, full blood count; MCV, mean corpuscular volume; NSAID, non-steroidal anti-inflammatory drugs; TSH, thyroid stimulating hormone; WBC, white blood cell. 1. Methotrexate – once weekly dosing. MedSafe. Available at: https://www.medsafe.govt.nz/profs/PUArticles/December2017/Methotrexate.htm (Accessed Oct, 2020).

Methotrexate – practical advice

Tips to help avoid errors associated with methotrexate dosing:

- ☐ Confirm that the patient (and/or carer) understands their dosing regimen; specifically that it is weekly, not daily dosing
- ☐ Do not write "take as directed" on prescriptions
- ☐ Agree on a day of the week to take methotrexate; specify this on the prescription in full
- ☐ Only prescribe (and dispense) one tablet strength

Folic acid (5mg, once weekly) should be prescribed concurrently with methotrexate, on a different day

- E.g. "**M**ethotrexate on **M**onday, **F**olic acid on **F**riday"

Night-time dosing just before sleep may help with the patient's perception of nausea

Methotrexate is contraindicated during pregnancy

- Discuss child-planning/contraception options with woman of child-bearing age
- Advise the use of effective contraception during and for at least three months after treatment with methotrexate in women or men

For a patient info guide on methotrexate, see:
www.saferx.co.nz/assets/Documents/3fe06fa9a3/methotrexate-patient-guide.pdf

See our previous article for more information on safe methotrexate prescribing
bpac.org.nz/bpj/2014/october/safer-prescribing.aspx

1. Methotrexate – once weekly dosing. MedSafe. Available at: https://www.medsafe.govt.nz/profs/PUArticles/December2017/Methotrexate.htm (Accessed Oct, 2020); 2. Drug treatment for rheumatoid arthritis. National Institute for Health and Care Excellence (NICE). Available at: http://pathways.nice.org.uk/pathways/rheumatoid-arthritis (Accessed Oct, 2020); 3. Methotrexate. Auckland Rheumatology and Sports Medicine. Available at: https://aucklandrheumatology.co.nz/methotrexate.html (Accessed Oct, 2020)

Assessing the effectiveness of treatment

The long-term objective is remission

Remission of RA is defined as having the sustained absence of inflammatory joint pain (pain due to damage may be unavoidable), with no swelling or morning stiffness, and normalised inflammatory marker levels

Possible markers to assess changes in disease activity:

- Tender joint counts/swollen joint counts
- Asking the patient about their level of pain or discomfort, and effect on daily function/QOL
- Laboratory testing, particularly CRP levels
- Imaging of affected joints, e.g. with x-ray, ultrasound, MRI

Consider using a scoring criteria which combines these factors, e.g. DAS28

Also consider:

CVD risk

People with RA have a 50% higher risk of CVD-related morbidity and mortality compared to the general population

Management of **extra-articular manifestations** and **co-morbidities**

Anti-CCP, anti-cyclic citrullinated peptide/protein antibody; CRP, C-reactive protein; CVD, cardiovascular disease; DAS, disease activity score (28 refers to the 28 joints that are assessed); ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; MRI, magnetic resonance imaging; QOL, quality of life; RA, rheumatoid arthritis. 1. Aletaha D, Smolen JS. JAMA. 2018;320:1360–72; 2. Drug treatment for rheumatoid arthritis. National Institute for Health and Care Excellence (NICE). Available at: http://pathways.nice.org.uk/pathways/rheumatoid-arthritis (Accessed Oct, 2020).

Optimising the long-term treatment of patients with RA

DMARD monotherapy initiated ASAP
- Methotrexate preferred
- Progressively increase dose, as tolerated and as dictated by disease activity
- Short-term NSAIDs or corticosteroids as needed for symptom relief

Dual DMARD treatment
Ideally methotrexate + another DMARD

Alternative DMARD monotherapy
(more information in next slides)

Most commonly used:
- Leflunomide
- Sulfasalazine
- Hydroxychloroquine

Less commonly used:
- Azathioprine
- Ciclosporin
- Gold injections

Triple DMARD treatment
Ideally with methotrexate, sulfasalazine and hydroxychloroquine

Biologics

See later slide for more information on biologics

The choice of treatment, and method of treatment escalation, depends on:
- The stage and severity of RA
- Patient co-morbidities and clinical characteristics
- Current medicine use

DMARD, disease modifying anti-rheumatic drugs; RA, rheumatoid arthritis.

1. Aletaha D, Smolen JS. JAMA. 2018;320:1360–72.

Alternatives to methotrexate monotherapy: the most commonly used options

Treatment	When might it be used?	Notes	Monitoring **Note:** specific requirements will be directed by the rheumatologist
Leflunomide	• Alone or in combination with methotrexate when it is contraindicated, not tolerated, or ineffective • Often the first choice alternative to methotrexate	• Comparable efficacy to methotrexate • Contraindicated during pregnancy; contraception is required during use and after until serum levels are not detectable (which may take several months to years due to the long half-life; a washout is possible if required) • Advise limited alcohol consumption	• Similar to methotrexate; particularly liver monitoring • Also ensure blood pressure is closely monitored at each visit as leflunomide can increase blood pressure
Sulfasalazine	• Alone or in combination with methotrexate when it is contraindicated, not tolerated, or ineffective • Patients with mild RA • Patients with liver disease • Patients who are pregnant (or planning); there is a theoretical risk of neonatal haemolysis in third trimester; prescribe folic acid throughout pregnancy	• Is a yellow-orange colour which may affect the colour of urine, tears, sweat and soft contact lenses • Ensure patients drink ≥2L fluid/daily • Can cause reversible oligospermia • May take ≥1–2 months to improve symptoms	• Similar to methotrexate • Small risk of severe neutropenia
Hydroxy-chloroquine	• Alone or in combination with methotrexate when it is contraindicated, not tolerated, or ineffective • Patients with very mild RA • Patients who are pregnant (or planning pregnancy)	• Increased risk of cardiomyopathy and QT prolongation and damage to the retina • May cause photosensitivity of skin • Dose based on body-weight; may take ≥2–3 months to improve symptoms	• A baseline ophthalmological review is essential; if normal examination and low risk (age <60 years, no liver disease, no retinal disease), 5 yearly visual acuity test; if high risk, annual visual acuity test is needed • Consider performing baseline ECG
Dual or triple combination treatment	• When monotherapy alone is ineffective • Some patients with a high level of disease activity will be moved straight to triple therapy if methotrexate alone is ineffective (vs dual therapy)	• The most effective triple combination is methotrexate, sulfasalazine and hydroxychloroquine	• As directed by rheumatologist

RA, rheumatoid arthritis.

1. NZ Formulary. NZF v100. Available from: www.nzf.org.nz (Accessed Oct, 2020); 2. Aletaha D, Smolen JS. JAMA. 2018;320:1360–72; 3. Drug treatment for rheumatoid arthritis. National Institute for Health and Care Excellence (NICE). Available at: http://pathways.nice.org.uk/pathways/rheumatoid-arthritis (Accessed Oct, 2020).

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Biologics

Note: see the current SA application form for full requirements according to the specific biologic

In general, to meet the Special Authority (SA)* criteria for a biologic, patients need:

- ☐ To have severe, active and erosive RA for ≥6 months (i.e. not early disease); ***and***
- ☐ To have trialled optimal dosing† of **methotrexate, triple combination treatment** (methotrexate, sulfasalazine and hydroxychloroquine), as well as an **additional DMARD** (e.g. leflunomide, azathioprine, ciclosporin or gold injections; alone or in combination with methotrexate) first; ***and***
- ☐ To have 20 total joints that are swollen or tender or symptoms of poorly controlled and active disease in at least 4 of the following joints: wrist, elbow, knee, ankle, and either shoulder or hip; ***and***
- ☐ To have an elevated CRP (>15 mg/L) ***unless*** the patient is currently on prednisone dose >5mg/daily and has been for more than three months

* Initial applications can only come from a rheumatologist. Renewals can also come from a GP on rheumatologist recommendation; † Optimal dosing refers to when the patient has not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose. **Abbreviations**: DMARD, disease modifying anti-rheumatic drugs; RA, rheumatoid arthritis. 1. NZ Formulary. NZF v100. Available from: www.nzf.org.nz (Accessed Oct, 2020).

Biologic DMARDs (biologics) – the next step after conventional DMARD treatment

	Biologics (all approved for use in patients with RA)	Structure	Route of administration	Target	Most common adverse effects and notes
Funded with Special Authority approval	**Adalimumab**	Human mAb	Subcutaneous injection	TNFα	• Infections • Re-activation of latent TB • Psoriasiform dermatoses • Exacerbation of demyelinating diseases • Drug-induced lupus • Non-melanoma skin cancer • Avoid in pregnancy
	Etanercept	Receptor construct			
	Infliximab	Chimeric mAb	IV infusion		
	Rituximab	Human mAb	IV infusion	CD20	• Reactivation of hep B • Leukocytopenia • Hypersensitivity reactions • Avoid in pregnancy
	Tocilizumab	Humanised mAb	IV infusion	IL-6R	• Infections • Re-activation of latent TB • Bowel perforation • Hypersensitivity reactions • Neutropenia • Hyperlipidaemia • Often selected if the patient is methotrexate intolerant
Not funded	**Abatacept**	Receptor construct	IV infusion or subcutaneous Injection	CD80R and CD86R	• Infections • Re-activation of latent TB • Leukocytopenia • Avoid in pregnancy

IV, intravenous; mAb, monoclonal antibody; TB, tuberculosis; TNFα, tumour necrosis factor α.

Given in combination with methotrexate (where possible)

No major head-to-head trials for biologics; most have comparable efficacy

Very effective at slowing the progression of structural damage as measured by X-ray, e.g. erosions

Check for latent TB prior to initiation (and for hep B in the case of rituximab)

1. Aletaha D, Smolen JS. JAMA. 2018;320:1360–72; 2. NZ Formulary. NZF v100. Available from: www.nzf.org.nz (Accessed Oct, 2020).

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	Tocilizumab	Humanised mAb	IV infusion	IL-6R	• Infections • Re-activation of latent TB • Bowel perforation • Hypersensitivity reactions • Neutropenia • Hyperlipidaemia • Often selected if the patient is methotrexate intolerant
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For a more in depth look into contraindications and cautions relating to biologic use, see the NZ Formulary

IV, intravenous; mAb, monoclonal antibody; TB, tuberculosis; TNFα, tumour necrosis factor α.

1. Aletaha D, Smolen JS. JAMA. 2018;320:1360–72; 2. NZ Formulary. NZF v100. Available from: www.nzf.org.nz (Accessed Oct, 2020).

Review the patients immunisation status before prescribing DMARDs or biologics

In addition to the National Immunisation Schedule:

Strongly consider:

- ☐ Annual influenza (funded) – set up a recall
- ☐ Five-yearly pneumococcal vaccine (generally not funded*)

Risk of pneumonia decreases by **approximately 75%**

Also consider:

- ☐ Hepatitis B vaccination, particularly with rituximab
- ☐ HPV vaccination for people aged nine to 26 years
- ☐ Shingles vaccination (Zostavax) – but not *during* biologic treatment (see below)

Do not give live vaccines to patients already receiving biologics, e.g. Varilix, Zostavax

Live vaccine recommendations for patients taking DMARDs

Patient treatment	Live vaccination **before** treatment?	Live vaccination **during** treatment?	Live vaccination **after** treatment?
Methotrexate (dose ≤ 0.4 mg/kg/week)	Any time	Yes	Any time
Methotrexate (dose > 0.4 mg/kg/week)	1 month before	No	3 months after
Leflunomide	1 month before	No	6 months after
Sulfasalazine	Any time	Yes	Any time
Hydroxychloroquine	Any time	Yes	Any time
Biologics	1 month before	No	12 months after

From: Diseases and medications when live vaccines may be contraindicated. The Immunisation Advisory Centre. Available at: https://www.immune.org.nz/sites/default/files/resources/Written%20Resources/AdministrationImmunecompLiveVac20180507V02Final.pdf (Accessed Sep, 2020)

* Government funding is not generally available for people older than five years unless they meet specific high risk criteria (see https://www.pharmac.govt.nz/information-for/covid-19-pharmacs-response/pneumococcal-vaccine/ for more information) DMARD, disease-modifying anti-rheumatic drug; HPV, human papilloma virus.

1. Friedman MA, Winthrop K. Curr Opin Rheumatol. 2016;28:330; 2. Singh JA, Saag KG, Bridges S, et al. Arthritis Care Res. 2016;68:1–25; 3. Immunisation Handbook 2017. Ministry of Health. Available at: https://www.health.govt.nz/system/files/documents/publications/immunisation-handbook-2017-2nd-edition-mar18-v9_1.html#_Toc44416788 (Accessed Oct, 2020).

Non-pharmacological measures should underpin RA management for all patients

1. Vliet Vlieland TPM, van den Ende, CH. Curr Opin Rheumatol. 2011;23:259–64.

A common question: *Can treatment for RA ever be de-escalated?*

International guidelines do not recommend completely stopping DMARDs for patients in sustained remission; however, **dose tapering or reducing from combination treatment to monotherapy can be considered for some**

Relapses and flares are common in patients that de-escalate their treatment; patients should be aware of this, and decreases should be gradual

DMARD, disease modifying anti-rheumatic drug

1. Aletaha D, Smolen JS. JAMA. 2018;320:1360–72; 2. Drug treatment for rheumatoid arthritis. National Institute for Health and Care Excellence (NICE). Available at: http://pathways.nice.org.uk/pathways/rheumatoid-arthritis (Accessed Oct, 2020).