Rheumatoid arthritis
How can we improve remission?

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Early diagnosis, referral and initiation of disease-modifying antirheumatic drug (DMARD) therapy, along with regular disease monitoring and treating to target, are crucial to give patients with rheumatoid arthritis the best chance of achieving remission.

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterised by joint inflammation and functional impairment, and potentially leading to permanent disability and reduced life expectancy. The past decade has seen substantial improvement in patient outcomes, as RA is diagnosed earlier, and disease-modifying antirheumatic drug (DMARD) treatments are complemented by biological DMARD (bDMARD) therapies. The ultimate goal of RA treatment is to achieve remission and stop the progression of joint damage. This article will discuss how we can achieve better outcomes in patients with RA.

EARLY DIAGNOSIS

RA is characterised by symmetrical polyarthritis with joint swelling and early morning stiffness. It can be associated with extra-articular features such as subcutaneous nodules, vasculitis and interstitial lung disease. Accurate diagnosis and early intervention can significantly reduce the progression of disease and increase the chance of achieving remission.

New definition of rheumatoid arthritis

To facilitate earlier diagnosis, new classification criteria for RA were introduced in 2010 by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). 'Definite RA' is suggested if there is:

- at least one swollen joint (indicating definite synovitis)
- a score of 6 or more in the ACR-EULAR scoring system (Table 1), and
- no alternative diagnosis.[1]

It is, however, important to note that RA may still be diagnosed by rheumatologists in patients who do not satisfy these criteria, as they are a tool designed to improve the ability to discriminate RA from undifferentiated synovitis for the purpose of clinical trials and other studies.

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TABLE 1. 2010 ACR–EULAR SCORING SYSTEM FOR RHEUMATOID ARTHRITIS[1]

Add scores from items A to D. A score ≥ 6/10 indicates 'definite rheumatoid arthritis'.

	Score
A. Swollen or tender joint(s)	
1 large joint*	0
2–10 large joints	1
1–3 small joints† (± any large joint involvement)	2
4–10 small joints (± any large joint involvement)	3
> 10 joints (at least 1 small joint)	5
B. Serology	
Negative RF and negative anti-CCP	0
Low positive RF or anti-CCP (< 3 times upper limit of normal)	2
High positive RF or anti-CCP (≥ 3 times upper limit of normal)	3
C. Acute phase reactants	
Normal CRP and normal ESR (as per local laboratory standard)	0
Elevated CRP or ESR (as per local laboratory standard)	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

ABBREVIATIONS: ACR = American College of Rheumatology; anti-CCP = anti-cyclic citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; RF = rheumatoid factor.

* Large joints = shoulders, elbows, hips, knees, ankles.

† Small joints = metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists.

Figure. Squeeze test: a gentle squeeze of the metacarpophalangeal and metatarsophalangeal joints determines the number of affected joints.

Rapid screening tool for rheumatoid arthritis

A rapid screening tool to alert clinicians to the clinical suspicion of 'probable RA' has also been developed. RA should be considered if any of the following is present:

- more than three swollen joints
- early morning stiffness of 30 minutes or longer
- a positive 'squeeze' test in the metacarpophalangeal and metatarsophalangeal joints (see the Figure).

Patients with suspected RA should be referred to a rheumatologist, ideally within six weeks of symptom onset. Many tertiary referral centres around Australia have established 'early arthritis clinics' to facilitate the early diagnosis of inflammatory arthritis.

ACHIEVING REMISSION

Remission re-defined

At first glance, the definition of remission seems relatively straightforward: remission would be the elimination of all disease or the 'absence of articular and extra-articular inflammation and disease activity'.[2] However, even when there are no clinical findings of disease activity, ongoing subclinical inflammation has been shown using ultrasound or magnetic resonance imaging or histopathologically in a proportion of patients.[3] In 2011, ACR and EULAR re-defined remission in RA, suggesting two alternatives:

- a score of 1 or less for each of tender joint count, swollen joint count, C-reactive protein level (CRP, in mg/dL, with 1 mg/dL equivalent to 10 mg/L) and Patient Global Assessment score (on a 0 to 10 Likert scale) or
- a score of 3.3 or less on the Simplified Disease Activity Index (SDAI; see Box 1).[4]

Early initiation of therapy

The chances of patients with RA achieving remission improve with early diagnosis and early initiation of DMARD therapy. In particular, there seems to be a window of opportunity in the first three months following symptom onset, when the course of RA can potentially be altered. This was illustrated in a prospective study of 800 patients with RA, which found that those treated early (within 12 weeks of disease onset) with DMARD therapy were

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1. ACR AND EULAR DEFINITIONS OF REMISSION IN RHEUMATOID ARTHRITIS[4*]

Boolean-based definition

At any time point, patient has all of the following:

- tender joint count ≤ 1
- swollen joint count ≤ 1
- C-reactive protein level (mg/dL) ≤ 1[†]
- Patient Global Assessment score ≤ 1[‡]

Simplified Disease Activity Index (SDAI)

At any time point, the patient's SDAI is ≤ 3.3

SDAI is the numerical sum of:

- tender joint count[§]
- swollen joint count[§]
- Patient Global Assessment score[‡]
- Physician Global Assessment score[‡]
- C-reactive protein level (expressed in mg/dL)

ABBREVIATIONS: ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.

* Felson D, Smolen J, Wells G. Arthritis Rheum 2011; 63: 573-586.
† Equivalent to 10 mg/L.
‡ On a 0 to 10 Likert scale, where 0 is the best assessment and 10 is the worst assessment.
§ Using a 28 joints count (shoulders, elbows, wrists, knees, metacarpophalangeal and proximal interphalangeal joints).

TABLE 2. DMARDS AND BIOLOGICAL DMARDS CURRENTLY AVAILABLE FOR RHEUMATOID ARTHRITIS AND THEIR SIDE EFFECTS

Drug	Common side effects
Traditional synthetic DMARDs	
Methotrexate	Mouth ulcers, nausea, abnormal LFT, leucopenia
Leflunomide	Diarrhoea, abnormal LFT, alopecia
Sulfasalazine	Mouth ulcers, nausea, abnormal LFT, rash
Hydroxychloroquine	Nausea, rash, retinopathy (rare)
Gold	Rash, nephrotic syndrome
Cyclosporin	Hypertension, renal impairment, gum hypertrophy, hirsutism
Biological DMARDs	
Tumour necrosis factor (TNF) inhibitors:	Injection site reaction, infections (especially respiratory and skin infections), worsened congestive cardiac failure
Adalimumab	
Certolizumab	
Etanercept	
Golimumab	
Infliximab	
Interleukin-6 receptor inhibitor:	
Tocilizumab	Infusion reaction, abnormal LFT, hyperlipidaemia, infections (especially respiratory and skin infections)
Destroys B cells:	
Rituximab	Infusion reaction, headaches, gastrointestinal discomfort
T cell inhibitor:	
Abatacept	Headaches, dizziness, sore throat, runny nose, rash

ABBREVIATION: DMARD = disease-modifying antirheumatic drug; LFT = liver function tests.

1.65 times more likely than those treated later to achieve remission of their disease at 1 year. Furthermore, those treated early were also three times less likely to require a bDMARD.[5] Hence, GPs can improve outcomes for patients with RA through early recognition of inflammatory joint symptoms and subsequent early referral to a rheumatologist for DMARD therapy.

The armamentarium used to treat RA has expanded substantially in the past decade. The various DMARD and bDMARD therapies used in the treatment of RA, and their side effects, are summarised in Table 2. In Australia, the PBS restricts bDMARD use to patients in whom traditional DMARDs have been unsuccessful in achieving a low disease state. Prescription of bDMARDs requires a rheumatologist or consultant physician who is experienced in their use.

Treating to target

Remission is more likely to be achieved in RA when there is tight control of the disease through titration of DMARD and bDMARD therapy to a disease-monitoring index, such as the SDAI.[6] For example, an SDAI score of 3.3 or less is one of the targets for remission, and an SDAI score of 11 or less is a 'low disease activity state', where there is generally less progression of joint damage.[7] If RA disease activity

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2. PREDICTORS OF MEDICATION-FREE REMISSION[13,14]

- Male sex
- Milder rheumatoid arthritis at baseline
- Shorter disease duration
- Little radiographic damage at baseline
- Absence of rheumatoid factor and anti-CCP antibodies
- Nonsmoker

does not reach the target then adapting therapy promptly has been shown in many studies to optimise patient outcome.[8] In particular, if monotherapy is not adequate to bring the patient into a low disease activity state or remission then combination therapy (with multiple DMARDs or addition of a bDMARD) should be instituted to more effectively induce remission or a low disease activity state.[9]

Early review of patients requiring dose adjustments because of unsuppressed disease activity is an important aspect of the treat to target approach.

Treat to target trials have shown that achieving tight control of RA can achieve a 'low disease activity state' in about 50% of patients, while remission is achieved in about 30% of patients.[10]

SUSTAINING REMISSION

There are currently no guidelines as to whether or when antirheumatic medications should be ceased once a patient with RA has achieved remission. Studies have shown that up to 15% of patients with RA who initially obtained remission with DMARD therapy could sustain this remission without continuing with the DMARD agent(s).[11-13] Predictors of patients who might achieve a medication-free remission are listed in Box 2.[13,14]

Nevertheless, half of those who achieved a medication-free remission eventually relapsed, and DMARD therapy had to be restarted, often requiring higher dosages or combination therapy, and a low disease activity state was harder to obtain subsequently.[10] The low numbers needed to treat to avoid relapse suggest that complete withdrawal of treatment in patients in remission and without unwanted effects from their prevailing regimen should not be advised or encouraged.

CONCLUSION

Early diagnosis, early initiation of therapy, regular disease monitoring, and treating to target are all crucial to give patients with RA the best chance of achieving remission with DMARD therapy. Remission is a realistic and achievable goal that will alleviate pain and restore a patient's quality of life. MT

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COMPETING INTERESTS: Dr Tong has received honoraria from Janssen and Pfizer for attending educational conferences.

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