Management of rheumatoid arthritis

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Abstract

Successful management of rheumatoid arthritis (RA) requires suppression of the autoimmune response, which results in synovial inflammation, cartilage and bone damage and is associated with a range of extra-articular manifestations including accelerated atherogenesis, cancer and sepsis. The strategy to achieve this is called 'treat-to-target' and requires frequent patient review to escalate therapy until remission or at least low disease activity is achieved. Numerous therapeutic agents are licensed to achieve this, starting with glucocorticoids and conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, followed by four different mode of action biologic DMARDs (targeting tumour necrosis factor, interleukin-6, B cells and T cell co-stimulation) and targeted synthetic DMARDs (inhibitors of JAK). For newly diagnosed patients, especially if treated within 3 months of onset, the outlook is immeasurably better than two decades ago before the treat-to-target strategy and biologic therapies were introduced. As a consequence the outcomes for many newly diagnosed patients include preserved function, maintained quality of life and no impact on mortality. For patients with long-standing disease, further joint damage can be prevented and severe complications of RA such as vasculitis and amyloidosis are now a rarity. Nonetheless RA is an aggressive destructive disease and its tendency to relapse requires disease-long patient review and treatment optimization to maintain control.

Keywords Biologic therapies; co-morbidities; DMARD; MRCP; rheumatoid arthritis; treat-to-target

Key points

- The wide range of consequences of rheumatoid arthritis (RA), including adverse musculoskeletal function, cardiovascular, bone, septic and malignant effects, requires life-long holistic management by a multidisciplinary team
- The inflammatory response is managed robustly using a treat-to-target strategy, in which patients are assessed frequently, and treatment escalated if remission or low disease activity is not achieved
- Treatment starts with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and short-term glucocorticoids. Methotrexate is the anchor DMARD
- Treatment escalation options when csDMARDs fail include biologic DMARDs targeting tumour necrosis factor, B cells, T cell co-stimulation and interleukin-6, and targeted synthetic DMARDs which inhibit intracellular signalling by Janus kinases
- The combination of treat-to-target and the expanded range of therapeutic agents has profoundly changed the natural history of RA. Rates of orthopaedic surgery have dropped, mortality principally from cardiovascular disease has reduced, severe erosive deforming joint changes and complications such as vasculitis and amyloidosis are now a rarity

Introduction

Rheumatoid arthritis (RA) is a destructive inflammatory joint disease, principally affecting synovial joints. If not treated promptly, patients can be constrained from functioning or working, with long-lasting effects on mental and physical well-being. Accelerated atherosclerosis and cardiovascular morbidity, infection, some cancers including lymphoma, and chronic mental ill-health are just some of the key co-morbid conditions adding to the lifetime burden of RA and increasing mortality.

The treat-to-target (T2T) principle and therapeutic window of opportunity

Suppression of inflammation represents a key management principle, with the recommended strategy focusing on T2T. This requires the selection of an objective measurement (the target) of remission or low disease activity, frequent reviews and treatment optimization to achieve and maintain this.[1] The controversies and variability in current practice relate to:

- the chosen target— whether this should be an inflammation, a patient-reported outcome or a combination of these (Table 1)
- the necessary frequency of review, enabling treatment escalation if the chosen target has not been achieved; 4—6 weeks is recommended[1,2]
- the choice and sequence of therapeutic agents.

It is not clear how 'deep' the goal of remission should be in T2T terms (Table 1), for example based on clinical (swollen joint counts, acute-phase markers) and patient-reported (tender joint

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T2T composite disease activity measures in RA and contributing components

Disease activity measure	Components	Interpretation
DAS	SJC, TJC, ESR/CRP, patient global	Remission ≤1.6
DAS28	SJC, TJC, ESR/CRP, patient global	Remission ≤2.6; disease activity: low 2.6–3.2, moderate 3.3–5.0, high ≥5.1
CDAI	SJC, TJC, patient global, physician global	Remission ≤2.8; disease activity: low>2.8 and ≤10, moderate >10 and ≤22, high >22
SDAI	SJC, TJC, ESR/CRP, patient global, physician global	Remission <3.3; disease activity: low 3.4–11, moderate 11.1–26, high 26.1–86
ACR-EULAR Boolean	SJC28, TJC28, ESR/CRP, patient global	Remission: all scores ≤1 on a 1–10 scale
RAPID 3	patient global, pain, HAQ[a]	Remission ≤3; low severity 3.1–6.0, moderate severity 6.1–12, high severity >12
RAID	Pain, fatigue, functional disability, physical well-being, emotional well-being, coping	Patient acceptable status <2, change of 3 or 50% considered relevant

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score based on 53 tender and 44 swollen joint counts; DAS28, Disease Activity Score based on 28 joint counts and either ESR or CRP; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RAPID 3, Routine Assessment of Patient Index Data 3; RAID, Rheumatoid Arthritis Impact of Disease; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count.

[a] A subset of core values from the HAQ used in RAPID 3.

Table 1

counts, pain scores, global scores) criteria, or also requiring imaging criteria to be satisfied; these can include the absence of ultrasound power Doppler signal or inflammatory features on magnetic resonance imaging, or even serological remission in those positive for anti-citrullinated peptide antibodies (ACPAs). In contrast, for those presenting late or with established disease, a less stringent target such as low disease activity, rather than remission, is acceptable because the composite measures used to assess RA (Table 1) are influenced by accrued irreversible damage.

Much emphasis is rightly placed on early detection, rapid referral and prompt institution of treatment with an aspirational 'window of opportunity' of 3 months from symptom onset to commencing disease-modifying treatment. In general terms, patients with newly diagnosed disease presenting with a short history are the most likely to achieve remission (even applying the most stringent remission criteria), if started on treatment within 3 months when a T2T strategy is applied.

Securing the diagnosis of RA is crucial to commencing treatment within the window of opportunity. This relies on the person's health-seeking behaviour and recognition of the features of inflammatory arthritis in primary care. This can be difficult as symptoms of inflammatory joint disease, such as early morning stiffness, precede clinically detectable signs of synovial swelling, as do ACPAs, which can predate symptoms by 10 years or more. To assist early diagnosis, classification criteria for RA, while developed for harmonized enrolment into clinical trials, provide a useful tool in clinical practice.[3]

In secondary care, ultrasonography has enhanced clinical diagnosis and decision-making by enabling the identification of synovial hypertrophy (Gray scale) and hyperaemia (power Doppler) in cases where symptomatic joints are not clinically swollen.

Treatment choice

The treatment of RA must be based on two-way communication and shared decision-making between the patient and the rheumatologist, with the support of a multidisciplinary team (MDT) including a specialist nurse, physician associate, physiotherapist, occupational therapist and podiatrist.[2]

Conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs)

For newly diagnosed patients, the cornerstone of pharmacological treatment starts with a combination of fast-acting glucocorticoid (intramuscularly, intra-articularly, orally) and slow-acting csDMARDs to maintain corticosteroid-free disease suppression in the long term. A key principle is administering enough glucocorticoid to reverse the symptoms and signs rapidly, but not an unnecessarily high dose, without treating for too long, to avoid adverse effects on bone density, infection risk, hypertension, glycaemic balance and mental health.

csDMARD choices include methotrexate (MTX), hydroxychloroquine, sulfasalazine and leflunomide. Historically, gold and D-penicillamine have been used, but they now have no prominence in routine care. Other immunosuppressing drugs, such as ciclosporin A, tacrolimus, azathioprine, cyclophosphamide and mycophenolate mofetil, although useful in some immune-driven diseases, are generally not favoured in RA, other than in resistant cases. MTX is considered the anchor and first-line csDMARD in RA, either in monotherapy or in combination with other csDMARDs.

High disease activity at diagnosis, a large number of involved joints, baseline erosions on plain X-ray, high-titre rheumatoid factor (RF) or ACPA and poor functional scores generally indicate a higher likelihood of erosive and progressive disease, especially if suboptimally treated. The presence of any of these stratifiers

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