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CHAPTER 2

Recent advances
in the management
of rheumatoid
arthritis

A clinical review

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ABSTRACT

Until the 1990s patients with rheumatoid arthritis were initially treated with aspirin or other non-steroidal anti-inflammatory drugs; disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate, were introduced only as the disease progressed. Combined treatment with more than one DMARD was reserved for patients with the most severe disease. The outcome for most patients was functional deterioration with progressive damage. However, innovations in drugs, better tools for monitoring treatment, and tight control strategies have improved the outlook for patients with rheumatoid arthritis. Remission with limited radiological damage and no functional deterioration is now a realistic treatment goal. Several randomised controlled trials have shown that treatment with DMARDs, corticosteroids, and biological agents early in the course of disease can retard progression of disease, reduce joint destruction, and improve functional ability and health related quality of life. This, along with the introduction of new tools to monitor response to treatment, has led to a new treatment approach and improved outcomes.¹ We review evidence from randomised trials, systematic reviews, and recently published guidelines and outline the new approach to treatment, emphasising the importance of early diagnosis, referral, and treatment.

REVIEW

Sources and selection criteria

We used recently published recommendations on the treatment of rheumatoid arthritis. We also searched the Cochrane Database of Systematic Reviews (without time limits) and performed PubMed and Embase searches (October 2008 to July 2010) using the keywords “rheumatoid arthritis” and “disease modifying anti-rheumatic drugs” or “biologicals” and the names and the synonyms of the most commonly used disease modifying anti-rheumatic drugs separately. We selected well conducted systematic reviews, meta-analyses, and large randomised controlled trials. When no such studies were available, we considered small randomised control trials, cohort studies, and observational studies.

What is rheumatoid arthritis and who gets it?

Rheumatoid arthritis is a systemic inflammatory autoimmune disease with localised and general manifestations. It is characterised by polyarticular inflammation of synovial tissue, which causes pain, swelling, and stiffness of the joints of the hands, wrists, and feet in particular.² It also results in functional limitations and may progress to joint destruction and extra-articular disease (*box 1*). Observational studies have shown that mortality rates in patients with rheumatoid arthritis are higher than in the general population.³ Rheumatoid arthritis has an estimated prevalence of 0.5-1.1% and an incidence of 20-50 per 100 000 person years in northern Europe and North America. Lower prevalences (0.1-0.7%) have been reported in southern Europe, South America, Asia, and the Middle East, with very low prevalences in some parts of Africa. Prevalence is high in Native Americans.⁴ The disease is more prevalent in women than in men (3:1 to 2:1). Cohort studies suggest that prevalence rises with age and peaks at 65-74 years.

Box 1 Extra-articular manifestations of rheumatoid arthritis

- Rheumatoid nodules
- Osteoporosis
- Vasculitis
- Lung fibrosis
- Pleuritis
- Scleritis
- Pericarditis
- Lymphadenopathy
- Peripheral neuropathy
- Splenomegaly
- Amyloidosis

How is rheumatoid arthritis diagnosed?

History

Patients have pain, stiffness, and limited joint movement. Presentation may be classic, with symmetrical polyarthritis of the small joints of the hands and feet, but monoarthritis or oligoarthritis, including large joints as first manifestation, is not uncommon.⁵ Observational studies suggest that patients who present with monoarthritis or oligoarthritis are as likely to develop progressive joint damage as those who present with polyarthritis. Patients often report general symptoms, such as morning stiffness (not only in affected joints, lasting more than an hour), fatigue, fever, sweats, and weight loss.⁶ In early disease, functional limitations are determined by the presence of active synovitis, but in the long term joint damage is also a contributory factor.

Examination

Synovitis can be clinically diagnosed by examination of the joints (box 2). Palpation shows swelling within the joint, sometimes with bulging and pain on pressure. Movement, particularly (over)extension or rotation, is limited, and force is reduced—for example, when making a fist. Because the small joints of the feet may be difficult to assess separately, inflammation may be easier to detect if the metatarsal joints are squeezed together. Heat and redness may be apparent, but absence of these signs does not preclude inflammation. In later stages of disease, rheumatic nodules or deformation might be seen, typically with ulnary deviation of the metacarpophalangeal joints. No single test or set of criteria is available to diagnose rheumatoid arthritis. Classification criteria have been developed for use in research populations only, although they are sometimes used in clinical practice. Until recently, the 1987 classification criteria of the American College of Rheumatology (ACR) were used (box 3).⁷ New classification criteria with a higher sensitivity in early disease were developed in 2010 (table).⁵

Box 2 Signs of inflammatory arthritis

- Pain
- Swelling
- Loss of function of the affected joint (flexion or rotation, resistance to hyper-extension)
- Sometimes heat
- Occasionally redness
- Morning stiffness (not only in swollen joints)
- Squeeze test: put tangential pressure on the metatarsophalangeal and metacarpophalangeal joints; if tender, suspect synovitis
- General symptoms such as fatigue, fever, weight loss, and sweats

Box 3 1987 American College of Rheumatology classification criteria

- At least 4 items should be present; items 1-4 should be of at least 6 weeks' duration
- 1 Morning stiffness for at least one hour
 - 2 Synovitis in three or more joints
 - 3 Synovitis in hands or wrists
 - 4 Symmetrical distribution
 - 5 Subcutaneous nodules
 - 6 Positive rheumatoid factor
 - 7 Radiographic changes on radiographs of hands or wrists

Investigations by general practitioner

Patients with clinical signs and symptoms of arthritis should be referred to a rheumatologist as early as possible.⁶ More than a 12 week delay in referral is associated with a reduced chance of drug-free remission and increased risk for progressive joint damage.⁸ Radiographs and laboratory assessments are not necessary before referral and may delay treatment. Once the presence of arthritis is established, these tests may help identify monoarthritis or oligoarthritis in the early phases of disease.

Investigations by a specialist

Investigations in newly diagnosed patients include measurement of acute phase reactants (to calculate disease activity), a full blood count, and autoantibody tests. When an infectious cause or crystal induced (poly)arthritis is suspected, aspiration of synovial fluid or synovial biopsy may be helpful. Ultrasound may show synovitis in joints that are clinically difficult to assess and may help guide synovial fluid aspiration. Addi-

TABLE 1 New classification criteria for rheumatoid arthritis*

Symptom	Score
Joint involvement (0-5)	
1 medium-large joint	0
2-10 medium large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint)	5
Serology (0-3)	
Low positive rheumatoid factor or low positive anti-citrullinated protein antibodies	2
High positive rheumatoid factor or high positive anti-citrullinated protein antibodies	3
Acute phase reactants (0-1)	
Normal C-reactive protein and normal erythrocyte sedimentation rate	0
Abnormal C-reactive protein or abnormal erythrocyte sedimentation rate	1
Duration of symptoms (0-1)	
<6 weeks	0
≥6 weeks	1

*Patients need at least 6 points or the presence of joint erosion to be classified as having rheumatoid arthritis.

tional radiological and laboratory assessments might be needed to exclude alternative diagnoses. Radiographs of hands, wrists, and feet are recommended early in the disease to assess early structural damage and should be repeated annually to monitor disease severity and response to treatment.⁶ In research settings, changes on ultrasound and magnetic resonance imaging seem to be predictive of future progression, but it is unclear if and how these modalities should be integrated into daily practice.

Autoantibodies

Laboratory studies, observational trials, and randomised trials have shown that rheumatoid factor, directed against IgG, and antibodies against citrullinated proteins are seen in about two thirds of patients with rheumatoid arthritis. Several observational studies have shown that the presence of autoantibodies predicts a more severe disease course. In patients with undifferentiated arthritis, the presence of anti-citrullinated protein antibodies predicts progression to rheumatoid arthritis.^{9,10} Patients with and without these autoantibodies seem to differ genetically from one another, suggesting that anti-citrullinated protein positive and negative arthritis may be two distinct disease entities. Evidence from laboratory studies suggests that these antibodies play a pathogenic role in the disease, although the exact mechanism is unknown. Both types of autoantibody can be present years before onset of disease.

What are the treatment goals?

The ultimate goal of treatment is sustained clinical and radiological remission after cessation of anti-rheumatic drugs—essentially a “cure.” A systematic review and meta-analysis of randomised trials that informed the latest European League Against Rheumatism (EULAR) recommendations concluded that treatment should aim to suppress disease activity as soon as possible, reduce symptoms, and retard the progression of joint damage and associated functional limitations.¹¹ Several, partially overlapping, definitions of clinical remission are in use. In practice, clinical remission denotes absence of inflammation as determined by joint and laboratory evaluation and the patient’s assessment. In 2011 the EULAR/ACR remission committee proposed new remission criteria that include no more than one swollen and one painful joint on examination, a patient’s global assessment of less than 10 mm on a 0-100 mm visual analogue scale, and normal concentrations of acute phase reactants.

Evaluation of treatment response

For decades treatment was adjusted on the basis of the doctor-patient interview and clinical examination. More objective ways of calculating disease activity have made it possible to set predefined goals and change drugs accordingly. Box 4 and the figures 1 and 2 show the most commonly used outcome measures in rheumatoid arthritis. The concept of tight control was introduced in the TICORA and CAMERA trials. Both trials found reduced disease activity and radiographic progression and increased function and clinical remission in patients whose treatment was regularly adjusted than in those

treated conventionally.^{12,13} The BeSt study used a disease activity score of 2.4 or lower to guide all treatments, including drug tapering and discontinuation steps, while comparing four different treatment strategies. Patients starting with a combination of DMARDs and prednisone or infliximab showed earlier clinical improvement and reduced progression of joint damage.¹⁴

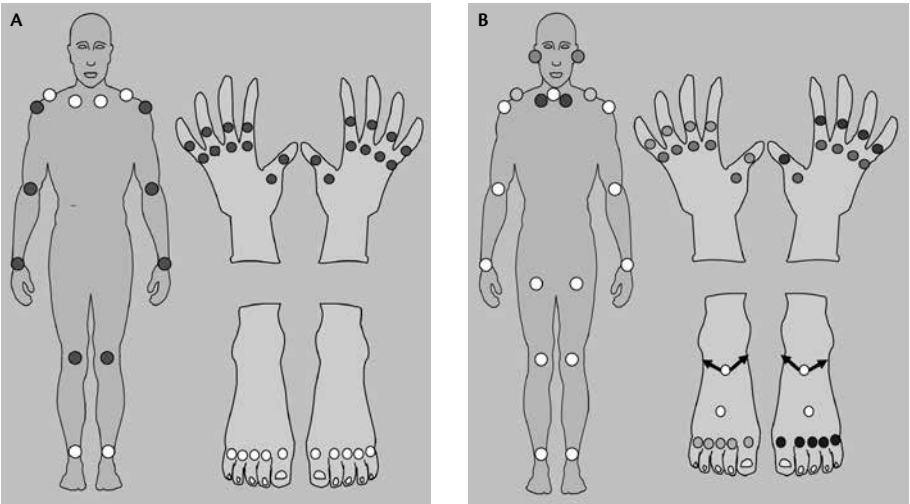


FIGURE 1 Overview of swollen and tender joint counts as components of disease activity scores. Part (A) shows the joints assessed for swelling in the 44 swollen joint count (white and dark grey; assessed for the presence (score 1) or absence (0) of swelling). For the 28 swollen and tender joint counts only the joints depicted in dark grey are assessed for the presence or absence of swelling or tenderness. Part B shows the Ritchie articular index. For each joint, tenderness is graded from 0 to 3 (0=not tender, 1=pain on pressure, 2=winced; 3=winced and withdrew). With this index joints are grouped, and for each group (depicted in separate grey teints; maximal 5 joints per group) the highest score is used. The white joints count as separate joints.

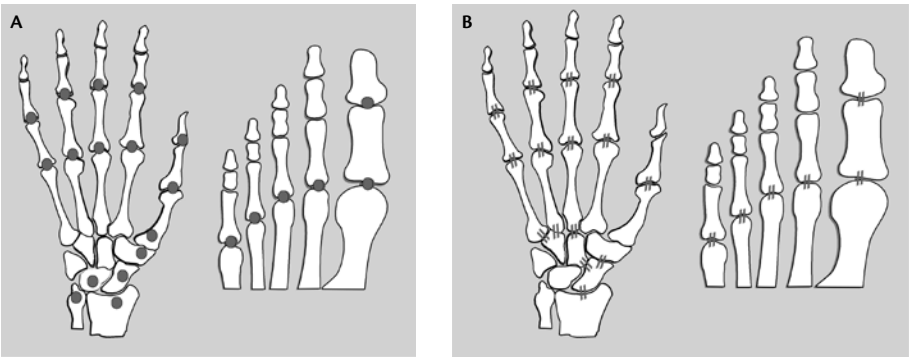


FIGURE 2 Several methods are available to quantify joint damage on radiographs of hands and feet. The modified Sharp method is well validated and often used in clinical trials.²⁹ In total, 44 joints of hands and feet are assessed for erosions (part A; score range per joint 0-5 in hands, 0-10 in feet) and 42 joints of hands and feet for joint space narrowing (part B; range per joint 0-4). The maximum score is 448. An increase in total score of 5 in one year is considered to be rapid radiological progression and carries a poor prognosis.

Current treatment strategies can achieve a mean Health Assessment Questionnaire score of 0.6, 43% clinical remission, and 13% drug-free remission.¹⁵ Recently, an international taskforce published 10 recommendations on targeted treatment, which were based on high level evidence and expert opinion.¹⁶ It recommended that clinicians base treatment on a shared decision between patient and rheumatologist; maximise long term health related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation, particularly through “abrogation of inflammation”; and target treatment by measuring disease activity and adjusting treatment accordingly.

When should treatment start?

A meta-analysis of trials and observational studies published in 2006 showed that early introduction of DMARDs prevents joint damage.¹⁷ Patients with more aggressive disease seemed to benefit most. Recent data from a large observational cohort suggest that the crucial “window of opportunity,” when the immune response is more responsive to treatment and the disease course can be altered, may be as short as 12 weeks.⁸

Box 4 Clinical and radiological outcome measures

Disease activity

Composite indices incorporate the results of a joint assessment (*figure 1*), laboratory evaluation of inflammation (erythrocyte sedimentation rate or C reactive protein), and the patient’s opinion, measured on a 100 mm visual analogue scale. Most commonly used indices are the disease activity score (DAS) and the derived DAS28 (see also www.dascalculator.nl). Alternative indices are the simplified disease activity index (SDAI) and clinical disease activity index (CDAI).

Functional ability

The Health Assessment Questionnaire (HAQ) consists of questions on eight domains of daily activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and chores or activities with four possible answers: 0, without any difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to do. The use of aids or devices and help from another person is taken into consideration. The sum of the highest score per domain is divided by eight, resulting in a total score ranging from 0 to 3 (0=best; 3=worst).

Progression of joint damage

See figure 2.

What drugs are effective early in disease?

Conventional disease modifying anti-rheumatic drugs

Many synthetic DMARDs are available for the treatment of rheumatoid arthritis, but methotrexate is the first line treatment. A recent meta-analysis found that it improves clinical and radiological outcomes; has an acceptable long term toxicity profile; is acceptable to patients, with good adherence rates; and is cost effective.^{6,11,18} EULAR guidelines published in 2010 consider methotrexate to be safe and effective in combination with other DMARDs.¹¹ Methotrexate also seems to increase the efficacy of biological agents when given concurrently. The most common side effects are gastrointestinal problems and reversible liver toxicity, which can be reduced by subcutaneous administration and dose reduction or concomitant use of folic acid, according to recent international consensus guidelines.¹⁹ Other synthetic DMARDs that may be useful are sulfasalazine, leflunomide, hydroxychloroquine, and less often injectable gold, ciclosporin, and azathioprine. As with methotrexate, all conventional DMARDs need regular monitoring for safety.²⁰ A recent systematic review and meta-analysis found that leflunomide was as effective as methotrexate; that sulfasalazine and injectable gold reduced signs and symptoms of rheumatoid arthritis and structural damage; and that ciclosporin, minocycline, tacrolimus, and hydroxychloroquine showed some efficacy in reducing the number of swollen joints.¹⁸

Corticosteroids

A systematic review of randomised controlled trials found that low to moderate dose (7.5-15 mg/day) oral glucocorticoids reduce joint destruction and improve symptoms.²¹ Glucocorticoids reduce disease activity quickly, so are useful as “bridging drugs” when treatment begins. Adding glucocorticoids to DMARD monotherapy or combinations of synthetic DMARDs retards the clinical course of disease and inhibits radiographic progression, an effect that can last for years.²¹ Randomised controlled trials have shown that temporary treatment with prednisolone combined with methotrexate and sulfasalazine (and hydroxychloroquine) early in the disease induces more rapid reduction of inflammation and, as a result, earlier reduction of clinical symptoms and prevention of radiological damage than DMARD monotherapy.^{22,23} Intra-articular glucocorticosteroids in combination with methotrexate can reduce local symptoms and may also prevent progression of joint damage. The optimal dose of glucocorticoids in combination treatment is unknown.

Because long term use of glucocorticoids may increase risk of cardiovascular disease, the occurrence of mood disturbances, and osteoporosis, experts advise cautious use of these drugs, with tapering as soon as symptoms are controlled.^{6,11} In 2007 a EULAR taskforce published recommendations for the use of oral glucocorticoids in rheumatoid arthritis with a focus on toxicity.

Biological agents

Several drugs have been developed that target cytokines and cells of the immune sys-

Box 5 Biologicals

TNF-α inhibitors

Adalimumab: humanised monoclonal antibody against TNF-α
Certolizumab: Fab fragment of a humanised TNF-α inhibitor monoclonal antibody
Etanercept: humanised soluble recombinant TNF-α type II receptor-IgG1 fusion protein
Golimumab: human monoclonal antibody against TNF-α
Infliximab: a chimeric mouse-human monoclonal antibody against TNF-α

Others

Anakinra: human recombinant interleukin 1 receptor antagonist
Abatacept: an immunoglobulin and extracellular CTLA4 domain fusion protein that selectively inhibits T cell co-stimulation
Rituximab: chimeric monoclonal anti-CD20 antibody that depletes B cells
Tocilizumab: humanised monoclonal anti-interleukin 6 receptor antibody

tem that play a role in the disease process. These new treatments are generally referred to as “biologicals” (box 5).

Drugs that target TNF-α

The introduction of tumour necrosis factor α (TNF-α) inhibitors has changed treatment and treatment targets greatly. Evidence from randomised controlled trials shows that the combination of methotrexate and a TNF-α inhibitor is better than either drug alone at reducing clinical symptoms and progression of joint damage in patients with early disease and in those who do not respond to conventional DMARDs.^{6,11} Five TNF-α blocking agents are currently licensed for the treatment of rheumatoid arthritis (box 5).

Several cohort studies found a small but increased risk for bacterial infections in patients treated with methotrexate and TNF-α inhibitors.²⁴ An increased incidence of tuberculosis was seen in patients treated with TNF-α inhibitors, mainly as a result of reactivation of latent infections.²⁵ Screening before starting treatment and anti-tuberculosis pretreatment if appropriate have greatly reduced this complication.

There is no convincing evidence that the overall risk for cancer is higher for patients given anti-TNF-α than for other patients with rheumatoid arthritis.²⁴

Other biologicals

Several biologicals with other targets have been developed and are being investigated.²⁶ Expert guidelines recommend TNF-α inhibitors as first choice of biological agent. If a patient does not respond to a first anti-TNF-α agent, then a second one—rituximab,

abatacept, or tocilizumab—can be considered, preferably in combination with methotrexate.^{6,11} No evidence supports the use of one second line treatment over another.

Risk of cardiovascular disease

Recommendations on managing the risk of cardiovascular disease in patients with rheumatoid arthritis, based on systematic literature reviews, have recently been published.²⁷ Rheumatoid arthritis carries a higher than normal risk for cardiovascular disease, probably as a result of the increased prevalence of traditional risk factors and the inflammatory burden. Observational studies suggest that risk scores should be multiplied by 1.5 if two of the following criteria are met: presence of rheumatoid factor or anti-citrullinated protein antibodies, disease duration greater than 10 years, or presence of extra-articular manifestations. Ongoing cardiovascular risk assessment is recommended for all patients. To reduce risk, good control of disease activity is mandatory, as well as adequate management of cardiovascular risk according to local guidelines.

An evidence-based approach to treatment

Early recognition of arthritis and rapid referral to a rheumatologist are essential. Begin treatment immediately after diagnosis and aim for clinical remission or low disease activity.^{6,11} Start treatment with a single DMARD, preferably methotrexate (although NICE recommends adding another DMARD), combined with short term glucocorticoids.^{6,11,20} If no response is seen, consider introducing a TNF-α blocker rather than switching to a combination of traditional DMARDs.²⁸ Some guidelines recommend TNF-α blockers and methotrexate as initial treatment in high risk patients.^{11,20} Consider cautiously reducing and stopping treatment in patients in stable clinical remission, with prompt reintroduction if the diseases recurs.^{6,11}

Further improvements in diagnostics and targeted treatments are needed to halt the disease process. The new classification criteria will enable patients with earlier stage disease to enter clinical trials. Future developments may enable chronicity and deterioration to be avoided and provide a cure for rheumatoid arthritis.

Summary points

- Rheumatoid arthritis is a common autoimmune disease that can lead to serious functional limitations, joint destruction, extra-articular disease, poor quality of life, and premature death
- Early recognition of arthritis and speedy referral to a rheumatologist are essential
- Treatment should start early and aggressively to prevent functional limitations and structural damage
- Innovations in treatment and monitoring have resulted in patients achieving early and sustained clinical and radiographic remission
- Methotrexate is the first line drug, but in high risk patients early combination of methotrexate with prednisone or a tumour necrosis factor inhibitor improves outcomes

Tips for non-specialists

- Refer all patients with suspected inflammatory arthritis to a rheumatologist as soon as possible
- Rheumatoid arthritis can have a gradual onset but damage still starts early. Avoid a wait and see approach or time consuming radiographs and laboratory tests
- Early treatment is essential for improving and maintaining functional ability and quality of life, and prevention of joint damage
- Be aware of and treat risk factors for cardiovascular disease because rheumatoid arthritis carries an increased risk
- Be aware of possible infectious episodes in patients treated with prednisone or biologicals (or both), which may require earlier treatment

Ongoing research

- Constructing prediction models including biomarkers to optimise early diagnosis of rheumatoid arthritis and individualised treatments
- Identifying biomarkers of disease activity and severity to guide treatment
- Identifying the optimal target for targeted treatment
- Developing a uniform definition of remission as the ultimate treatment goal
- Directly comparing the efficacy and safety of various biologicals
- Comparing biologicals to combination treatment, including prednisone in patients who have not been treated with disease modifying anti-rheumatic drugs
- Identifying mechanisms and processes that can be targeted with new drugs
- Identifying treatments and strategies that cure rheumatoid arthritis

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