Rheumatoid arthritis

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Rheumatoid arthritis is characterised by persistent synovitis, systemic inflammation, and autoantibodies (particularly to rheumatoid factor and citrullinated peptide). 50% of the risk for development of rheumatoid arthritis is attributable to genetic factors. Smoking is the main environmental risk. In industrialised countries, rheumatoid arthritis affects 0·5–1·0% of adults, with 5–50 per 100 000 new cases annually. The disorder is most typical in women and elderly people. Uncontrolled active rheumatoid arthritis causes joint damage, disability, decreased quality of life, and cardiovascular and other comorbidities. Disease-modifying antirheumatic drugs (DMARDs), the key therapeutic agents, reduce synovitis and systemic inflammation and improve function. The leading DMARD is methotrexate, which can be combined with other drugs of this type. Biological agents are used when arthritis is uncontrolled or toxic effects arise with DMARDs. Tumour necrosis factor inhibitors were the first biological agents, followed by abatacept, rituximab, and tocilizumab. Infections and high costs restrict prescription of biological agents. Long-term remission induced by intensive, short-term treatment selected by biomarker profiles is the ultimate goal.

Introduction

Rheumatoid arthritis has 19th century roots and a 20th century pedigree. Although its name was introduced in the 1850s,[1] classification criteria were only developed 50 years ago.[2,3] Observational studies in which these criteria are used portray treated rheumatoid arthritis as a serious long-term disease with dominant extra-articular features, limited treatment options, and poor outcomes.[4,5]

Tumour necrosis factor (TNF) inhibitors and other biological agents have heralded a so-called therapeutic revolution, transforming the outlook for patients with rheumatoid arthritis. However, improved disease outcomes preceded biological agents, reflecting early use of conventional drugs, ambitious treatment goals, and better management of comorbidities. An historic parallel is the 1950s revolution in tuberculosis care, when improved conventional management followed by effective chemotherapy made tuberculosis curable.[6]

Pathophysiology

Rheumatoid arthritis is best considered a clinical syndrome spanning several disease subsets.[7] These different subsets entail several inflammatory cascades,[8] which all lead towards a final common pathway in which persistent synovial inflammation and associated damage to articular cartilage and underlying bone are present.

Inflammation

One key inflammatory cascade includes overproduction and overexpression of TNF.[9] This pathway drives both synovial inflammation and joint destruction. TNF overproduction has several causes, including interactions between T and B lymphocytes, synovial-like fibroblasts, and macrophages. This process leads to overproduction of many cytokines such as interleukin 6, which also drives persistent inflammation and joint destruction.[10] Overproduction of other proinflammatory cytokines (eg, interleukin 1) differs from the process for interleukin 6 in that production is either less marked or is specific to one or more disease subsets, as best shown by the effects of interleukin 1 blockade in subforms of juvenile idiopathic arthritis or adult-onset Still's disease.

Synovial cells and cartilage cells

The dominant local cell populations in joints affected by rheumatoid arthritis are synovial and cartilage cells. Synovial cells can be divided into fibroblast-like and macrophage-like synoviocytes. Overproduction of proinflammatory cytokines is believed to be led predominantly by macrophage-like synoviocytes. Fibroblast-like synoviocytes show abnormal behaviour in rheumatoid arthritis. In experimental models, co-implantation of fibroblast-like synoviocytes with cartilage leads to fibroblasts invading cartilage,[11] behaviour that correlates with joint destruction.[12] Considerable information has accumulated about joint destruction and the role of osteoclast activation as a key process leading to bone erosion. This association is proven because specific inhibition of osteoclast activation can reduce joint destruction yet not affect joint

Search strategy and selection criteria

We searched the Cochrane Library (2000–09), Medline (2000–09), and Embase (2000–09). We used the search term "rheumatoid arthritis" in combination with terms relevant for every section of the article, including: "cytokines", auto-antibodies", genetic risk factors", "prevalence", "incidence", "assessments", "outcome measures", "co-morbidities", and every specific treatment approach. We mainly selected publications from the past 5 years, although we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. We selected high-quality systematic reviews in preference to individual studies. Other review articles and books were cited to provide readers with more details and references than this Seminar can accommodate.

inflammation.[13] We are unclear about whether arthritis starts as a primary problem in the bone and subsequently moves to the joint, or the other way around.[14] One argument for rheumatoid arthritis starting in the joint is the observation that fibroblast-like synoviocytes showing altered behaviour can spread between joints, suggesting how polyarthritis might develop.[15]

Regulation of immune inflammation depends on balances between the number and strength of different cell types. Control of arthritogenic immunoresponses has been studied in mice in which the specific antigen is known. Infusion of low numbers of T cells with specific characteristics ameliorates arthritis in a rodent model of the disease, showing T cells can be protective.[16,17] Ongoing research should translate these experimental findings into clinical practice.

Autoantibodies

Rheumatoid factor is the classic autoantibody in rheumatoid arthritis. IgM and IgA rheumatoid factors are key pathogenic markers directed against the Fc fragment of IgG. Additional (and increasingly important) types of antibodies are those directed against citrullinated peptides (ACPA). Although most, but not all, ACPA-positive patients are also positive for rheumatoid factor, ACPA seem more specific and sensitive for diagnosis and seem to be better predictors of poor prognostic features such as progressive joint destruction.[18]

Ongoing research aims to identify antibody specificities relevant for different patients' subsets and disease stages. 50–80% of individuals with rheumatoid arthritis have rheumatoid factor, ACPA, or both. Composition of the antibody response varies over time, with limited

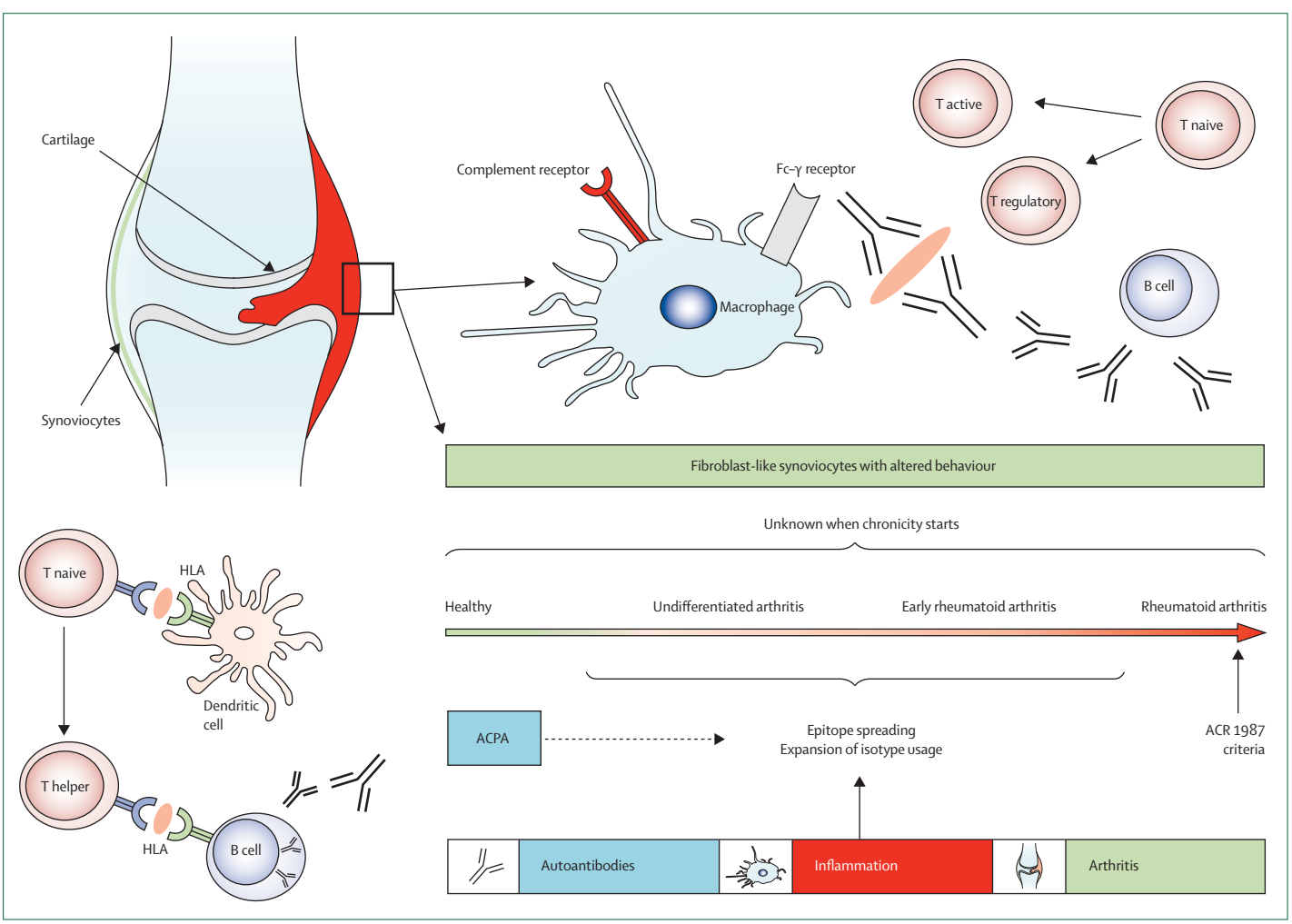

Figure 1: **Key pathological changes in the synovium in rheumatoid arthritis**
The joint consists of two bones covered by cartilage and aligned by a capsule. The inner surface of the capsule consists of fibroblast-like synoviocytes that produce synovial fluid. In a joint affected by rheumatoid arthritis, the synovium is swollen due to an infiltrate consisting of fibroblast-like and macrophage-like synoviocytes, macrophages, several populations of T cells, and B cells. Macrophages are activated to produce all kind of proinflammatory products (eg, tumour necrosis factor) partly by immune complexes binding to Fc-γ receptors and complement receptors on their surface. Evolution of chronicity in joint inflammation is controlled by so-called master switches, and prediction models suggest a pathway of autoantibodies, inflammation, and arthritis. Autoantibodies binding to citrullinated antigens (ACPA) have confined specificity and limited isotype use in healthy individuals, but epitope spreading and expansion of isotype usage happens in those with rheumatoid arthritis. ACR=American College of Rheumatology.

specificities in early rheumatoid arthritis and a mature response—in which more epitopes are recognised and more isotypes used—in late disease (figure 1).[19,20] Evidence from animal models and in-vivo data suggest that ACPA are pathogenic on the basis of induction of arthritis in rodent models and because immunological responses are present in ACPA-positive patients in a citrulline-specific manner.[21,22]

Findings of clinical studies show that patients with rheumatoid arthritis and both rheumatoid factor and ACPA (autoantibody-positive disease) differ from individuals with so-called autoantibody-negative disease. For example, histologically, people with ACPA-positive disease have more lymphocytes in synovial tissue, whereas those with ACPA-negative rheumatoid arthritis have more fibrosis and increased thickness of the synovial lining layer.[8] ACPA-positive disease is associated with increased joint damage and low remission rates.[23]

Genetics

50% of risk of developing rheumatoid arthritis is attributable to genetic factors.[24] Much progress has been made in identification of genetic regions tagged by structural variation (single nucleotide polymorphisms); more than 30 genetic regions are associated with rheumatoid arthritis.[25–28] At present, apart from *PTPN22* and *HLA* genes, no major pathogenic insights have come from these genetic associations. However progress is shown by the realisation that from a putative 2 m of DNA harbouring candidate variants, these 30 regions are all contained within 2 mm of DNA. With current sequencing methodology, 2 mm of DNA allows sequencing in large cohorts. So, we can reasonably expect new mechanisms to be identified in the next few years. Many risk alleles discovered in recent years are fairly common in the population as a whole; individually, they have modest effects on the risk of rheumatoid arthritis. However, ongoing research suggests that several risk loci are linked to other autoimmune diseases, and some genes fall within discrete biological pathways that are driving inflammation.

Findings of genetic studies show differences in ACPA status of patients with rheumatoid arthritis, related to the number of specific HLA-DRB1 alleles (figure 1).[29] These HLA alleles share a common motive, which is known as the shared epitope. Currently, antigens are believed to be modified by a process called citrullination; this step entails post-translational modification of the aminoacid arginine to citrulline. This change is thought to allow antigens to fit in the HLA alleles that harbour this shared epitope. The end result is breaking of tolerance that allows antibody formation against these antigens.[30]

Genetic risk factors associated with rheumatoid arthritis are, in the main, thought to be specifically associated with either ACPA-positive or ACPA-negative disease. The best-studied environmental factor for rheumatoid arthritis—smoking—seems to be a risk factor for ACPA-positive disease, especially in the context of positivity for HLA-DRB1 shared epitope alleles.[31] Genetic research supports the idea that rheumatoid arthritis is a heterogeneous group of overlapping syndromes.

Classification and diagnosis

Early classification criteria[2,3] were designed to distinguish established rheumatoid arthritis from other types of established joint diseases (figure 2). They ensured researchers studied homogeneous patients' groups, particularly in clinical trials.

Classification of early arthritis

The American College of Rheumatology (ACR) 1987 criteria[3] are limited by poor sensitivity and specificity for classification of patients with early inflammatory arthritis as having rheumatoid arthritis.[32] They fail to identify individuals with very early arthritis who subsequently develop rheumatoid arthritis.[33] Effective treatment in early arthritis averts or delays patients fulfilling these 1987 criteria,[34] and two criteria—erosive joint damage and extra-articular disease—are late changes prevented by modern treatment.

Prediction models have been developed from prospective observational studies of treated patients with early arthritis. These models are designed to forecast outcomes in individuals with early arthritis who do not currently meet the 1987 criteria (figure 2).[35–38] Several factors can establish whether patients are likely to develop rheumatoid arthritis (figure 1). In the presence of inflammatory arthritis, evidence of systemic inflammation—shown by high acute-phase reactants and prolonged morning stiffness and autoantibodies in serum, particularly ACPA and rheumatoid factor—increases the likelihood of individuals having rheumatoid arthritis.

Rethinking diagnostic classification

As a result of these concerns and developments, the ACR and European League Against Rheumatism (EULAR) have devised new classification criteria for early arthritis,[39] which assess joint involvement, autoantibody status, and acute-phase response and symptom duration (figure 2). These criteria were developed in three phases. Phase one was a data-driven approach, based on cohorts of patients with early arthritis, to identify factors and their relative weights associated with the decision by a doctor to start methotrexate. Phase two was a consensus-driven approach refining these factors with a series of paper patients (ie, written summaries of anonymised cases that provide sufficient information to make decisions about the patient's diagnostic classification) to allow input of current clinical thinking. Phase three summarised all data to arrive at a prediction model and cut off for the probability score. The effect on diagnosis and management of these new criteria will become clear over the next few years.

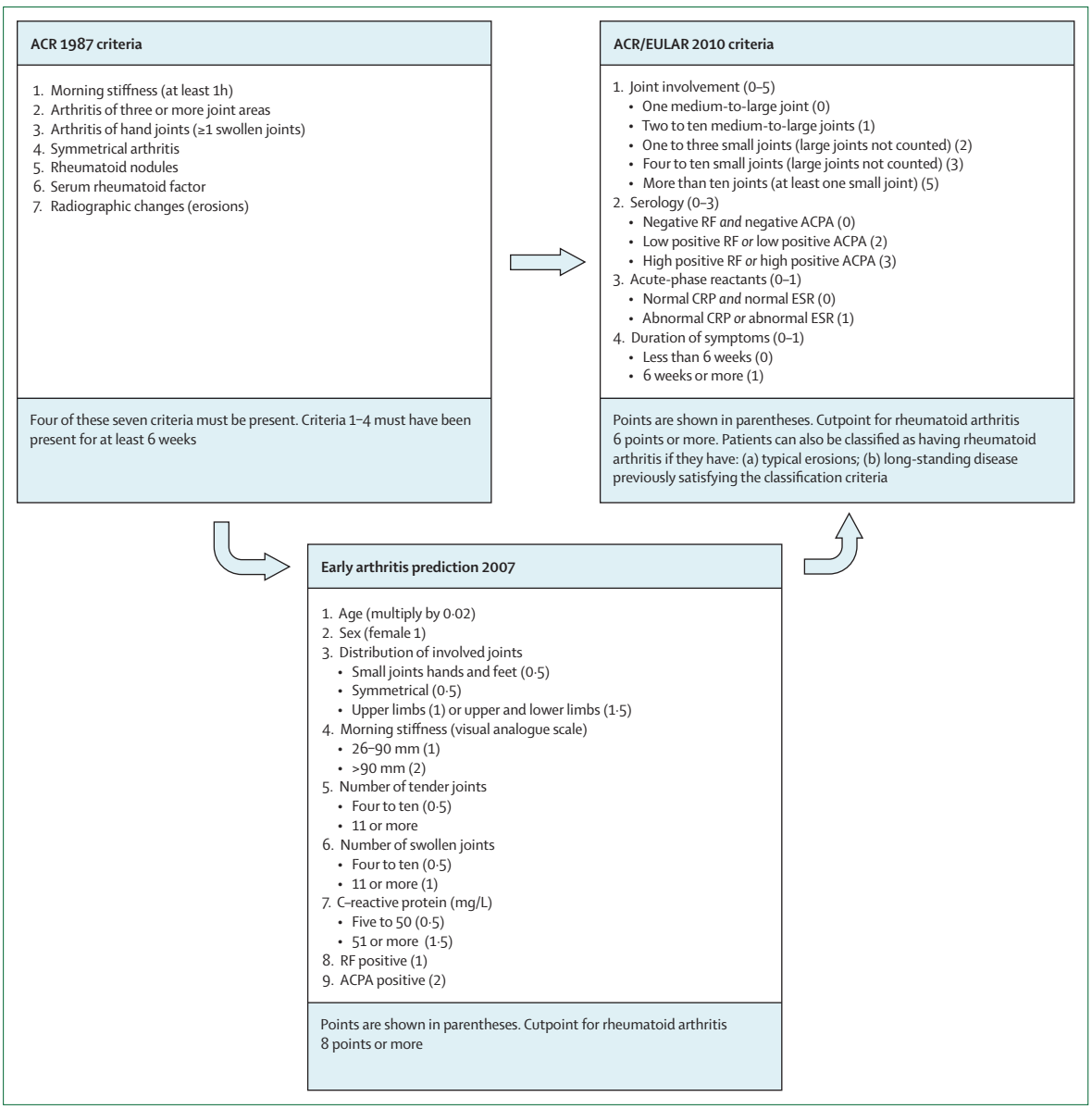

Figure 2: **Conventional and new classification criteria for rheumatoid arthritis**
ACR=American College of Rheumatology. EULAR=European League Against Rheumatism. RF=rheumatoid factor. ACPA=antibodies against citrullinated antigens. CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. ACR 1987 criteria[3] (left panel) were designed to classify established rheumatoid arthritis. 2010 ACR/EULAR criteria[39] (right panel) are intended to classify both early and established disease. Prediction models such as the van der Helm model[36] (lower panel) represent an intermediate phase; they were designed to identify patients with early undifferentiated arthritis who are most likely to subsequently meet criteria for rheumatoid arthritis; such models are somewhat more complex than the new criteria.

Epidemiology

Frequency

Findings of population-based studies show rheumatoid arthritis affects 0·5–1·0% of adults in developed countries. The disease is three times more frequent in women than men. Prevalence rises with age and is highest in women older than 65 years, suggesting hormonal factors could have a pathogenic role.[40] Estimates of the frequency of rheumatoid arthritis vary depending on the methods used to ascertain its presence.[41,42] Incidence ranges from 5 to 50 per 100 000 adults in developed countries and increases with age.[43,44]

Prevalence of rheumatoid arthritis varies geographically.[45,46] The disease is common in northern Europe and North America compared with parts of the developing world, such as rural west Africa.[47] These variations are indicative of different genetic risks and environmental exposures. Some evidence suggests incidence of rheumatoid arthritis might be declining, with onset happening later in life.[48,49]

Environmental risk factors

Smoking is the dominant environmental risk factor and doubles risk of developing rheumatoid arthritis.[50] Its effect is restricted to patients with ACPA-positive disease.[31,51] Although pathogenetically very important (see Genetics), on a population level, the risk is too low to be clinically relevant. Other potential environmental risk factors include alcohol intake, coffee intake, vitamin D status, oral contraceptive use, and low socioeconomic status, although supporting evidence for these other factors is weak.[52]

Clinical assessment

Core measures

Assessments in rheumatoid arthritis mainly look at joint inflammation (panel).[53] Doctor-based reviews include swollen and tender joint counts and global assessment (ie, overall estimates of disease activity and health status). Standard joint counts focus on 28 joints in the hands, upper limbs, and knees; joints in the feet, although important, are omitted. Some experts prefer extended 66 and 68 joint counts, which include the feet. Laboratory measures encompass erythrocyte sedimentation rate, C-reactive protein, or both. Patient-based measures appraise pain, global assessment, and disability.[54] The health assessment questionnaire (HAQ) measures disability. Patients record other relevant areas, such as fatigue and depression. Patient-based measures are especially important because they measure the individual's perspective of the burden of their rheumatoid arthritis.

Combined indices

Indices amalgamate individual assessments.[53] They are used widely in clinical trials and observational studies. The disease activity score 28 (DAS28) combines 28 swollen and 28 tender joints (hands, arms, and knees), patient's global assessment, and erythrocyte sedimentation rate to indicate the patient's current status. Because calculation of DAS28 entails application of a complex mathematical formula, simplified variants have been devised. The simplified disease activity index uses 28 tender and swollen joint counts, doctors' and patients' global assessments, and C-reactive protein.[55] The clinical disease activity index is similar but omits C-reactive protein. ACR improvement criteria, which gauge change in status in clinical trials, include falls in joint counts and several other measures (patient's and doctor's global assessments, erythrocyte sedimentation rate, pain, and HAQ). They record 20% (ACR20), 50% (ACR50), and 70% (ACR70) improvements in five of the seven measures. Combined indices need cautious interpretation because high scores can show active arthritis or high pain levels.[56]

Imaging

Juxta-articular erosions characterise progressive established rheumatoid arthritis and are usually irreversible. They are identified readily by radiography of the hands and feet. Two typical erosions are sufficient for diagnosis.[57] Extensive damage seen on radiographs suggests rheumatoid arthritis is inadequately controlled, and rapid progression of joint damage needs intensive treatment. Scoring systems in which damage seen on radiographs is recorded are mainly used in research.[58]

Panel: **Assessments in rheumatoid arthritis**

Disease activity

Core assessments

- Joint counts (tender and swollen joint counts)
- Global assessment (doctor and patient) and pain score
- Laboratory (erythrocyte sedimentation rate and C-reactive protein)
- Disability (eg, health assessment questionnaire)

Additional assessment

- Fatigue
- Radiological damage

Combined status indices

- Disease activity score
- Simple disease activity score
- Clinical disease activity score

Change in status (trials only)

- ACR20, ACR50, and ACR70 responders

Extra-articular disease

- Nodules
- Pulmonary
  - Pulmonary nodules
  - Pleural effusion
  - Fibrosing alveolitis
- Ocular
  - Keratoconjunctivitis sicca
  - Episcleritis
  - Scleritis
- Vasculitis
  - Nail fold
  - Systemic
- Cardiac
  - Pericarditis
  - Pericardial effusion
  - Valvular heart disease
  - Conduction defects
- Neurological
  - Nerve entrapment
  - Cervical myelopathy
  - Peripheral neuropathy
  - Mononeuritis multiplex
- Cutaneous
  - Palmar erythema
  - Pyoderma gangrenosum
  - Vasculitic rashes
  - Leg ulceration
- Amyloidosis

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Comorbidities*

Cardiovascular
- Myocardial infarction
- Heart failure
- Stroke
- Peripheral vascular disease
- Hypertension

Cancer
- Lymphoma and lymphoproliferative diseases
- Lung cancer
- Skin cancer

Infection
- General
- Bacterial

Other
- Depression
- Gastrointestinal disease
- Osteoporosis
- Psoriasis
- Renal disease

ACR20, ACR50, and ACR70=20%, 50%, and 70% improvements in five of the seven measures of American College of Rheumatology criteria. *Some comorbidities are mainly associated with rheumatoid arthritis (eg, cardiovascular), some with treatment (eg, gastrointestinal disease), and some with both disease and treatment (eg, infection).

Extensive interest has arisen in new imaging modalities, particularly ultrasound and MRI, which can assess irreversible and reversible structural changes.[59,60] Striking interobserver variability has somewhat restricted their value in routine practice, despite wide use in research. One exception is negative ultrasound findings; these have useful negative predictive value in patients with high pre-test probabilities of development of rheumatoid arthritis.[61]

Frequency of assessment

The best frequencies for clinical and imaging assessments are unknown. Custom and practice dictate clinical assessments are undertaken every few months in early active disease and annually in established stable rheumatoid arthritis.[62] Some clinicians think patients should drive the frequency of assessment.[63]

Outcomes

Assessments

Key outcomes in rheumatoid arthritis are persistent joint inflammation, progressive joint damage, and continuing functional decline.[64] Other important outcomes include extra-articular features (eg, vasculitis), comorbidities (eg, cardiac disease and infections),[65] and patient-related factors (eg, fatigue).[66] The key treatment goal in rheumatoid arthritis is remission with no active joint inflammation and no erosive or functional deterioration. 10–50% of patients with early rheumatoid arthritis achieve remission. Frequency of remission depends on how remission is defined, and the intensity of treatment for rheumatoid arthritis affects development of remission.[67,68] Other important goals are reduced disease activity and pain, maintenance of function, and preservation of work and recreational activities.

Generic measures—such as short form 36—capture the effect of rheumatoid arthritis on patients' overall health and quality of life.[69] Work disability (loss of employment) is an important personal and societal indicator of the burden of disease.[70] Finally, rheumatoid arthritis increases mortality, although its effect on death rates varies across patients' populations and over time.[71]

Improvement

The severity of rheumatoid arthritis might be lessening.[72] Inflammatory markers such as erythrocyte sedimentation rate[73] and extra-articular features such as vasculitis[74] are declining (figure 3). Admissions to hospital[75] and joint replacement rates[76] for rheumatoid arthritis are decreasing. Previously high mortality rates, particularly in severe cases of disease, may be falling. Changes in care delivery could account for some improvements; for example, identification of more ACPA-negative patients with mild rheumatoid arthritis improves average outcomes. However, better treatment seems the dominant factor. Since improvements preceded widespread use of biological agents, better conventional treatment seems especially important.

Management

Several national and regional guidelines for management of rheumatoid arthritis exist, including recommendations from ACR, EULAR, and the UK's National Institute for Health and Clinical Excellence.[77–79] Caution is needed in patients of childbearing age because many treatments have negative effects on conception and pregnancy.[80]

Treatment of symptoms

Analgesics reduce pain, and non-steroidal anti-inflammatory drugs (NSAIDs) lessen pain and stiffness. Both groups of drugs are used widely to control symptoms of rheumatoid arthritis. Evidence for use of analgesics is modest but uncontroversial;[81] support for use of NSAIDs is considerably stronger.[82] NSAIDs have lost their historical role as first-line treatment because of concerns about their limited effectiveness, inability to modify the long-term course of disease, and gastrointestinal and cardiac toxic effects.[83,84] These agents should be given with proton-pump inhibitors for gastroprotection, with short-acting drugs administered for short periods to minimise risks.

Disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs) are a heterogeneous collection of agents grouped together by use and convention. They are the mainstay of treatment

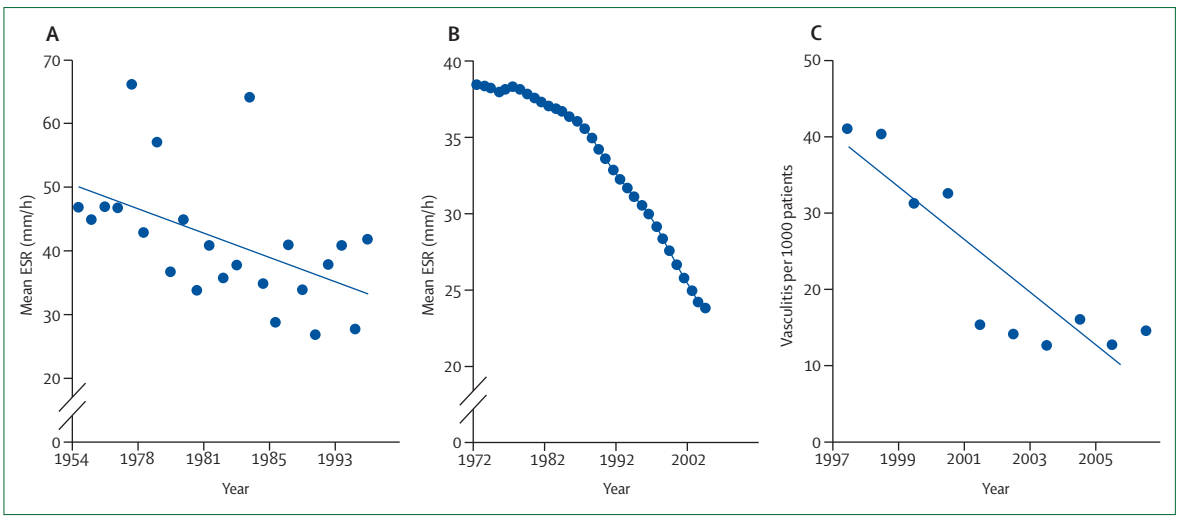

Figure 3: **Evidence for improvement in rheumatoid arthritis over time**
(A) Mean erythrocyte sedimentation rate (ESR) from international cohort studies (initial mean ESR, by year cohort established).[73] (B) Mean ESR, by year, from US national data bank (previously unpublished analysis of mixed-model regression of 25 343 observations from 2107 patients with rheumatoid arthritis, adjusted for age, sex, education, and follow-up duration). (C) Number of inpatients in the USA with rheumatoid arthritis and vasculitis.[74]

for rheumatoid arthritis.[85] Their diverse mechanisms of action are incompletely understood. They reduce joint swelling and pain, decrease acute-phase markers, limit progressive joint damage, and improve function.

Methotrexate is the dominant DMARD. Sulfasalazine and leflunomide are also widely used. Their efficacy has been established in placebo-controlled trials (figure 4).[85–88] Hydroxychloroquine and chloroquine have DMARD-like properties. Gold (rINN sodium aurothiomalate) and ciclosporin are additional DMARDs; their use is limited by toxic effects.

DMARDs are sometimes combined, and several combinations of DMARDs have proven efficacy.[89] An example is methotrexate, sulfasalazine, and hydroxychloroquine—termed triple therapy. Use of DMARD combinations varies across different countries; in some regions they are used rarely.

Adverse effects of DMARDs include those that are minor (eg, nausea) and serious (eg, hepatotoxicity, blood dyscrasias, and interstitial lung disease).[90,91] Monitoring of adverse effects requires pretreatment screening and subsequent safety recording of blood counts and liver function tests.[92]

Biological agents

TNF inhibitors were the first licensed biological agents, followed by abatacept, rituximab, and tocilizumab: they are highly effective (figure 4).[93–99] Caution is needed when comparing treatments because populations of patients with rheumatoid arthritis in various trials are dissimilar. The efficacy of biological agents is most obvious in short-term studies in late disease, when placebo responses are low; it is generally less clearcut in early disease (figure 4), when active comparators can achieve good responses. Effects of biological agents can be especially striking in the subset of inadequately treated or non-responsive patients selected for trials. Uncertainty exists about the extent to which the strongly positive trial results for use of these agents translates into routine clinical practice, when drugs can be given to people with less active disease who will have diminished responses.[100]

Biological agents are combined conventionally with methotrexate. Initially, this combination was to reduce antibody formation,[101] but it potentially increases efficacy. Leflunomide can replace methotrexate.[102] Some biological agents are self-injected at twice weekly to monthly intervals; others are given by infusion.

Adverse events span reactions and infections at infusion and injection sites. The increased risk of tuberculosis with TNF inhibitors is important,[103] and appropriate screening (chest radiography, skin testing, or whole-blood testing for *Mycobacterium tuberculosis*) should follow local guidance. Screening is also needed for hepatitis B and C infection. The long-term risks of biological agents have been studied by meta-analysis of trials[104] and routine-practice registries.[105] Infection is the main concern. Risk spans bacterial infections (eg, sepsis, cellulitis, and abscesses), fungal infections (eg, candidiasis), and viral infections (eg, herpes zoster).[106] Concerns have also been raised about demyelination and cancer; lymphoma risk in particular has been investigated in detail.[107] Risk of lymphomas is increased in severe rheumatoid arthritis, and these patients are most likely to receive biological agents. No convincing evidence supports the idea that these drugs increase risk of lymphoma above that of rheumatoid arthritis.[108]

Glucocorticoids

The striking entry of steroids into management of rheumatoid arthritis more than 60 years ago was

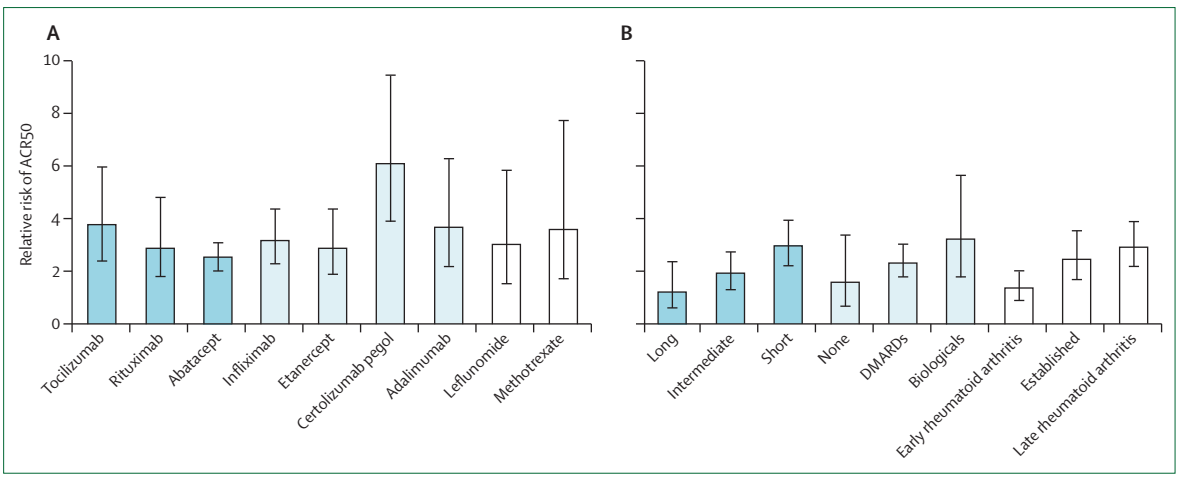

Figure 4: **ACR50 responses in trials of DMARDs and biological agents**
ACR50=50% improvements in five of the seven measures of American College of Rheumatology criteria. Error bars=95% CIs. (A) Trials of individual disease-modifying antirheumatic drugs (DMARDs; methotrexate and leflunomide), tumour necrosis factor inhibitors (adalimumab, certolizumab, etanercept, and infliximab), and new biological agents (abatacept, rituximab, and tocilizumab).[86,87,95,96] ACR50 responses in trials are broadly similar with DMARDs and different biological agents. (B) Cochrane-stratified meta-analysis of effects of disease duration (late, established, and early), previous treatment (biological agents, DMARDs, and none), and treatment duration (short, intermediate, and long).[96] The difference between patients treated with active drug and placebo is greatest in those with late rheumatoid arthritis who have failed biological treatment and whose disease is managed for short periods. The difference is smallest in individuals with early rheumatoid arthritis who have not previously received DMARDs and are treated for long periods of time.

followed by uncertainty about their value. Short-term glucocorticoids reduce synovitis. In the long term they decrease joint damage[109] but incur substantial adverse risks, such as infections and osteoporosis, and their overall risk/benefit ratio is deemed unfavourable.[110]

Glucocorticoids can be especially useful in two settings. First, short-term use during flare-ups in disease can lead to rapid improvement and allow other treatments—such as DMARDs, which have a slower onset of action—to be adjusted. Use of steroids in this way is low risk. Oral or intramuscular glucocorticoids are administered by many centres in this setting. Second, intra-articular glucocorticoids are a highly effective local treatment for individual active joints.[111]

Supportive treatment

Effective non-drug treatments span exercise, joint protection, foot care, and psychological support.[112,113] Patients' education is also of crucial importance. All these strategies are best delivered by a multidisciplinary team of rheumatologists, nurses, therapists, and podiatrists.

Management of comorbidities is important; they reflect both the disease process and its treatment. Comorbidities include cardiac disease, bone disease, and depression. Conventional guidance recommends annual reviews to detect and treat comorbidities. Systemic complications such as Sjögren's syndrome, lung disease, and vasculitis, need specific treatments, which range from eye drops to cytotoxic drugs. Surgical treatment, particularly joint replacement surgery, is vital to maintain function when joints fail, and collaboration with orthopaedic specialists is required.

New treatments

New biological agents in development include drugs that target proximal effects on the immune response (figure 1) and growth factors for T-cell subsets (such as interleukin 17).[114] New conventional drugs with DMARD-like properties might also have important future roles. Clinical trials of inhibitors of the kinases JAK and SYK have provided promising data, and other targets are under investigation.[115,116]

Care pathways

Effectiveness and cost-effectiveness

Management of rheumatoid arthritis must be effective and affordable; patients value effectiveness most whereas society emphasises affordability. Treatment costs are the first part of the economic equation. DMARDs are inexpensive whereas biological agents are costly, although technological advances could reduce future expenditure. A second component of the equation is medical costs, which are modest in the short-term but rise substantially when supportive long-term care is needed for disabling severe rheumatoid arthritis. Finally, societal costs usually exceed medical expenses and rise with disease duration and severity.[117] Biological agents have the greatest potential to reduce long-term medical and social expenditure, particularly if they are used for treatment of early disease when damage to joints is minimal. Such benefits cannot be established in short-term trials, and the cost-effectiveness of biological agents depends on economic modelling. Data suggest that, as currently used, biological agents are not cost effective as first-line treatment for early rheumatoid arthritis, although this conclusion remains controversial.[118,119]

Severe disability in rheumatoid arthritis equates with high health-care expenses.[120] Disability can progress rapidly in some patients treated with DMARDs. Economic models justify the high costs of biological agents by showing that they reduce progression of disability compared with conventional treatments, thus cutting long-term expenditure. Some models include increased workforce participation and productivity of people with rheumatoid arthritis, which is a result of biological treatment.

Economic models simplify complex issues and use historical data for comparison. Some models suggest TNF inhibitors—with costs for these biological agents in the region of £10 000 (US$14 900) per year—are generally cost effective;[121] others draw opposite conclusions.[122] To give no patients biological agents seems unsupportable, yet to treat all patients with them is economically unaffordable. Various health-care systems have made different choices about access to biological agents based on diverse interpretations of available evidence.

Tight control

The key treatment aim should be remission or sustained low disease. This goal can be achieved with DMARD monotherapy, combinations of DMARDs (with or without glucocorticoids), and DMARD–biological combinations. So-called tight control entails increasing treatment until remission or low disease activity is achieved. Many trials use DAS28[53] to monitor disease control; findings of most studies show tight control is effective.[123,124] Limitations of tight control include the need for frequent follow-up and reluctance of clinicians and patients with longstanding rheumatoid arthritis to adhere to intensive treatment strategies. Another drawback is that patients' perspectives of the benefits of intensive treatment differ from those of clinicians.[125] Many individuals find taking medication unpleasant, and many specialist appointments take time and result in loss of autonomy. The cost-effectiveness equation seems very different viewed from patients' perspectives.

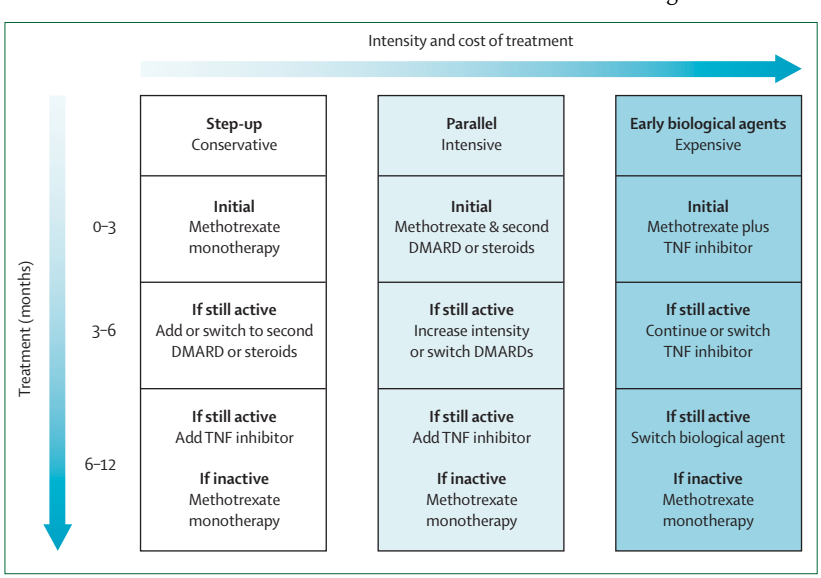

Figure 5: **Treatment strategies in early active rheumatoid arthritis**
DMARD=disease-modifying antirheumatic drug. TNF=tumour necrosis factor. These strategies follow recommendations from the American College of Rheumatology, European League Against Rheumatism, and the UK's National Institute for Health and Clinical Excellence.[77-79]

Treatment of early rheumatoid arthritis

Methotrexate is usually the first DMARD administered to people with rheumatoid arthritis. It should be initiated when the disease is first diagnosed. The dose used and escalation of dosing have increased in recent years. Folic acid is given to limit toxic effects. When methotrexate is contraindicated, sulfasalazine or leflunomide are alternatives. Findings of observational studies show many patients remain on methotrexate and it achieves good outcomes.[126]

Active rheumatoid arthritis needs intensive treatment. Figure 5 shows the main choices. Step-up DMARDs, with extra DMARDs added to achieve disease control, is the most conservative strategy. Initial methotrexate–biological combinations are the most expensive alternative. Parallel treatment, with several DMARDs started concurrently, is an intermediate option. DMARD combinations or methotrexate–TNF inhibitor regimens have similar efficacy (figure 6).[127] Early addition of biological agents for patients with incomplete responses to DMARDs seems highly effective, but cost-effectiveness of this approach is unknown.[128,129]

When patients achieve remission they should be stabilised on one DMARD alone. Biological agents have been tapered and stopped in individuals with early rheumatoid arthritis in remission,[130] although further research is needed to ensure withdrawal is feasible. Because cessation of all DMARDs risks flare-ups of rheumatoid arthritis, this approach is not currently recommended for most patients.[131] However, some individuals can have treatment then withdraw methotrexate without the disease flaring up. Whatever strategy is followed, patients with persistently active synovitis will eventually receive biological agents.

One unresolved difficulty is identification of subgroups of patients who are most likely to benefit from intensive initial treatment. Another issue is deciding the best care for people with very mild early rheumatoid arthritis.

Treatment of established rheumatoid arthritis

The key aim of treatment for established rheumatoid arthritis is minimisation of disease activity. This goal can be achieved with DMARDs and biological agents singly or in combination, with or without glucocorticoids. Flare-ups and persistently active disease are treated by switching or combining DMARDs, adding glucocorticoids, and starting or switching biological agents.

TNF inhibitors are the dominant biological agent. In established disease they are usually continued unless they become ineffective or a relevant adverse effect arises; this

situation differs from that in early rheumatoid arthritis. Patients who fail to respond to TNF inhibitors usually receive an alternative biological agent if their disease remains active. Uncertainty exists about whether this drug should be a second TNF inhibitor or a biological treatment from another class (eg, rituximab, abatacept, or tocilizumab); all these approaches are effective in clinical trials. Some experts favour switching TNF inhibitors when treatment is stopped because of adverse events, but not when treatment is stopped for lack of effect.[132]

Can biological agents be tapered or stopped? What is the relative effectiveness and cost-effectiveness of DMARD combinations versus biological agents? These unresolved questions are economically relevant because they might reduce the need for ongoing biological treatment.

Complications

Death and comorbidities

Patients with rheumatoid arthritis continue to have increased risks of mortality, mostly from cardiovascular disease and infection. The major causes of mortality mirror rises in specific comorbid disorders. Risks of both myocardial infarctions and strokes are amplified in individuals with rheumatoid arthritis (panel).[133] Although this increase could indicate inflammation-associated vascular damage, identification and treatment of cardiovascular risk factors is important; some evidence shows that methotrexate reduces cardiovascular risks in patients with rheumatoid arthritis.[71,134] Comorbid disorders are associated with increased disability and frequent medical consultations, shown by high HAQ scores (figure 7).[134]

A slightly elevated risk of lymphoma and lymphoproliferative malignant disease is associated with rheumatoid arthritis activity.[108] Prevalence of lung cancer is also raised, potentially due to increased cigarette smoking in patients with rheumatoid arthritis.[135] Further, risk of melanotic and non-melanotic skin cancers is raised.[136] Slight reductions in bowel malignant disease are noted in patients with rheumatoid arthritis, potentially reflecting NSAID use. Breast cancers are also diminished.

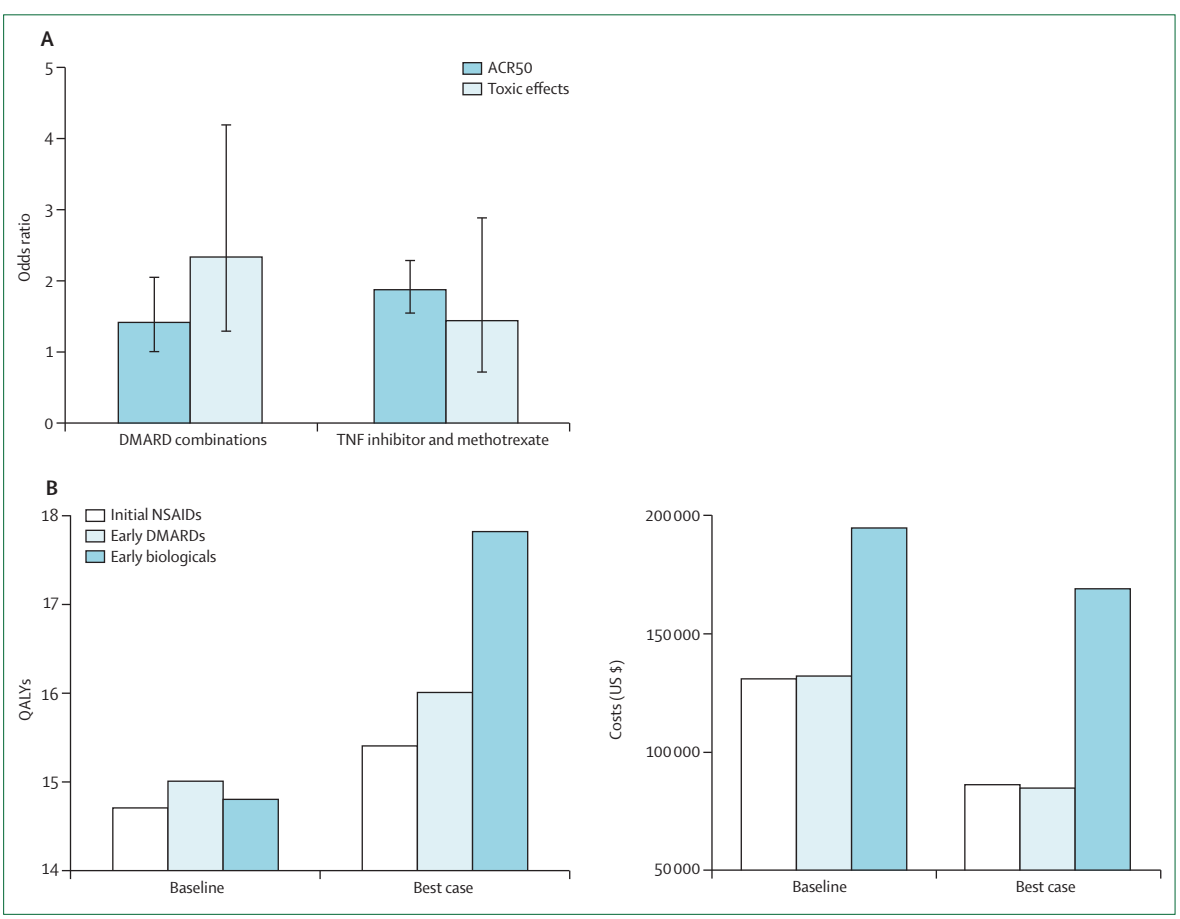

Figure 6: **Comparisons of DMARDs and biological agents in early rheumatoid arthritis**
(A) ACR50 (50% improvements in five of the seven measures of American College of Rheumatology criteria) and toxic effects reported in a systematic review of intensive early treatment of methotrexate combined with other disease-modifying antirheumatic drugs (DMARDs) or tumour necrosis factor (TNF) inhibitors.[127] Error bars=95% CIs. (B) Economic analysis of effects of different treatments in early rheumatoid arthritis on quality-adjusted life years (QALYs) and cost of treatment.[119] NSAIDs=non-steroidal anti-inflammatory drugs. Best case=most favourable assumptions for biological agents (ie, given to selected patients with all costs considered).

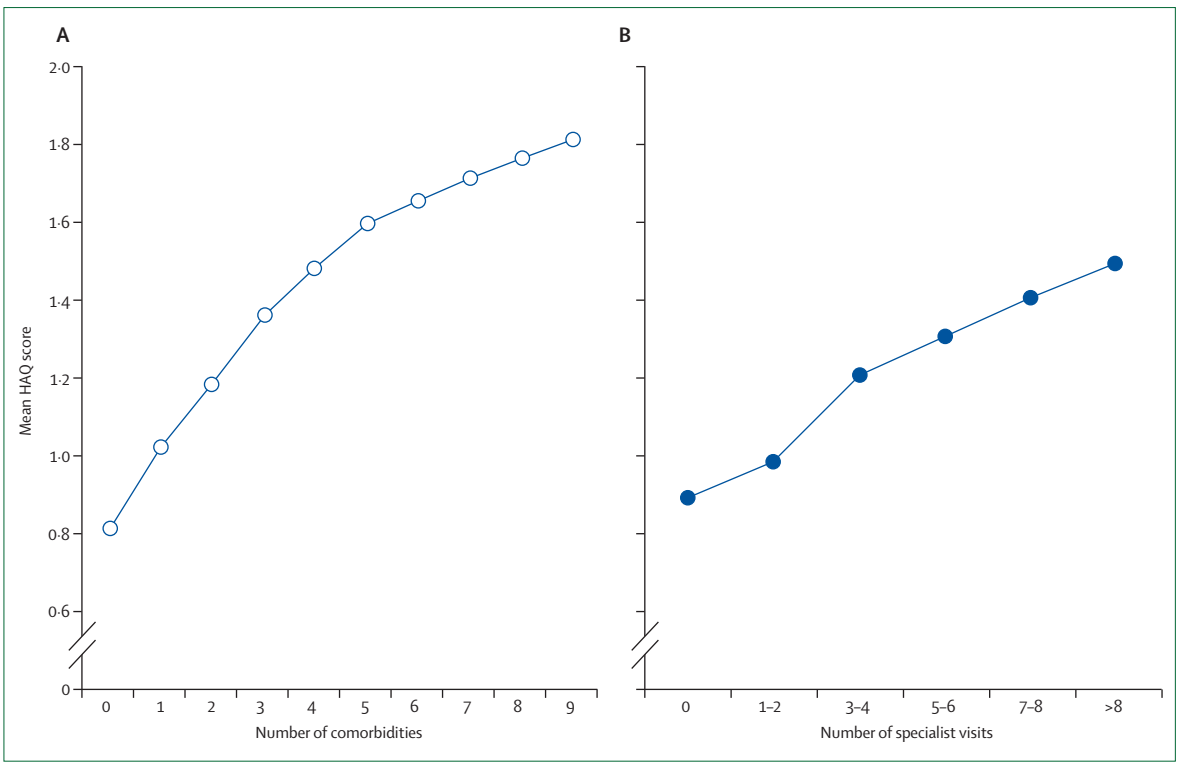

Figure 7: **Effect of health assessment questionnaire on comorbidities and specialist visits**
(A) Number of comorbidities.[134] (B) Visits to specialist rheumatologists (previously unpublished). Data taken from US national data bank; they were derived from more than 24 000 patients with rheumatoid arthritis and represent the average or *de facto* association of the health assessment questionnaire (HAQ) with comorbidity. They are not adjusted, so they represent the observed association.

Extra-articular disease

A range of extra-articular features can cause complications of rheumatoid arthritis, ranging from problems with subcutaneous nodules, secondary Sjögren's syndrome, interstitial lung disease, pericarditis and pleuritis, Felty's syndrome, amyloidosis, and rheumatoid vasculitis. Up to 30% of patients can be affected by these extra-articular disorders,[65] and they are worse in individuals with active disease.[137] Some extra-articular features, such as vasculitis, are declining in frequency.[74]

Treatment-associated comorbidities

Treatment-associated comorbid disorders include osteoporosis and cataract (steroids), gastrointestinal ulceration (NSAIDs), and infections and melanoma (biological agents and steroids). Many of these associations are confounded by rheumatoid arthritis activity.[137]

Prevention

With respect to primary prevention, decreasing the number of people who smoke within the population should reduce risk of rheumatoid arthritis developing,[138] and this initiative is a realistic preventive strategy with wide health benefits. Modification of diet to prevent rheumatoid arthritis is an area of speculation; however, at present, insufficient evidence exists to support this idea.[139]

Looking at secondary prevention of disease, 5–15% of patients with rheumatoid arthritis from historical cohorts (treated less intensively than nowadays) achieved drug-free remission.[67,68] Modern, intensive, very early treatment aims to increase the frequency of drug-free remission and achieve long-term disease modification. Benefits of this approach must be offset against risks of overtreatment of patients with mild self-limiting disease.

Future perspectives

Although many unresolved difficulties exist for people with rheumatoid arthritis, continuing introduction of innovative treatments can overcome many of them. One key need is definition of disease subsets in individuals with early arthritis so that intensive treatment regimens can be targeted at patients who most need them and are likely to respond. We also need to move beyond long-term suppressive treatment towards short intensive therapeutic courses that result in remission. This progression requires improved drugs and biomarkers that accurately predict patients' status, using pathological information summarised in figure 1.

Contributors
DLS was mainly responsible for sections on historical introduction, epidemiology, outcomes, management, and care pathways. FW was mainly responsible for sections on clinical assessments, prevention, and

complications. TWH was mainly responsible for sections on pathophysiology and classification and diagnosis. All authors contributed equally to revision of the report and finalisation of the text. The corresponding author had final responsibility for the decision to submit for publication.

Conflicts of interest

DLS has received lecture fees from Merck Sharp and Dhome, Pfizer, Novartis, Roche, and Wyeth, consultancy fees from Novartis and Schering Plough, and support for travelling to EULAR meetings from Pfizer, Bristol-Myers Squibb, and Schering Plough. FW is director of the National Data Bank for Rheumatic Diseases, which has received support for implementing safety registries from Bristol-Myers Squibb, UCB, and Centocor, and for research studies from Pfizer, Amgen, and Abbott. TWJH has received lecture or consultancy fees from Schering Plough, Bristol-Myers Squibb, Biotest AG, Wyeth and Pfizer, Novartis, Roche, Sanofi-Aventis, Abbott, and Axis-Shield diagnostics, and support for travelling to EULAR and ACR meetings from Roche.

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