

Review

Rheumatoid arthritis

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Rheumatoid arthritis is a systemic inflammatory disorder that mainly affects the diarthrodial joint. It is the most common form of inflammatory arthritis, and has a substantial societal effect in terms of cost, disability, and lost productivity. Although the pathogenesis of rheumatoid arthritis remains incompletely understood, much insight into the cellular and molecular mechanisms involved has been gained in the past decade. On the basis of these insights, new therapies have been developed, and clinical trials have shown the efficacy of aggressive treatment of patients with active disease. In this review, we discuss improvements in our understanding of the pathophysiology of inflammatory synovitis in rheumatoid arthritis, and improvements in therapy for patients with the disorder. The past decade has seen substantial advances in these areas. Future studies will be directed at improving methods for early diagnosis and identification of patients with progressive disease, and at improving methods to identify candidates for subclasses of disease-modifying antirheumatic drugs (DMARDs). Long-term safety and efficacy data for the new DMARD agents and combination regimens will also further delineate efficacy and toxicity and thus the appropriate clinical context for use of these therapeutic approaches. The continuing elucidation of pathophysiological pathways relevant in rheumatoid arthritis, coupled with continuing advances in biotechnology and rational drug design, offer substantial hope for the continued development of increasingly potent and specific pharmacotherapy for treatment of rheumatoid arthritis.

Rheumatoid arthritis affects about 1% of the population, in a female/male ratio of 2.5/1. The disease can occur at any age, but it is most common among those aged 40–70 years, its incidence increasing with age. The geographic distribution of rheumatoid arthritis is worldwide, with a notably low prevalence in rural Africa and high prevalence in specific tribes of Native Americans (Pima and Chippewa). There is no clear association between prevalence of rheumatoid arthritis and socioeconomic status.

Clinical features

The range of presentations of rheumatoid arthritis is broad, but disease onset is insidious in most cases, and several months can elapse before a firm diagnosis can be ascertained. The predominant symptoms are pain, stiffness, and swelling of peripheral joints (panel 1). The clinical course of the disorder is extremely variable, ranging from mild, self-limiting arthritis to rapidly progressive multisystem inflammation with profound morbidity and mortality (panel 2). Analyses of the clinical course and of laboratory and radiological abnormalities have defined negative prognostic factors for progressive joint destruction (panel 3); unfortunately, none are reliable enough to allow therapeutic decision making. For now, frequent assessment of disease activity and response to therapy is crucial for successful long-term management of rheumatoid arthritis.

Joint destruction from synovitis can occur rapidly and early in the course of the disorder: radiographic evidence is present in more than 70% of patients within the first 2 years. More sensitive techniques, such

as magnetic resonance imaging (MRI), can identify substantial synovial hypertrophy, bone oedema, and early erosive changes as early as 4 months after onset of disease.^{1,2} These radiographic changes predate malalignment and functional disability by years; by the time physical deformity is evident, substantial irreversible articular damage has commonly occurred. Furthermore, biopsy analysis of clinically symptomless knee joints in patients with early rheumatoid arthritis show active synovitis,³ highlighting the poor correlation between clinical assessment and

Panel 1: Clinical features of rheumatoid arthritis

Symptoms

- Joint swelling
- Pain/stiffness (commonly in morning and lasting >1 h)
- Weakness
- Deformity
- Fatigue
- Malaise
- Fever
- Weight loss
- Depression

Articular characteristics

- Palpation tenderness
- Synovial thickening
- Effusion (early on)
- Erythema (early on)
- Decreased range of motion (later on)
- Ankylosis (later on)
- Subluxation (later on)

Distribution

- Symmetrical (especially later on)
- Distal more commonly than proximal
- PIP, MCP/MTP, wrist/ankle more commonly than elbow/knee, shoulder/hip

PIP=proximal interphalangeal joint. MCP=metacarpophalangeal joint. MTP=metatarsophalangeal joint.

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Panel 2: Extra-articular involvement

Organ system	Involvement
Skin	Rheumatoid nodules, vasculitis
Ocular	Keratoconjunctivitis sicca, iritis, episcleritis
Oral	Salivary inflammation (sicca symptoms)
Respiratory	Pulmonary fibrosis, pleural effusion, cricoarytenoid inflammation
Cardiac	Pericardial inflammation, valvular nodule formation, myocarditis
Neurological	Mononeuritis, nerve entrapment, cervical instability
Hepatic	Increased aminotransferase concentrations
Haematological	Anaemia, thrombocytosis, leucocytosis, lymphadenopathy Felty's syndrome: splenomegaly, thrombocytopenia
Vascular	Vasculitis

disease progression, and the rapid development of polyarticular synovitis.

The rate of disease progression in rheumatoid arthritis is being debated. Results of some studies suggest non-linear, first-order kinetics with rapid progression during the early years of disease, whereas others^{4,5} suggest continuous, linear, long-term progression for up to 19 years. However, all analyses show progression and accumulation of irreversible joint destruction at all phases of disease.

Pathophysiology*Genetic data*

The results of several studies have shown a higher disease concordance among monozygotic twins (12–15%) than dizygotic twins (4%), implying the influence of genetic factors.^{6,7} Heritability analysis of these studies suggests that about 60% of a population's predisposition to rheumatoid arthritis can be accounted for by genetic factors,⁸ although on analysis of twin pairs concordant for rheumatoid arthritis, striking diversity in disease severity was noted.^{8,9}

Analysis of genetic markers has revealed an association between development of rheumatoid

Panel 3: Prognostic factors for severity

- Presence of rheumatoid factor
- Presence of HLA DR4 alleles
- Early development of joint erosions
- Increasing number of affected joints
- Early disability
- Older age at onset
- Fewer years of formal education
- Presence of extra-articular features

arthritis and the presence of a shared epitope on small regions of the DRB1*0401 and *0404 alleles.^{10,11} These analyses have also suggested that certain HLA alleles correlate with features of worse disease such as rheumatoid factor, nodules, and erosion;¹² rapid advances in genetic methods also hold promise for identification of non-HLA disease-association genes.¹³

Histological changes

An inflamed synovium is central to the pathophysiology of rheumatoid arthritis. It is histologically striking, showing pronounced angiogenesis; cellular hyperplasia; an influx of inflammatory leucocytes; and changes in the expression of cell-surface adhesion molecules, proteinases, proteinase inhibitors, and many cytokines. Synovial changes in rheumatoid arthritis vary with disease progression. In the first weeks of the disease, tissue oedema and fibrin deposition are prominent and can manifest clinically as joint swelling and pain. Within a short period, the synovial lining becomes hyperplastic, commonly becoming ten or more cells deep and consisting of type A (macrophage-like) and type B (fibroblast-like) synoviocytes. The sublining also undergoes striking alterations in cellular number and content, with prominent infiltration of mononuclear cells including T cells, B cells, macrophages, and plasma cells (figures 1 and 2). Synovial-vessel endothelial cells transform into high endothelial venules early in the course of the disease.¹⁴ High endothelial venules are specialised post-capillary venules found in secondary lymphoid tissue or inflamed non-lymphoid tissues; they facilitate the transit of leucocytes from the bloodstream into tissues (figure 2).

The formation of locally invasive synovial tissue—pannus—is a characteristic feature of rheumatoid

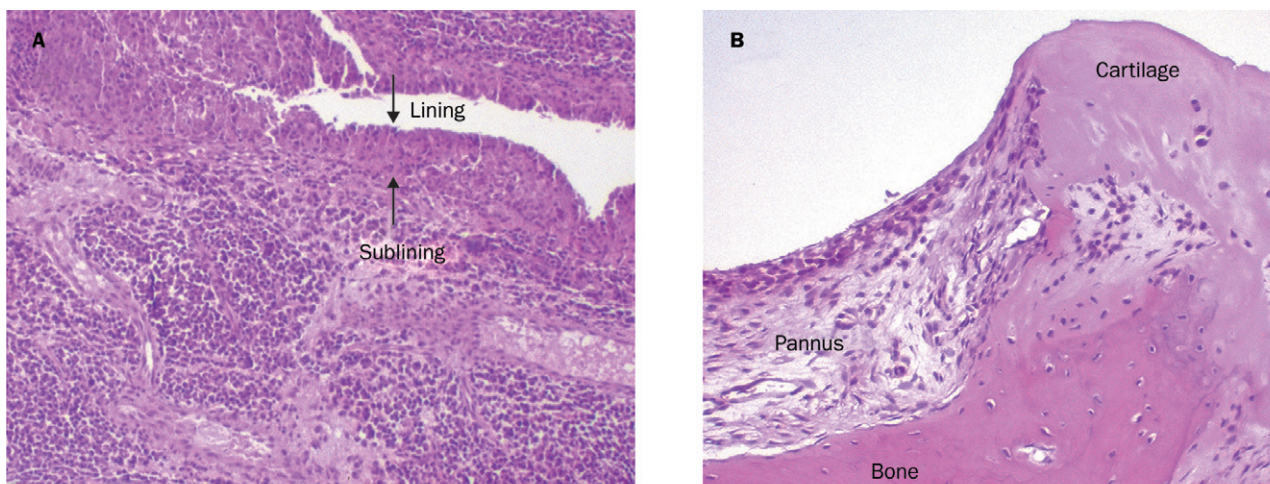


Figure 1: Haematoxylin and eosin stains of joint tissues from patients with rheumatoid arthritis

A: inflamed synovium with hyperplasia of synovial lining layer outlined by arrows. Deep in lining layer is a dense inflammatory infiltrate (original magnification $\times 40$). B: synovial pannus invading bone and cartilage (original magnification $\times 100$).

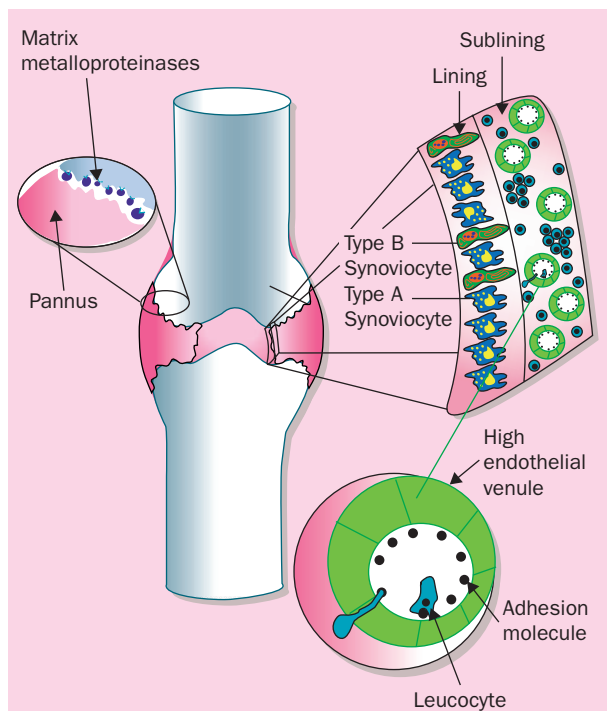


Figure 2: Major anatomical features of inflamed joint in rheumatoid arthritis

Enlarged image of synovium highlights type A (macrophage-like) and type B (fibroblast-like) composition of lining layer. Sublining shows leucocyte infiltrate and high endothelial venules with increased adhesion-molecule expression facilitating recruitment of leucocytes to inflamed synovium. Erosive interface between pannus and cartilage/bone is shown with high-level expression of matrix metalloproteinases.

arthritis. This tissue is involved in the joint erosions seen in rheumatoid arthritis (figure 1). Pannus is histologically distinct from other regions of the synovium and shows phases of progression. Initially, there is penetration of the cartilage by synovial pannus composed of mononuclear cells and fibroblasts¹⁵ with high-level expression of matrix metalloproteinases by synovial lining cells (figure 2).^{16,17} In later phases of the disease, cellular pannus can be replaced by fibrous pannus comprised of a minimally vascularised layer of pannus cells and collagen overlying cartilage.¹⁸ The tissue derivation of pannus cells has not been fully elucidated, although they are thought to arise from fibroblast-like cells (type B synoviocytes). In-vitro work shows that these fibroblast-like synoviocytes have anchorage-independent proliferation and loss of contact inhibition,¹⁹ which are phenotypes shown by transformed cells. However, the molecular pathogenic mechanisms driving pannus formation remain poorly understood.

T cells

Several lines of evidence implicate the participation of T cells in the pathogenesis of rheumatoid arthritis. T cells account for part of the mononuclear infiltrate in the synovial sublining, and with slight differences, these lymphocytes can organise into aggregates similar to those found in lymph nodes and Peyer's patches.²⁰ The genetic evidence implicating HLA-DR (MHC class II) alleles also suggests a role for T lymphocytes. CD4 T-cell specificity is mediated by interaction of a specific T-cell receptor with a peptide presented by an MHC class II molecule. Thus, the predilection for HLA-DR alleles in rheumatoid arthritis suggests a pathogenic

process either at the level of antigen presentation by the MHC molecule or at the level of MHC plus antigen recognition by CD4 T cells. To delineate further the restricting elements defining potential autoreactive T-cell clones, precise use of T-cell-receptor chains in rheumatoid arthritis has been defined in synovial and peripheral T cells. Although these studies suggest over-representation of certain receptor chains, they also document heterogeneous receptor populations in the inflamed synovium, arguing against a single pathogenic T-cell-receptor allele.^{21,22} Further analysis of peripheral T-cell homeostasis in populations of patients with rheumatoid arthritis shows decreased general diversity of T-cell-receptor use, specific changes in receptor selection, and clonal outgrowth of subsets of CD4 cells.²³ Thus, one hypothesis for rheumatoid arthritis pathogenesis is aberrant systemic selection or activation of T cells via MHC class II alleles interacting with several T-cell receptors of limited diversity. The molecular bases underlying the synovial predilection for disease activity remain unknown.

Despite the evidence implicating T cells in the pathogenesis of rheumatoid arthritis, other evidence suggests that T cells do not directly cause synovitis in the joint microenvironment. Analysis of synovial infiltrating T cells does not show much proliferation of this population.²⁴ Furthermore, comparison of CD45 isoforms in synovial T cells with peripheral blood T cells reveals an enrichment of cells expressing CD45 isoforms characteristic of memory T cells in the rheumatoid arthritis synovium.^{25,26} This phenotype suggests recruitment of previously stimulated and mature T cells as opposed to in-situ maturation of these cells. Finally, by contrast with known T-cell dependent inflammatory processes, analysis of synovial T-cell lymphokine production has shown a small T-cell contribution to cytokine profiles.²⁷ Thus, although T cells probably play a part in the systemic initiation of the processes in rheumatoid arthritis, their direct role in synovitis and joint destruction is unclear.

Cytokines

Cytokines—small soluble proteins that mediate intercellular communication between cells involved in immune responses—affect cell division, differentiation, and chemotaxis, as well as more broadly defined proinflammatory or anti-inflammatory actions. Quantitative analyses suggest that there are few T-cell-derived cytokines (such as interleukins 2 and 17, and interferon gamma) in inflamed synovial tissue; however, many other cytokines are present in moderate to high concentrations in rheumatoid arthritis. Tumour necrosis factor α (TNF- α) and interleukin 1 are both present in large quantities in affected synovial fluid and synovial tissue. Immunohistochemical and mRNA in-situ hybridisation analysis has shown the presence of these cytokines in cells of the synovial lining and sublining, including type-A synoviocytes and other macrophage-like populations.^{28,29} Both TNF- α and interleukin 1 are potent in-vitro stimulators of synovial tissue effector functions including proliferation, metalloproteinase expression, adhesion-molecule expression, secretion of other cytokines, and prostaglandin production (figure 3). TNF and interleukin 1 seem to function synergistically in inducing effector function.

To provide a means for homeostasis and down-regulation of inflammatory responses, a subclass of cytokines and cytokine receptors are thought to exert anti-inflammatory activity in the synovium. There are

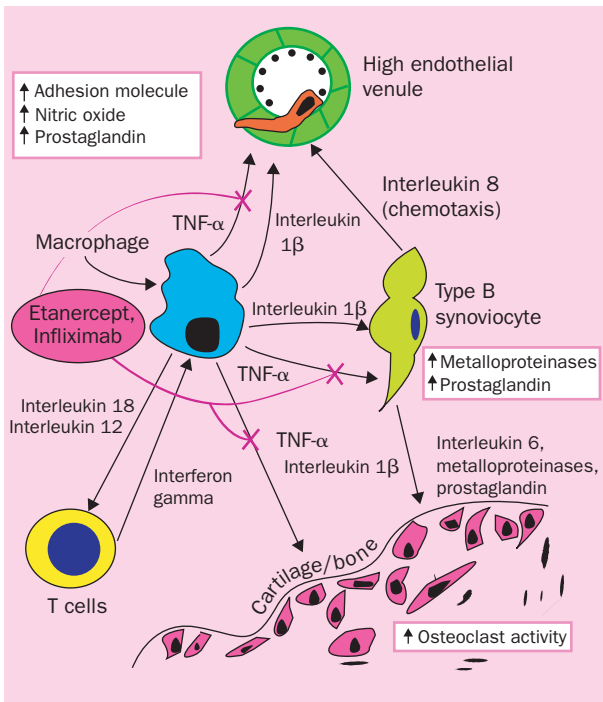


Figure 3: **Simplified schematic representation of cytokine network in rheumatoid arthritis**

TNF=tumour necrosis factor. Black arrows indicate upregulatory effects, red arrows indicate downregulatory effects. Red crosses represent pathways blocked by anti-TNF drugs.

two TNF receptors (p55 and p75), both of which occur naturally in synovial fluid in soluble form,³⁰ inhibiting TNF- α activity by competing with cell-surface receptors for binding. Similarly, the two interleukin 1 receptors (IL-1R1 and IL-1R2) also occur in soluble form in synovial fluid; these receptors are capable of binding interleukin 1 β , thus forming competition for cell-surface receptors.³¹ Additionally, a naturally occurring competitive inhibitor for interleukin 1 at the IL-1 receptor (IL-1 receptor antagonist [IL-1RA]) is also present in rheumatoid arthritis synovial fluid.³² This member of the interleukin 1 family binds to IL-1R1 without transducing a signal, thus blocking the receptor binding ability of interleukin 1 α or 1 β .

Results of work in animals have suggested a central role for TNF- α and interleukin 1 in the process of synovitis and joint destruction. Addition of exogenous interleukin 1 or TNF into experimental models of arthritis induces or exacerbates synovitis. Furthermore, mice transgenic for TNF- α , and mice with dysregulated TNF- α production develop arthritis.^{33,34} Treatment of murine models of arthritis with antibodies against TNF or interleukin 1 or with soluble TNF receptor ameliorates or abrogates disease.³⁴⁻³⁶ Although not perfect models for human rheumatoid arthritis, animal data such as these provided organismal proof of concept and provided a rationale for therapeutic trials in man.

Chemokines

Chemokines are small chemoattractant proteins that have a prominent role in leucocyte recruitment and activation in sites of inflammation. They are ligands for G-protein-coupled receptors on the surface of leucocytes. The distribution of chemokine and receptor expression is variable, which means that specific leucocyte subsets can be recruited. Numerous chemokines are thought to be active in the synovium of

patients with rheumatoid arthritis, but their function with regard to leucocyte subset recruitment and activation is unknown.

Matrix metalloproteinases

Metalloproteinases are produced at high levels by type B synoviocytes in rheumatoid arthritis. Metalloproteinases are a family of enzymes required for remodelling and destruction of extracellular matrix. The activity of the matrix metalloproteinases is regulated by molecules such as tissue inhibitors of metalloproteinases (TIMPs), serine proteinase inhibitors (SERPINS), and α_2 -macroglobulin. In rheumatoid arthritis, high levels of metalloproteinase activity are thought to contribute to cartilage and bone degradation.^{16,17,37} Inflammatory cytokines present in rheumatoid arthritis upregulate production of metalloproteinases; in cultured synoviocytes, both TNF- α and interleukin 1 are potent inducers of metalloproteinase production (figure 3).³⁸ The combinations of matrix metalloproteinases present in the synovial fluid of patients with rheumatoid arthritis are capable of degrading virtually all structural proteins present in joints. Furthermore, analysis of synovial tissue in rheumatoid arthritis reveals particularly intense staining of metalloproteinases at the intimal lining layer and at interface sites of erosive activity.^{16,17,39}

Adhesion molecules

Adhesion molecules are thought to have a role in recruitment of inflammatory cells to the joints in rheumatoid arthritis. The presence of adhesion molecules, which confer cells with the ability to adhere to each other and to the extracellular matrix, is central to various biological processes including homeostasis, vascular and epithelial integrity, immune responses, and organogenesis. Analysis of rheumatoid arthritis synovial tissue indicates that many families of adhesion molecules are expressed in patterns appropriate for modulating cell retention in the rheumatoid arthritis synovium.^{40,41} The ability of T cells to bind to type B synoviocytes can be substantially inhibited *in vitro* by blockade of these adhesion molecules, suggesting the functional relevance of these molecular interactions. Thus, expression of adhesion molecules in synovial tissue probably represents a regulatory mechanism for recruitment and retention of leucocytes, the dysregulation of which might contribute to the pathogenesis of rheumatoid arthritis.

Angiogenesis

Angiogenesis—the process of new blood-vessel formation—is highly active in rheumatoid arthritis, particularly early-onset disease.⁴² The newly formed vessels provide oxygen and nutrients to the hypertrophic synovium, and provide the means for recruitment of inflammatory cells to the joint anatomical compartment. Generally, angiogenesis is tightly regulated by many inducers and inhibitors. In the basal state, vascular endothelium is quiescent, and fewer than 0.01% of endothelial cells divide.⁴³ In physiological processes such as wound repair or the female reproductive cycle, and pathological processes such as tumour growth and rheumatoid arthritis, this quiescent tissue can be rapidly stimulated to proliferate. A growing list of angiogenic factors including cytokines, growth factors, colony-stimulating factors, and soluble adhesion molecules has been described in the synovium and synovial fluid of patients with rheumatoid arthritis.⁴³ However, these tissues also contain many inhibitors of angiogenesis,

Panel 4: Components of disease-activity measurements for rheumatoid arthritis

American College of Rheumatology disease activity measure*

- Tender joint count
- Swollen joint count
- Patient's assessment of pain (visual analogue scale)
- Patient's global assessment of disease activity (visual analogue scale)
- Physician's global assessment of disease activity (visual analogue scale)
- Patient's assessment of physical function/disability
- Acute-phase reactant value (ESR, C-reactive protein)

Disease activity score

- Tender joint count
- Swollen joint count
- Duration of morning stiffness
- Ritchie's articular index
- Patient's assessment of pain (visual analogue score)
- Patient's global assessment of disease activity (visual analogue score)
- Acute-phase reactant value (ESR, C-reactive protein)
- Haemoglobin concentration

ESR=erythrocyte sedimentation rate. *A 20% improvement is defined as at least 20% reduction in tender joint count and swollen joint count in addition to a 20% improvement in at least three of the remaining activity measures.

such as other cytokines, chemokines, and cryptic cleavage products of larger proteins, so whether the net increase in vascular volume noted in the joints of patients with rheumatoid arthritis results from an overabundance of angiogenic factors or a deficit of angiostatic factors (or both) is unclear.

Other inflammatory mediators

Many other families of inflammatory mediators are active in the synovitis of rheumatoid arthritis; however, their role in the pathogenesis of the disease is less clear. The synthesis of cyclo-oxygenases, nitric oxide synthase, and neutral proteases is increased in inflammatory synovitis, and these enzymes might mediate parts of the disease process.

Treatment

Paradigm shift

The past decade has seen a major transformation in the treatment of rheumatoid arthritis in terms of approach and choice of drugs. The previous therapeutic approach, termed the therapeutic pyramid, generally involved initial conservative management with non-steroidal anti-inflammatory drugs (NSAIDs) for several years; disease-modifying antirheumatic drugs (DMARDs) were withheld until clear evidence of erosions was seen. DMARDs were then added individually in slow succession as the disease progressed. This form of treatment has been supplanted by early initiation of DMARDs and combination DMARD therapy in patients with the potential for progressive disease. The idea of early intervention with DMARDs has been validated in several randomised trials.^{44,45}

This paradigm shift partly resulted from unsatisfactory outcomes with the pyramid approach, and an increased awareness of the cost,⁴⁶ lost productivity, morbidity,⁴⁷ and decreased life expectancy⁴⁸ associated with rheumatoid arthritis. These

findings are the consequences of progressive disease, and have provided the impetus for development of more effective therapies to prevent joint destruction and maintain functional status.

Outcome measures

An important advance in the assessment of treatments for rheumatoid arthritis has been the adoption of standardised and validated clinical outcome measurements such as the disease activity score (DAS), used in Europe, and the American College of Rheumatology (ACR) response, in North America (panel 4).^{49,50} Both measures attempt to allow longitudinal analysis and comparison of disease activity in different groups of patients. The DAS and ACR provide some assessment of functional outcome (eg, the health assessment questionnaire)⁵¹ and quality of life and do not directly assess joint destruction. Because of the substantial cost associated with newly approved therapies for rheumatoid arthritis, there is increasing interest in assessment of pharmacoeconomic indices associated with therapy. Quality-adjusted life-year (QALY)⁵² and other instruments provide methods for analytical measurements. Since joint destruction might not correlate directly with clinical signs of inflammation as assessed by the DAS and ACR instruments, methods for radiographic assessment of joint destruction—eg, the Larsen⁵³ and Sharp⁵⁴ scores—have been developed and are used widely. These radiographic instruments assess presence and severity of erosions and joint-space narrowing to assign a numerical value to articular destruction. These values allow longitudinal assessment of joint destruction for an individual patient and comparison of articular disease between groups. Most clinical trials now use these instruments to assess drugs used to treat rheumatoid arthritis.

DMARD monotherapy

The ability of medical therapy to affect the long-term increase in joint destruction and progressive decline in functional status has been unsatisfactory: few drugs were both remittive and tolerable. Before 1999, therapeutic options for rheumatoid arthritis included glucocorticoids, NSAIDs, and DMARDs. DMARDs—which included drugs from many classes—improved inflammatory symptoms or slowed progression of joint erosions for a subset of patients, often via incompletely understood mechanisms. These agents included methotrexate, gold salts, hydroxychloroquine, sulfasalazine, ciclosporin, and azathioprine.

DMARDs were often only partly effective and poorly tolerated in long-term therapy. In meta-analyses of dropout rates from clinical trials, 20–40% of patients discontinued use of DMARDs assessed as monotherapy during the duration of the trial,^{55–57} and in clinical practice, the median duration of DMARD monotherapy was less than 2 years for non-methotrexate agents.^{56,57} Although there were many reasons for lack of long-term adherence to treatment, poor efficacy, delayed onset of action, and toxic effects were major considerations.⁵⁸ Additionally, most DMARD therapy required patients to undergo frequent monitoring of blood and physical examinations for toxic effects.⁵⁹

Results from clinical trials showed that DMARD therapy decreased markers of inflammation such as erythrocyte sedimentation rate and swollen joint counts, and that symptoms improved in subsets of patients; however, most patients continued to show progression of irreversible joint destruction on radiography.⁶⁰

Methotrexate

The introduction of low-dose weekly methotrexate as monotherapy for rheumatoid arthritis provided an incremental improvement in tolerability and efficacy for many patients. Although no durable remissions were reported, results of clinical trials of methotrexate showed a consistent 50–80% clinical response relative to baseline, with long-term stabilisation of functional status.^{61–63} Furthermore, methotrexate slowed the rate of joint destruction as measured by radiography, and improved quality of life.^{63–65} In these studies, patients showed long-term adherence to low-dose weekly methotrexate monotherapy: 46–64% of patients continued to use the drug for 5 years, and 34–38% continued to use it for more than 10 years.^{61,62,66,67} Low-dose weekly methotrexate has therefore become the most widely prescribed DMARD; with extensive use, its safety and efficacy profiles have been well defined. Careful monitoring of blood counts, creatinine, hepatic aminotransferases, and pulmonary symptoms generally keep serious toxic effects resulting from therapy to a minimum.⁵⁹ Addition of oral folic acid (1 mg per day) or folinic acid (5 mg per week) reduces selective side-effects such as alopecia, stomatitis, gastrointestinal intolerance, and haemopoietic toxic effects without substantially lowering efficacy. Many rheumatologists start folic acid therapy concurrently with weekly methotrexate.

In clinical practice, methotrexate doses of more than 10 mg per week are generally needed, and many patients require dose escalations to 15–25 mg per week to achieve maximum response. Onset of action takes 4–8 weeks. Before declaring treatment failure, doses should be increased gradually until substantial benefit is achieved or until the maximum dose is reached (usually 25 mg per week or a dose that induces side-effects), and sufficient time should be allowed for onset of action. Because of its good tolerability and efficacy, methotrexate has become a benchmark agent with which other agents are compared in clinical trials. Furthermore, methotrexate is emerging as an anchor agent in combination therapeutic approaches.

Combination therapy

By use of the therapeutic principles applied to oncology, hypertension, and infectious disease, in which several agents of different classes are used in combination, recent trials in rheumatoid arthritis have assessed the efficacy of combination DMARD therapy for decreasing inflammatory symptoms and retarding joint destruction while maintaining a tolerable toxic-effect profile. Initial randomised controlled trials, however, yielded conflicting results.^{68,69} Potential explanations for those results include the short duration of study, use of surrogate markers of disease as endpoints, and choice of therapeutic agents. More recent studies have shown that combination therapy has clear benefits and tolerable toxic effects. These studies combined methotrexate with ciclosporin;⁷⁰ infliximab;^{71–73} etanercept;⁷⁴ leflunomide;⁷⁵ sulfasalazine and hydroxychloroquine;⁷⁶ sulfasalazine and prednisolone;⁷⁷ and sulfasalazine, hydroxychloroquine, and prednisolone.⁷⁸ Patients with new onset of symptoms and those with disease of several years' duration and who had failed previous DMARD therapy all benefited. These results suggest that patients in many stages of disease progression can benefit from more aggressive therapy. Recent trials also support slowing of joint erosions with combination therapy,^{73,77–79} suggesting that concurrent use of several DMARD agents is a valid form of disease management.

Newly approved drugs

During 1999, the US Food and Drug Administration approved three new DMARDs (leflunomide, etanercept, and infliximab) and a COX-2-specific NSAID (celecoxib) for the treatment of rheumatoid arthritis. New DMARDs approved within the past 24 months result from targeting of pathways active in inflammation. The development of etanercept and infliximab, both members of the new “biological-response modifier” pharmaceutical class, progressed from identification of an inflammatory pathway apparently relevant in rheumatoid arthritis pathogenesis to design of recombinant biological products with exquisite specificity for this pathway. Similarly, leflunomide represents the intentional development of a small-molecule inhibitor of a metabolic pathway active in inflammation.

Leflunomide

Leflunomide is an orally available inhibitor of dihydroorotate dehydrogenase—an enzyme required for de-novo pyrimidine synthesis. Although its specific mechanism of action in rheumatoid arthritis is not known, leflunomide affects lymphocyte function *in vivo* and *in vitro*.^{80,81} After ingestion, leflunomide is rapidly converted to its active metabolite A771726. Drug elimination occurs slowly via fecal and renal routes with a mean half-life of 14 days. Because of the length of time to achieve steady state with these kinetics, a loading dose of 100 mg daily is given over 3 days to hasten the process. Thereafter, leflunomide is dosed orally at 10–20 mg daily.

The efficacy of leflunomide has been shown in several double-blind placebo-controlled trials. In 6-month and 12-month studies that compared leflunomide with placebo, sulfasalazine, or methotrexate, leflunomide produced results similar to those of methotrexate and sulfasalazine, and was better than placebo.^{82–84} Of patients treated with leflunomide, 52% and 55% had a 20% improvement in ACR score at 24 weeks and 52 weeks, respectively, compared with 26% and 29%, respectively, of those on placebo. The corresponding rates for a 50% improvement in ACR score were 34% and 33% at 24 and 52 weeks for leflunomide, and 8% and 14% for placebo. Furthermore, other studies showed that leflunomide slowed the progression of joint destruction⁶⁵ and improved functional status and quality of life.⁶³ The onset of effect for leflunomide was slightly faster than that of sulfasalazine or methotrexate, with mean times to sustained response of 7–8 weeks.

Theoretically, the effects of leflunomide could complement those of methotrexate by affecting separate nucleic-acid metabolic pathways. The safety and efficacy of leflunomide used in combination with low-dose weekly methotrexate has been preliminarily assessed in a small open-label trial;⁷⁵ in a multicentre randomised controlled trial,⁸⁵ the investigators found that leflunomide plus methotrexate was more effective than methotrexate plus placebo (proportion with 20% improvement in ACR of 52 *vs* 23%). This combination was generally well tolerated; however, there remains concern about possible hepatotoxicity.

In clinical trials, the safety profile of leflunomide was generally similar to those of methotrexate and sulfasalazine.^{75,82–84,86} Diarrhoea was by far the most frequent adverse event: 33% of patients reported this complication compared with 17% of patients receiving placebo. Increased concentrations of aminotransferases were noted in 15% of patients receiving leflunomide compared with 12% of patients on methotrexate and 3% of patients on placebo.⁸³ Other adverse events included

alopecia (8–10%), allergic reactions (rash and pruritis, 24%), and rarely neutropenia, pancytopenia (<1%), or liver disease. Since leflunomide is teratogenic in animals, women of childbearing potential should avoid pregnancy while on therapy, and cholestyramine washout should be done before attempting pregnancy. The estimated yearly cost of leflunomide therapy is about US\$3000 plus laboratory monitoring costs.

TNF biological-response modifiers

Etanercept and infliximab are the first biological-response modifiers approved for treatment of rheumatoid arthritis. The rapidity of clinical development of the TNF biological-response modifiers has been remarkable. Initial trials of anti-TNF agents in human beings began in 1992, and results were available in 1993. Since then, analysis has proceeded to double-blind placebo-controlled trials. Both drugs are designed to bind to TNF- α and decrease its bioavailability. Etanercept is a recombinant form of the p75 TNF receptor (TNF-RII), dimerised via fusion with a portion of the human IgG1 Fc tail. Etanercept binds to both TNF- α and TNF- β . Infliximab is a partly humanised mouse monoclonal antibody directed against TNF- α but not TNF- β .

Etanercept

The results of clinical trials of etanercept have shown substantial efficacy in active refractory rheumatoid arthritis. Initial open-label dose-escalation analysis showed significant decreases in painful or swollen joints and concentrations of C-reactive protein.⁸⁷ Subsequent double-blind placebo-controlled trials that assessed etanercept as monotherapy or in combination with methotrexate confirmed previous findings—ie, 60–75% of patients achieved a 20% improvement in ACR at 3 months, and 40–57% of patients achieved a 50% improvement over 6 months, compared with placebo responses of 14–33% and 0–8%, respectively.^{74,88,89} Results of preliminary reports suggest that the benefits of the therapy are sustained over 24 months of analysis.⁹⁰ Furthermore, in results from a randomised controlled trial of patients with early rheumatoid arthritis (<3 years' duration), etanercept monotherapy was as effective as methotrexate in improving arthritis activity and in slowing the rate of joint destruction.⁹¹

Etanercept is generally well tolerated: no life-threatening adverse events or dose-limiting toxicities have been noted in randomised clinical trials. The only notable and most frequently reported adverse event was injection-site reaction in more than 40% of patients. However, life-threatening infections have been anecdotally reported in patients on etanercept and other anti-TNF therapy; impaired ability to clear micro-organisms due to TNF blockade remains a concern.

Etanercept is only available via the parenteral route, and standard dosing is a 25 mg subcutaneous injection twice weekly. The median half-life is 115 h. Listed contraindications to etanercept are presence of serious infection and known hypersensitivity to the drug. The estimated yearly cost of etanercept therapy is about \$12 000.

Infliximab

Clinical trials of infliximab have shown significant and clinically relevant improvements in active rheumatoid arthritis. In initial multicentre, double-blind, placebo-controlled trials of a single infusion of either 1 mg/kg or 10 mg/kg infliximab, substantial clinical response was noted.⁹² Subsequent multiple-infusion studies in patients

with active disease despite methotrexate monotherapy confirmed the results of initial studies.^{71–73,93} In these analyses, 50–59% of patients on infliximab had a 20% improvement in ACR score and 27–31% had a 50% improvement over 30 weeks, compared with 20% and 4%, respectively, of patients on placebo. This response remained for 54 weeks: the proportion of patients with a 20% improvement in ACR was 42–59% in all infliximab treatment groups.⁷³ Significant response rates were seen irrespective of whether a patient was taking methotrexate; however, patients receiving combinations of infliximab and methotrexate had higher rates and increased duration of response to therapy. Furthermore, development of antibodies against infliximab (human antichimeric antibodies) was lower in patients receiving concomitant methotrexate therapy.

Infliximab is available only via parenteral administration. The serum half-life of infliximab is variable and lengthy, ranging from 8.0 to 9.5 days. The dosing schedule approved by the US Food and Drug Administration is 3 mg/kg at weeks 0, 2, and 6, followed by maintenance dosing every 8 weeks thereafter, and its approved regimen mandates combination therapy with methotrexate. Adverse events with infliximab have been infrequent in clinical trials and consisted mainly of infusion reactions characterised by fevers, chills, urticaria, chest pain, dyspnoea, or hypotension. The formal contraindication to infliximab administration is known hypersensitivity to the medication. As with etanercept, a substantial increase in rate of infection has not been seen, but isolated cases of serious and even life-threatening infections have been reported. Because of concerns about TNF- α blockade and infection clearance, most authorities do not recommend therapy in the presence of active infection. The estimated yearly cost of infliximab therapy for the 3 mg/kg dose is about \$9000 plus infusion charges.

Conclusions

The ability of the new anti-TNF- α biological response modifiers to intervene in the disease process has generated enthusiasm for therapeutic interventions and for the possibility of future drugs that target individual inflammatory pathways. However, this excitement is tempered by the potential for long-term side-effects and toxicity. Rare events that have now been seen with anti-TNF therapy include infections (*Mycobacterium tuberculosis*, fungal and bacterial sepsis), a lupus-like syndrome, and a demyelinating syndrome. Continued surveillance for cumulative dosing effects and unexpected rare events are warranted for the foreseeable future. A wide array of biological response modifiers is presently at all stages of pharmaceutical development; eventually, we might be able to identify relevant inflammatory pathways operative within individual patients and tailor therapy accordingly.

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