Rheumatoid arthritis

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Rheumatoid arthritis is a systemic, inflammatory, autoimmune disorder. Enhanced understanding of molecular pathogenesis has enabled development of innovative biological agents that target specific parts of the immune system. These treatments have changed the course and face of rheumatoid arthritis and outcomes for patients and society. New knowledge has emerged of how environmental factors interact with susceptibility genes and the immune system in the pathogenesis of a major subset of rheumatoid arthritis. Research undertaken on the longitudinal disease process and molecular pathology of joint inflammation has led to new therapeutic strategies that promote early use of disease-modifying drugs with tight disease control and distinct and quantifiable treatment goals. Today, such approaches can halt most cases of joint destruction but not all instances of joint inflammation and comorbidity. Understanding the cause and pathogenesis of different rheumatoid arthritis subsets will lead not only to individualised treatments during early phases of the illness but also, possibly, to disease prevention.

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Introduction

Rheumatoid arthritis is a disorder in rapid transition. It has evolved from a syndrome of unknown cause to one for which distinct subsets of disease are emerging, and growing knowledge of risk factors calls for preventive strategies. Instead of being regarded as a disease of uncertain pathogenesis, rheumatoid arthritis has become a prototype for application of knowledge of molecular pathogenesis for development of new treatments. Previously, resources were used mainly for care and rehabilitation of accrued handicaps; now the disorder has become a modern-day medical dilemma, whereby early treatment can prevent disability in many patients but the most effective new drugs can be too expensive to administer to all people who might benefit. In this Seminar, we describe some of these developments and their results, which, we believe, extend beyond care and cure for the patient with rheumatoid arthritis.

Clinical expression and sub-classification

From Garrod's initial definition of rheumatoid arthritis as a disease in 1859, current classification criteria were developed by American rheumatologists in the mid 1980s (panel).[1] These criteria, which have served so well in selecting patients for clinical trials, are now becoming less relevant, partly because of the success of these same trials. At least two of the seven criteria (nodules and erosions) are generally not present at the best time for early diagnosis and initiation of treatment (table 1). Thus, we need new definitions for rheumatoid arthritis and its subsets, based on enhanced understanding of disease pathogenesis, which can be used for early diagnosis and treatment decisions. The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) are currently collaborating to produce such classification criteria.

Understanding rheumatoid arthritis also means appreciation of its longitudinal course and its different phases (figure 1). In genetically susceptible individuals, specific environmental factors can activate potentially pathogenic immune reactions, including antibody formation. Years later, additional events such as trauma or infection may contribute to disease development by focusing immune reactions to the joint, resulting in joint inflammation. If inflammation becomes chronic, the phenotype might fulfil criteria for rheumatoid arthritis, with inflammation leading to joint destruction and systemic complications, with increased comorbidity. Thus, despite increasing use of early and aggressive treatments, rheumatoid arthritis is still a chronic disorder with clinically important potential comorbidities;[2] to a large extent, comorbid conditions are the results of unopposed cumulative inflammatory activity. A major focus of this Seminar will be to show how new insights into cause and pathogenesis of different variants of rheumatoid arthritis might alter diagnostic and therapeutic strategies in all phases of disease.

Active treatment can lead to a striking change in the long-term course of rheumatoid arthritis, a finding proven by alterations that have already taken place. Thus, the so-called clinical face of the disorder is changing, in that previously feared extra-articular manifestations—such as amyloidosis, serositis, scleritis and episcleritis, and subcutaneous nodules—are diminishing in frequency,[3,4] making other long-term effects such as

Search strategy and selection criteria

We searched Medline with the terms "rheumatoid arthritis" and "diagnosis", "pathology", "pathogenesis", and "treatment", and other specific terms when needed, and included all reports published between March, 1968, and March, 2008. We reviewed abstracts and selected relevant papers. All types of articles were included (original work, review, case report, letter, etc). We tried to select the most recent publications and to refer to the original description (that means first publication on a certain finding), but other seminal and comprehensive studies and reviews were also included. For clinical studies, we reviewed all controlled studies in the Cochrane library (Cochrane reviews and clinical trials sections), searching for "rheumatoid arthritis" and the keywords "glucocorticoids", "methotrexate", "infliximab", "etanercept", "adalimumab", "rituximab", and "abatacept".

Panel: ACR criteria for rheumatoid arthritis[1]

A patient is said to have rheumatoid arthritis if he or she meets at least four criteria.

1. Morning stiffness lasting at least 1 h, present for at least 6 weeks
2. At least three joint areas simultaneously with soft-tissue swelling or fluid, for at least 6 weeks
3. At least one area swollen in a wrist, metacarpaophalangeal, or proximal interphalangeal joint, for at least 6 weeks
4. Simultaneous involvement of the same joint areas on both sides of the body, for at least 6 weeks
5. Subcutaneous nodules seen by a doctor
6. Positive rheumatoid factor
7. Radiographic changes on hand and wrist radiographs (erosions or unequivocal bony decalcification)

Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made.

	Limitations	Consequences
Polyarthritis (>3 joint areas) with hand involvement, symmetric distribution, and morning stiffness	Clinical variables that are not specific and sensitive enough for diagnosis in the absence of other markers	Criterion will still be valid but will most probably include fewer affected joints and a less typical distribution because development of new diagnostic methods will enable earlier diagnosis
Rheumatoid nodules	Better and earlier disease control reduces the likelihood of seeing rheumatoid nodules	Criterion will still be valid but will be relevant for only a few patients
Positive rheumatoid factor	Other serum markers with equal or better diagnostic power have been described	Other serum markers will be added to the criterion. ACPA presence has similar sensitivity to and better specificity than rheumatoid factor for diagnosis; rheumatoid factor and ACPA have similar value as prognostic factors
Radiographic changes on plain radiographs	Diagnostic value diminishes because diagnosis and treatment should ideally be started before erosions arise	Development of more sensitive joint-imaging methods will probably lead to earlier recognition and new definitions for joint destruction

Table 1: **Limitations of ACR criteria**

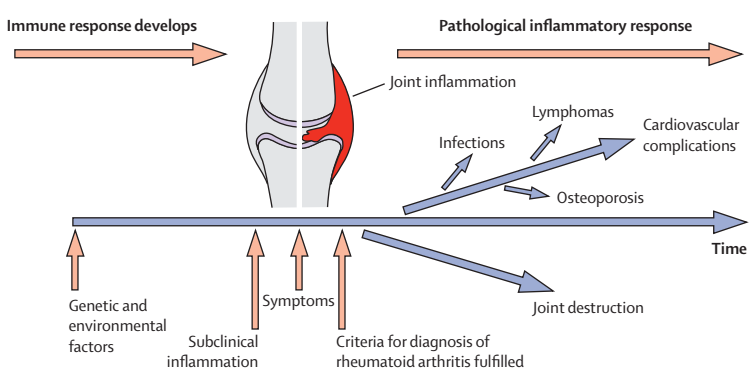

Figure 1: **Longitudinal course of rheumatoid arthritis**

cardiovascular disease and lymphomas and short-term outcomes such as pain and fatigue more important to understand and treat.

Increasingly, the value of dividing rheumatoid arthritis into subsets has been recognised so that potential strategies for prevention and treatment can be implemented efficiently. As will be described in detail below, growing evidence shows that the disease consists of at least two subsets, with different causes and severity. This subdivision has been built classically on presence or absence of rheumatoid factor,[5] but increasingly the separation is made on the basis of presence or absence of antibodies to citrullinated protein antigen (ACPA),[6] sometimes referred to as anti-CCP (cyclic citrullinated peptide).[7] The ACPA method is more specific for rheumatoid arthritis than is rheumatoid factor and is, thus, more informative as a diagnostic test for early disease. For prognosis in cases of already established rheumatoid arthritis, ACPA and rheumatoid factor define largely overlapping populations of patients. Notably, joint destruction, comorbidities such as cardiovascular disease, and other extra-articular manifestations are all most prominent in the subset of patients positive for rheumatoid factor and ACPA.[6,8]

Cause and pathogenesis

Rheumatoid arthritis is called a complex genetic disease, meaning that several genes, environmental factors, and stochastic (chance) factors act in concert to cause pathological events. Findings of twin studies have estimated the relative contribution of genetic factors to be about 50% for the entire syndrome of rheumatoid arthritis, leaving the remaining part to environment and chance.[9] In an elegant twin study published more than 10 years ago, the power of a causal approach was shown, whereby the genetic factor was kept under control while one environmental factor—smoking—was studied. In a series of 13 monozygotic twin pairs discordant for rheumatoid arthritis and smoking, the smoker was the one with the disease in 12 of 13 pairs.[10] This finding indicates why both genetics and environment need to be investigated in the same context. For a criterion-based disease such as rheumatoid arthritis, such studies must also account for different causes for different disease subsets.

Another pertinent issue is timing of exposure to the potential environmental factors. Workers on a few studies have suggested that accumulation of risk factors can begin even before birth, including the possibility that birthweight and the mother's MHC gene composition might affect future risk for rheumatoid arthritis in offspring.[11–13]

Below, we have described our current knowledge of genetic and environmental factors that are associated with risk for rheumatoid arthritis. Further, we discuss how these factors together can affect evolution of immune and inflammatory reactions that might cause different forms of the disease. Table 2 summarises the section.

Since the 1970s, knowledge about genetic susceptibility factors for rheumatoid arthritis has had a major effect on ideas about the disease's molecular pathogenesis. The reported association between presence of certain HLA *D/DR* alleles and risk for rheumatoid arthritis,[14,39] together with recognition of MHC class II-expressing antigen-presenting cells[40] and T cells[41] in inflamed joints, led to the idea that MHC class II-dependent T-cell and B-cell activation were major drivers of the disease.[40] This notion received strong support from the discovery that most HLA *DR* alleles that conferred susceptibility to rheumatoid arthritis had a common aminoacid motif—named the shared epitope—in the β chain of the HLA-DR molecule,[39] and presence or absence of genetic variants within the *DRB1* locus is an important genetic determinant of risk for the disease. *PTPN22*, the second confirmed susceptibility gene identified in 2005,[42] codes for a tyrosine phosphatase that has a role in T-cell and B-cell signalling, thus further strengthening the genetic argument for a T-cell and B-cell contribution to rheumatoid arthritis.[43]

Accumulating data from the past few years have indicated that the HLA *DRB1* shared epitope and *PTPN22* risk alleles are associated only with a subset of rheumatoid arthritis that is defined by presence of ACPA or rheumatoid factor, or both.[17,30,31,44,45] One implication of these findings is that the genetic hypothesis for involvement of adaptive, B-cell, and T-cell-mediated immunity in pathogenesis is valid only for the ACPA-positive or rheumatoid factor-positive disease subset. Another implication is that all further causal studies that include genetics need to judge these subsets of rheumatoid arthritis as separate entities.

Genetics research of complex diseases has had a major boost from new technologies that allow genome-wide association studies of risk alleles.[15] Findings of studies incorporating these technologies for rheumatoid arthritis confirmed that the MHC region harbours the most important genetic risk factors for ACPA-positive disease, with *PTPN22* as the second most important gene.[15,16] Several additional risk alleles for the disease have been identified in gene regions containing *TRAF1* (C5 locus), *STAT4*, and *OLIG3-AIP3* genes.[16,19,20] These new findings, and data from complementary candidate gene studies,[18,23] indicate how a series of variations together make up the genetic risk for rheumatoid arthritis, and they show how different patterns of genetic risk factors have emerged for subsets of disease positive and negative for ACPA or rheumatoid factor.[46] However, small odds ratios for most of these individual risk factors make these findings quite unimportant for use in prediction of disease risk. Instead, the main value of the new knowledge comes from the potential to identify distinct molecular pathways in which several genes work in concert during development of different forms of rheumatoid arthritis.

The best established environmental risk factor for rheumatoid arthritis is cigarette smoking.[29,47,48] Other potential factors include silica dust,[49] mineral oils,[34] and other airway exposures,[50] and in a historic report, researchers described a severe form of rheumatoid arthritis (Caplan's syndrome) in charcoal workers.[51] Factors such as postmenopausal hormone replacement have in many, but not all, studies been associated with protection.[52] Some data also indicate that moderate alcohol consumption can reduce risk for rheumatoid arthritis,[35,38] and it diminishes risk and severity of experimental arthritis in rodents.[36]

Investigation of environmental factors in rheumatoid arthritis initially focused on descriptive epidemiology. However, implementation of studies that accounted not only for genes and environment but also for immunity began to provide distinct clues to the molecular pathogenesis of the disease. Smoking was shown in several studies to be a risk factor for the rheumatoid factor-positive or ACPA-positive subset of rheumatoid arthritis and to have no or a very minor effect on the autoantibody-negative subset (figure 2).[30–33] A major environment interaction was noted between HLA-DR

	ACPA-positive disease	ACPA-negative disease	Comments and references
Genetic risk factors			
HLA-*DRB1* alleles	Yes	No	Strong evidence; associated also with rheumatoid factor-positive disease[14–16]
PTPN22	Yes	No	Strong evidence; associated also with rheumatoid factor-positive disease[17]
TRAF1-C5 locus	Yes	No	Strong evidence[16,18]
OLIG3-AIP3 locus	Yes	..	Strong evidence[19]
STAT4	Yes	..	Strong evidence[20]
Non-*DRB1* MHC genes	Yes	No	Needs confirmation[21,22]
IRF5	No	Yes	Needs confirmation[23]
CLEC4A	No	Yes	Needs confirmation[24]
HLA *DRB1*03*	No	Yes	Needs confirmation[25]
PADI4	–	–	Strong evidence for Asian population, but not for European population[26,27]
Genetic protective factors			
HLA-*DRB1* molecules containing aminoacid sequence DERAA	–	–	Needs confirmation[28]
Non-inherited maternal HLA-*DR*	–	–	Needs confirmation[13]
Host factors			
Female sex	–	–	Strong evidence
Perinatal factors	–	–	Debated[11,12]
Obesity	–	–	Needs confirmation[29]
Environmental risk factors			
Cigarette smoking	Yes	No	Strong evidence; associated also with rheumatoid factor[30–33]
Mineral oils	Yes	No	Needs confirmation[34]
Environmental protective factors			
Alcohol	Yes	Yes	Needs confirmation[35–38]

–=no division made between subsets.

Table 2: **Genetic and environmental factors associated with rheumatoid arthritis**

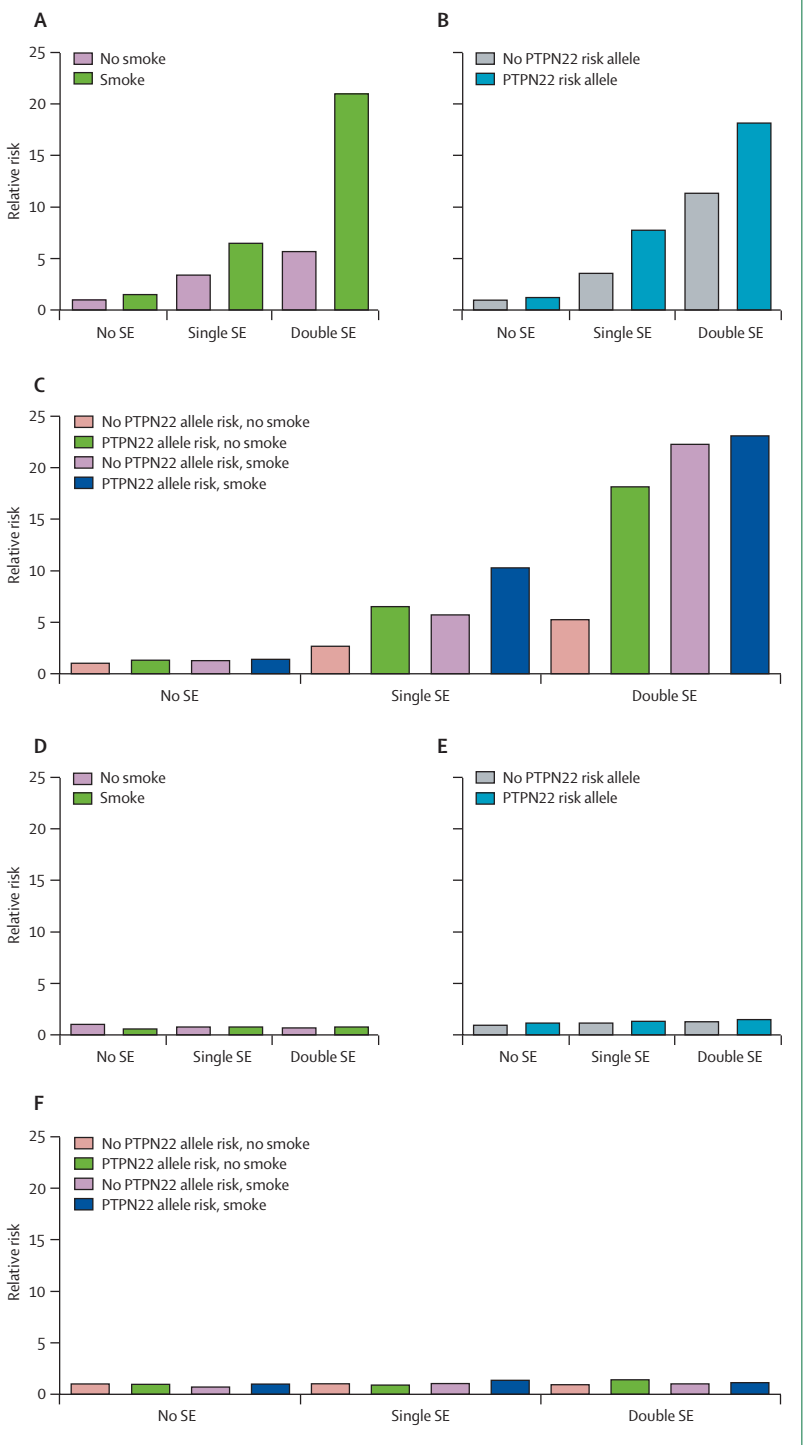

Figure 2: **Gene–environment and gene–gene interactions determining risk for rheumatoid arthritis**
Histograms show relative risks for development of rheumatoid arthritis (positive or negative for ACPA) with two different genetic variations and one environmental risk factor. Genetic variations are absence or presence of one or two copies of HLA *DRB1* alleles containing the shared epitope (SE), and absence or presence of the R620W allele of *PTPN22*. The environmental variation is smoking status, either no smoke (for individuals who never smoked) or smoke (for those who ever smoked cigarettes). (A) and (D) represent gene–environment interactions, (B) and (E) gene–gene interactions, and (C) and (F) gene–gene–environment interactions. Data are from the Swedish Eira study.[31,45]

risk alleles and smoking in patients who were positive for rheumatoid factor or ACPA, in three European investigations,[31–33] and to a smaller extent in one North American study.[53]

These findings suggest three main ideas: (1) that patients with rheumatoid arthritis who are positive for ACPA are fundamentally different from those who are ACPA-negative with respect to genetic and environmental risk factors; (2) that an environmental exposure (here, smoking) could change greatly the magnitude of a genetic association in a complex disease; and (3) that these striking data from genetic epidemiological studies need biological explanations for the combined effects of genetic and environmental risk factors and for why they act differently in subsets of rheumatoid arthritis divided by anti-citrulline immunity.

We now need to transform statistical data from genetic epidemiological studies into causal models of the disease that are testable in both the laboratory and the clinic. One such model has been created for smoking and HLA-DR shared epitope genes and has several components, described below (figure 3).

When the lung encounters smoke (and possibly many other irritants and adjuvants, such as dust from silica and charcoal, and infections) macrophages are activated and some cells go into apoptosis, necrosis, or both.[54] This process could lead to increased synthesis and activity of enzymes called peptidylarginine deiminases, which cause citrullination (change of the aminoacid arginine to citrulline) in certain proteins in the lungs.[31,55,56] Some of these post-translationally modified proteins bind specifically to HLA-DR molecules on antigen-presenting cells—such as dendritic cells or macrophages—that contain the shared epitope peptide-binding motif. This process determines the strength of the immune response to citrullinated peptides.[57,58] Smoking might further contribute to T-cell and B-cell activation by triggering antigen-presenting cells in the lung, thus enhancing cell–cell interactions (eg, T cell receptor–HLA-DR, CD40Ligand–CD40, and several other events), which finally result in high titres of ACPA. In many cases, antibodies to citrulline emerge years before onset of disease,[59] and could contribute ultimately to arthritis, possibly after citrullination has taken place in joints as part of non-specific synovial inflammation.[60,61] This event could lead to immune complex formation between ACPA and citrullinated proteins, which further bind to Fc receptors on the surface of synovial macrophages and contribute to the perpetuation of inflammation. Other antibodies, such as rheumatoid factor, directed against the Fc portion of immunoglobulin could also contribute to immune complex formation and disease pathogenesis. ACPA could enhance arthritis development in mice that already have mild synovitis,[62] indicating that these antibodies might—under certain circumstances—also be pathogenic in human beings.

This potential chain of events is one that can now be further tested empirically in the laboratory, with many

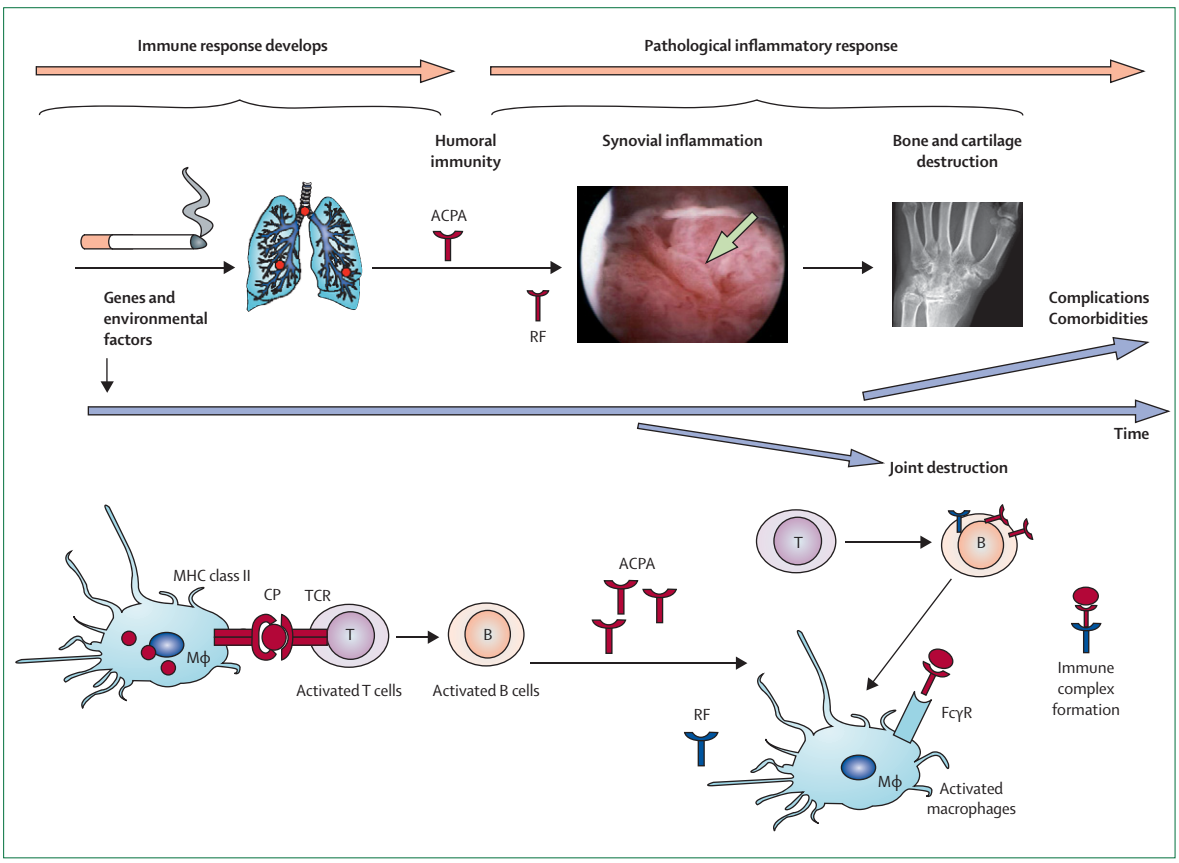

Figure 3: **Hypothetical model for molecular pathogenesis of ACPA-positive rheumatoid arthritis**
CP=citrullinated proteins and peptides. RF=rheumatoid factor.

new questions emerging. Which citrullinated antigens are recognised in the lungs and in the joints? Why and how can anti-citrulline immunity specifically target the joints? Which factors, other than cigarette smoke, are able to trigger anticitrulline immunity? Answers for these questions might lead us ultimately towards an understanding of which specific immune reactions contribute to the ACPA-positive form of rheumatoid arthritis. They could also give us access to the world of antigen-specific immunomodulation and curative treatment that is available in rodent systems, for which some of the answers to these questions are known.[63] Although these specific research questions about adaptive immunity can be posed for ACPA-positive rheumatoid arthritis, other causes must be considered for ACPA-negative disease (table 2, figure 4).

Joint inflammation

The causal factors described above emphasise differences between two major subsets of rheumatoid arthritis and suggest a role for adaptive immunity in the initiation of at least ACPA-positive disease. However, findings of direct studies of inflammation in the joints have, for a long time, shown how a series of inflammatory cascades are active, in many cases probably triggered by adaptive immunity. Current data also indicate that similar inflammatory mechanisms could be at work, both in patients who are positive or negative for rheumatoid factor or ACPA, as common final pathways of joint

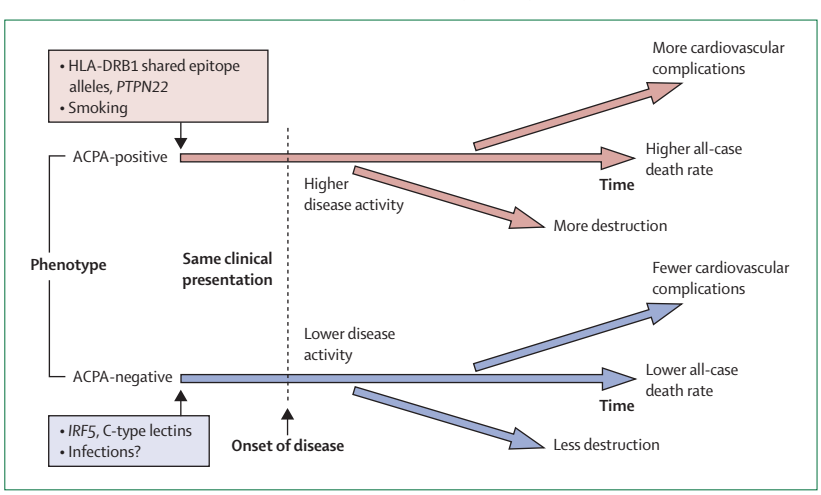

Figure 4: **Differences in risk factors, immune events, and disease course between two major subsets of rheumatoid arthritis**
Despite a similar clinical phenotype at presentation, the two disease subsets (ACPA-positive and ACPA-negative) are associated with different genetic and environmental risk factors and are likely to have partly different molecular pathogenesis.

inflammation. Eventually, such inflammatory activity could be transformed into a destructive behaviour by actions that include the innate system and, in particular, imbalances in regulation of cytokines and other inflammatory mediators.[64,65] From these studies on cytokine networks, a crucial role of tumour necrosis factor (TNF) in joint inflammation was originally postulated.[66] Similar data suggested important roles also for interleukin 6 in rheumatoid arthritis pathogenesis[67] and, in some cases, interleukin 1.[68] Work done on arthritic joints has furthermore shown the presence of activated T lymphocytes[41] and B cells[69] in most inflamed synovia, indicating that targeting of these cells might directly affect the local inflammatory process. Destructive behaviour has also been proved dependent on involvement of RANKL (receptor activator of NFκB ligand) in osteoclast activation and subsequent bone destruction.[70,71]

Figure 5 presents a schematic description of our current understanding of inflammation in joints during rheumatoid arthritis. Synovial inflammation is characterised by the presence of many different interacting immune cells. Antigen-presenting cells communicate with T cells through the T-cell receptor (TCR)–MHC interaction, and T-cell activation happens only in the presence of co-stimulatory signals mediated via the CD28–B7 receptor family (CD80/86). B cells can function both as antigen-presenting cells and as antibody-producing cells, which deliver antibodies entailed in immune complex formation. Macrophages activated by signals from T cells and by immune complexes produce many proinflammatory cytokines, such as TNF, interleukin 1, and interleukin 6, which can increase expression of cell-adhesion molecules and cytokine production. Dependent on the cytokine environment, activated T cells show distinct phenotypes, such as T-helper 17 (Th17) cells, which are dependent on interleukin-6 stimulation and produce interleukin 17. This molecule enhances cytokine release, production of cartilage-destructive enzymes, and expression of bone destruction-related molecules, such as RANKL.[64,65]

Outcomes

Fatigue—defined as low energy and constant tiredness—was some years ago assumed to be part of a so-called rheumatoid arthritis personality. We now know that fatigue is a physiological state caused by direct action of proinflammatory cytokines—in particular interleukins 6 and 1—on cytokine receptors on brain endothelial cells, which in turn use prostaglandin signalling pathways to

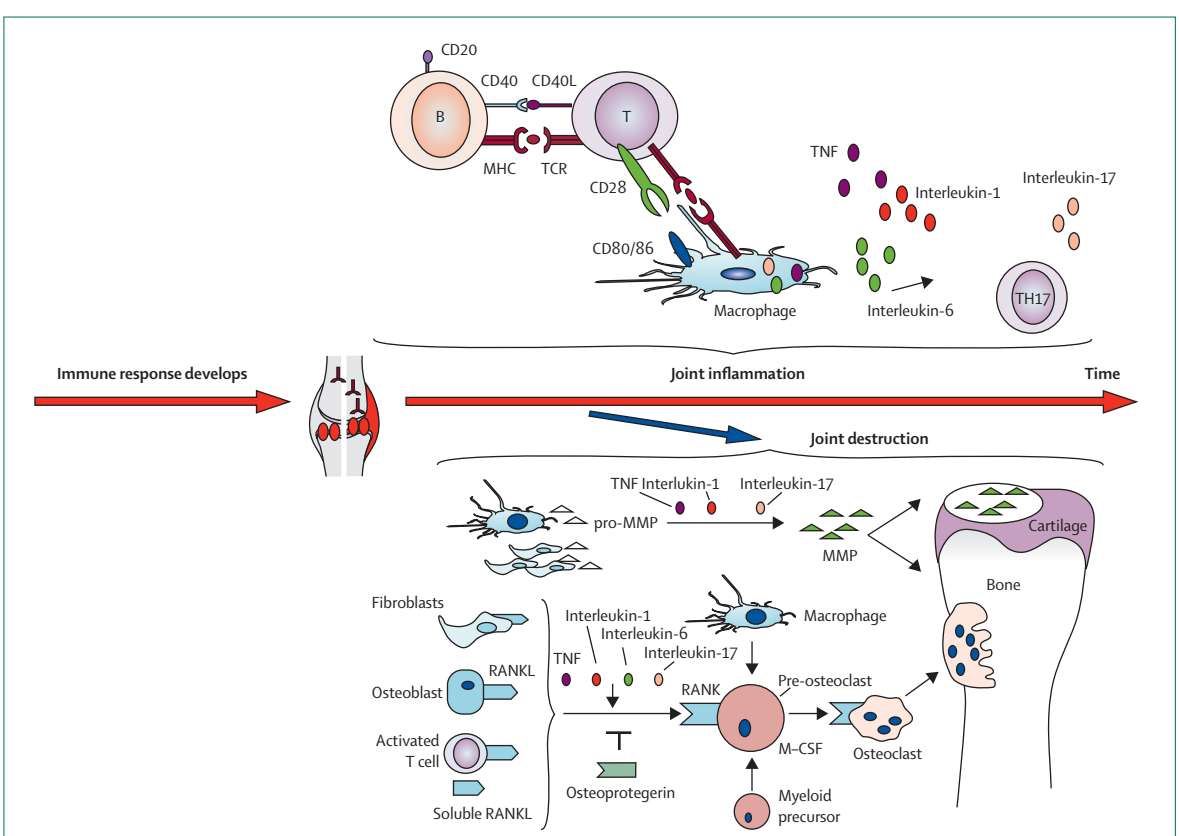

Figure 5: **Immunological pathways in the arthritic joint**
Upper part shows joint inflammation, and lower part joint destruction.

affect central parts of the brain.[72] Fatigue is, thus, a state that can and should be measured as part of a patient's outcome, and a positive effect on fatigue is one of the earliest and most prominent benefits of modern cytokine antagonists.[73]

Destruction of bone and cartilage—manifesting as erosions and joint-space narrowing, respectively, on radiographs—are major effects of rheumatoid arthritis, and joint destruction sometimes happens very early in the disease course.[74] The mechanisms behind destruction of bone and cartilage are quite different, although both are at least partly dependent on inflammation.[75–77] Proinflammatory cytokines, such as TNF, interleukin 1, and interleukin 17, act synergistically to release matrix metalloproteinases (MMPs) from cells such as fibroblasts and macrophages. At least 19 human MMPs are known, of which MMP1 and MMP3 possibly play an important part in rheumatoid arthritis, being able to degrade all important structural proteins in the extracellular matrix of cartilage (figure 5).

Rheumatoid arthritis causes local erosions and juxta-articular and general osteopenia of bone. Development of erosions is dependent on at least three different mechanisms. First, osteoclasts are activated from macrophage-like precursors after stimulation by RANKL. Second, activated T cells act directly on osteoclasts. Third, fibroblast-like synoviocytes are active in pannus tissue.[77] Treatment strategies that target destruction can be directed against all these pathways and could be most efficient when all three are targeted. Bisphosphonates can counteract osteopenia and erosions in rheumatoid arthritis.[78]

TNF, interleukin 1, and probably interleukin 6, can drive RANKL expression and its release from fibroblasts, T cells, and osteoblasts (figure 5). Both cell surface-bound and soluble RANKL activate RANK on the surface of osteoclast precursors (resulting from either myeloid precursors or macrophages). This process is counteracted by osteoprotegerin, a soluble protein of the TNF-receptor superfamily that functions as a decoy receptor for RANKL, being able to inhibit production of osteoclasts. Balance between RANKL and osteoprotegerin expression results in normal bone metabolism, with good equilibrium between bone production and destruction. Imbalance of the system, with relative predominance of RANKL (either by deficient osteoprotegerin expression or by increased RANKL expression) results in activation of osteoclasts with subsequent bone destruction.[77]

Cartilage destruction, and its attendant joint-space narrowing, is dependent mostly on the effects of proteolytic enzymes, the production of which can also be triggered by major proinflammatory cytokines (figure 5).[79] The clinical effect of separation of the two pathways, cartilage versus bone destruction, has been shown in a phase II trial of a RANKL inhibitor, which was effective at preventing erosions but not inflammation or joint-space narrowing.[80]

Excess mortality associated with rheumatoid arthritis is largely attributable to cardiovascular disease,[81] particularly ischaemic heart disease.[82] Also, patients with rheumatoid arthritis have more silent unrecognised heart attacks and sudden cardiac deaths than do people without rheumatoid arthritis.[83] Data from observational cohort and case-control studies suggest that heightened cardiac risk is not related mainly to traditional atherosclerosis risk factors or corticosteroid treatment, but inflammation associated with rheumatoid arthritis per se is likely to be of primary importance.[84,85] Augmented inflammation in patients with disease positive for rheumatoid factor or ACPA, and with extra-articular manifestations, can indicate an especially high risk for cardiovascular events, in particular ischaemic heart disease.[82,85,86]

Although not a frequent outcome of rheumatoid arthritis, increased lymphoma risk has long been associated with the disease. Researchers have clarified that raised lymphoma risk is mainly associated with long-term disease activity rather than immunosuppressive treatments used to treat rheumatoid arthritis.[87] This recognition was important not only to guide risk management and treatment of rheumatoid arthritis but also because it brings recognition to the fact that longstanding, polyclonal B-cell stimulation might lead to lymphomas. As in the case of cardiovascular disease, we do not know enough about which groups of patients with rheumatoid arthritis (eg, ACPA-positive) are at greatest risk for lymphoma, but this research area is of considerable importance since B-cell-directed strategies now exist that are effective against both rheumatoid arthritis and lymphomas.[88]

Disease progression and treatment

A major key to advances in both assessment and best use of disease-modifying anti-rheumatic drugs (DMARDs) has been development of valid and responsive methods that measure disease activity, functional status, and joint damage. Effects of treatment on disease activity can be measured either as relative improvement or in terms of the absolute value of disease activity that is reached. ACR response criteria[89] measure relative changes, whereas the disease activity score (DAS) is a compound index that provides an absolute value of disease activity. EULAR response criteria[90] combine the two principles in defining what is good, moderate, or no response to treatment.

Lately, achievement of a disease-free state, called remission, has become an achievable goal for many patients, something that calls for feasible and accurate remission criteria for use in clinical trials and in clinical practice. So far, however, no such universally accepted remission criteria have been defined, meaning that several different provisional criteria are in use. One of these is DAS28 remission, which is generally used for its feasibility but has the limitations that inflammation can still exist in joints not included in the 28 that are counted and that subclinical inflammation might still be able to cause joint damage.

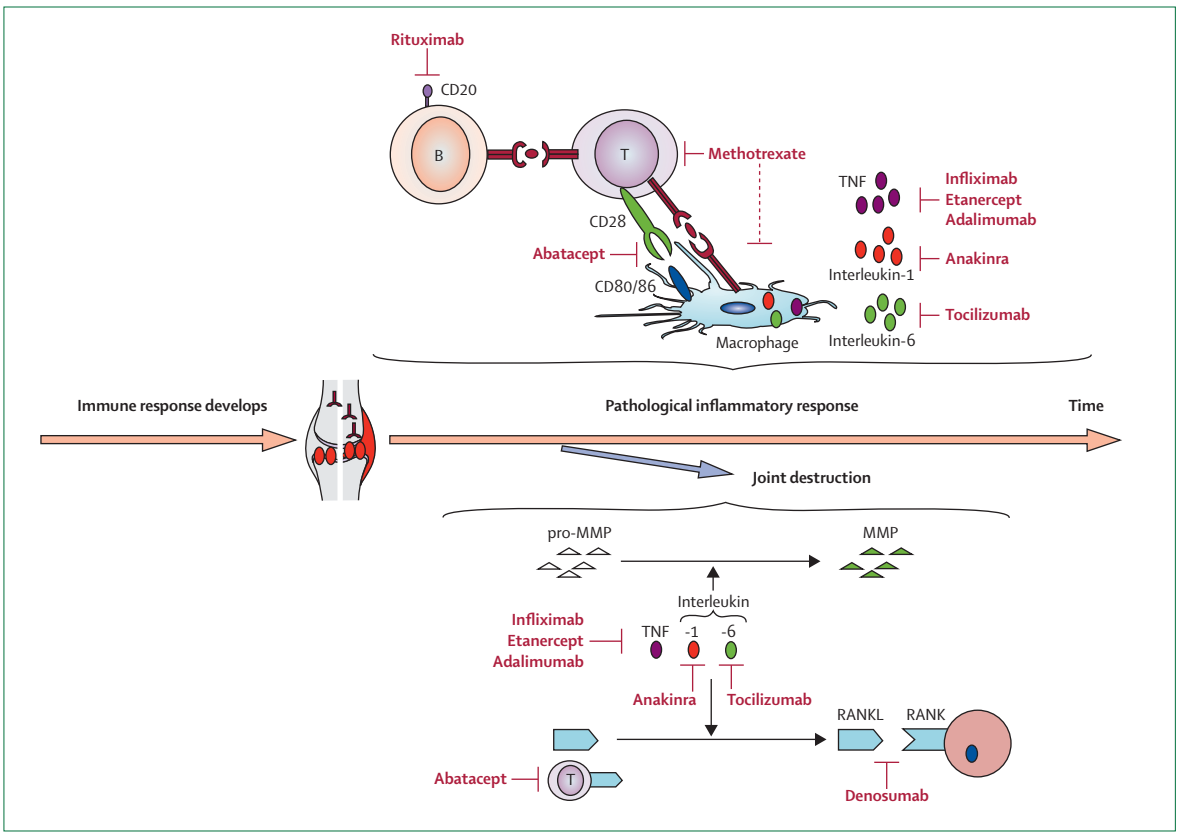

Figure 6: **Modes of action of targeted treatments that can be used in rheumatoid arthritis**
Upper part shows drug actions on joint inflammation and lower part, joint destruction.

Functional status is most traditionally measured with the health assessment questionnaire (HAQ) for arthritis,[91] whereby an index between 1 and 3 indicates both disease activity (a reversible component) and accrued damage. With growing ambitions for early and active treatment and achievement of a disease-free state, measurements of absolute disease activity become as important as the more traditional relative scores in assessment of treatment effects. The shift in thinking is well illustrated by the statement "It's good to feel better but it's better to feel good".[92]

With respect to assessment of treatment effects on joint destruction, traditional plain radiographs complemented by quantitative measurement of destruction are still the gold standard.[93] A major issue is, however, that up to 70% of patients who present with early inflammatory arthritis have typical radiographic results at the initial visit, whereas ultrasonography and MRI can detect erosions in much higher numbers and up to 2 years earlier than with plain radiographs.[94,95] Thus, we need to define new generally accepted and feasible standards for early signs of joint destruction.

Treatment strategies

Strategies for treatment of rheumatoid arthritis have changed greatly over the past decade. Three ideas have driven the alteration. First, early and consistent reduction of inflammation is key—ie, if no inflammation, there is little joint damage. Second, specific molecular mechanisms implicated in pathogenesis of the disorder should be targeted. Third, rheumatoid arthritis is a diverse and dynamic disease, for which different treatments work for individual patients and at various timepoints. The strategy of early dynamic and tightly controlled treatment could have contributed as much as targeted approaches have to the much improved health and function that we have witnessed in patients.

Findings of several studies during the past decade have provided definite proof that early and aggressive treatment with conventional DMARDs, such as methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and glucocorticoids, can be highly beneficial for control of inflammatory activity and development of erosions in many patients.[96–99] Typical of different protocols for monotherapies or combination regimens is the importance of good surveillance and rapid adjustment to achieve tight disease control. Findings of one study also indicated the potential value of starting treatment for unspecified arthritis even before formal rheumatoid arthritis criteria were met.[100] Here, methotrexate delayed onset of ACR-defined disease in an ACPA-positive group of patients with unspecific arthritis, whereas no such

effects were seen in a parallel ACPA-negative group. These data show not only how the effectiveness of one drug (here, methotrexate) can be different in ACPA-positive and ACPA-negative arthritis but also how very early treatment, even in patients not fulfilling ACR criteria for rheumatoid arthritis, can be beneficial if used selectively.

Development of strategies that target specific molecules and pathways in the pathogenesis of rheumatoid arthritis is an important step forward. Targeted treatments have changed the face of the disease, the fate of patients, and the practice and science of rheumatology. The basis for this progress is enhanced understanding of pathogenic pathways. Notably, most treatments that have so far reached clinical practice target the innate part of the immune response, whereas drugs targeting the adaptive immune response and early processes in pathology have only recently been introduced in the clinic. We are only at the beginning of a process whereby new knowledge about the division of rheumatoid arthritis into subsets and the specificity of immune reactions could have therapeutic results. Figure 6 shows the modes of action of some currently used targeted treatments.

The first breakthrough in development of treatments that target distinct parts of the innate immune system was made from findings of basic studies of cloning and biological characterisation of TNF and from research into cytokine biology in arthritic joints.[101] The key clinical contribution came when scientists at the Kennedy Institute in London defined an important role for TNF in rheumatoid arthritis with a small clinical study of TNF blockade in patients with this disease,[102] and confirmed their finding with randomised clinical trials.[103,104] TNF-blocking agents currently approved for clinical use are infliximab (chimeric anti-TNF), etanercept (soluble TNF receptor), and adalimumab (humanised anti-TNF); these drugs act by partly neutralising circulating and synovial TNF.

From subsequent studies done over several years, we now know that TNF blockade, undertaken by several different monoclonal antibodies or receptor constructs, is most effective when combined with methotrexate,[104–107] and this strategy not only reduces inflammation but also almost completely eradicates joint destruction, even in the presence of residual inflammatory activity.[108,109] The complementarity of methotrexate and TNF antagonism might reside in the specific effects of methotrexate; this drug acts by inhibition of adenosine metabolism[110,111] and T-cell activation,[112] and by affecting folate synthesis,[111] and it might also contribute to a reduction of the immune response to actual TNF-blocking drugs or to a change in their pharmacodynamics.[104]

The success of TNF blockade rapidly led to development and testing of a series of biological drugs targeting several different molecules in inflammatory pathways. First was anakinra, a recombinant version of the human interleukin 1-receptor antagonist that competitively inhibits binding of interleukin 1 to its receptor. This agent had some effect on erosions in patients with rheumatoid arthritis[113] but was never close to the effectiveness of TNF blockade in clinical practice.[68] Tocilizumab is a monoclonal antibody directed against the interleukin 6-receptor.[114] This drug is now approved for clinical use in Japan but not yet in other parts of the world. It seems to be efficient at reducing both inflammation and erosions.[115] In recent years, agents that specifically target T and B lymphocytes have been widely approved.[114,116,117] Abatacept is a recombinant fusion protein consisting of the extracellular domain of CTLA4 and a fragment of the Fc portion of IgG that inhibits co-stimulatory signals essential for T-cell activation; rituximab is a monoclonal antibody that binds to CD20 on the surface of pre-B and mature B cells and depletes these cells from circulation. A series of additional compounds with other targets are in advanced stages of trials or approval.

So far, treatment results with DMARDs and biological agents have shown variable responses in individual patients with rheumatoid arthritis. Biological explanations for these variations are not yet known, but tentative answers have been offered: large variability in cytokine expression has been noted between patients,[118] and findings of preliminary studies have suggested that people with high expression of TNF in their joints could be most responsive to TNF blockade[119] and individuals with high amounts of ACPA or rheumatoid factor and many synovial B cells might be more responsive than others to B cell-directed treatments.[120]

A major challenge now is to implement these growing therapeutic options for rheumatoid arthritis in clinical practice, with the ideas of early, tight, and targeted

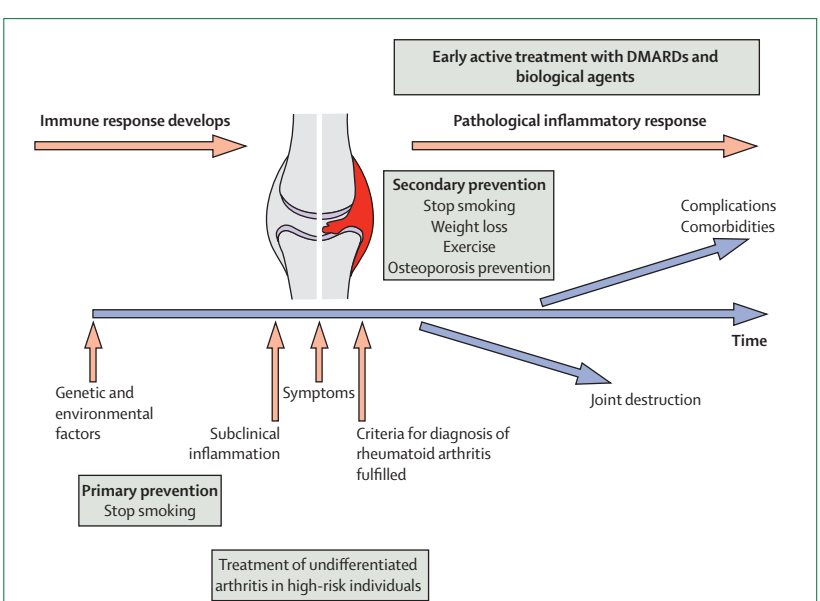

Figure 7: **Schematic outline of strategies for prevention and treatment of rheumatoid arthritis and its comorbidities**

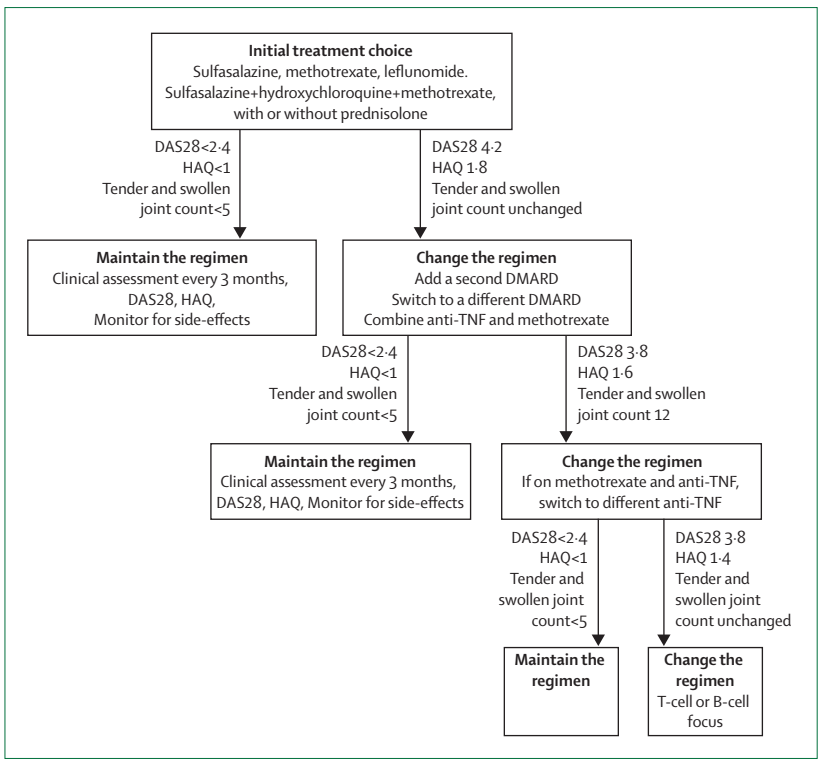

Figure 8: **Treatment algorithm for one patient with rheumatoid arthritis**
The patient in this example has severe fatigue, 15 tender and swollen joints, an erythrocyte sedimentation rate of 55 mm/h, a C-reactive protein amount of 4·2 mg/L, a concentration of haemoglobin of 110 g/L, a DAS28 response of 5·6, and an HAQ score of 2.

For the **Swedish Hip Arthroplasty Registry** see http://www.jru.orthop.gu.se

treatment (figure 7). At present, the most well documented and widely used pharmacological strategy is to begin treatment of early arthritis with methotrexate,[121] and in some cases low-dose steroids;[99] if tolerated, complementary drugs can be added if treatment goals are not met within 2–3 months (figure 8). Addition of TNF-blocking agents is highly efficient at reducing disease activity and at stopping joint progression in patients with an insufficient response to initial treatment with non-biological drugs.[105–107] For those who do not meet treatment goals on their first round of TNF blockade, options are to change from that strategy to either abatacept (CTLA4Ig) or rituximab (anti-CD20). Findings of observational studies indicate that switching to another TNF-blocking agent can also be effective.[122]

This entire therapeutic approach is currently challenged by data that suggest patients should begin with the most effective treatment available, which can then be downgraded gradually depending on results. This approach has been proposed after early reports of high initial doses of glucocorticoids[123] and combination of DMARDs[98] and from findings showing that initial treatment with TNF blockade and methotrexate enabled later tapering of TNF blockade in individuals who had reached a disease-free state.[124]

To ascertain which strategy is best suited for different patients in various phases of disease, the clinical community needs to engage in continuous practice-based studies. Establishment of structured surveillance systems (sometimes called registries) will enable such research, and use of registries can help with comparisons of effectiveness, safety, and cost. Importantly, such registries might also be able to show whether subsets of patients could benefit from certain drugs that might not be regarded as cost efficient in an unselected population,[125] and they could provide a new basis for health-economic assessments, as indicated by a decline in need for total hip replacements for rheumatoid arthritis from 1992 to 2006 in the Swedish Hip Arthroplasty Registry.

Rising use of drugs that greatly affect different parts of the immune system has driven development of strategies to monitor adverse events. Registry-based studies are increasingly being used to identify effects of long-term treatment and rare adverse events.[126] By combining analyses from controlled trials and registers, researchers have shown that TNF-blocking agents increase risk for specific infections,[127] in particular tuberculosis.[128] These infection-related side-effects have, so far, been handled reasonably well, provided that treating doctors are aware of the risks and screening and treatment are instituted for tuberculosis. Cancers, and in particular lymphomas, are another concern; data obtained up to now indicate that most of the raised risk for lymphoma in patients with rheumatoid arthritis who are treated by TNF blockade is attributable to disease activity rather than the drugs used.[87,129] For solid cancers, findings of randomised controlled trials and registry-based studies are somewhat contradictory: no indications of high cancer risk from TNF blockade have been obtained from registry-based studies, but an increased short-term risk has been noted in meta-analyses of randomised trials.[130,131] Other recently introduced biological agents are subject to longitudinal assessments, so far without major safety concerns.[132–134] Continued surveillance is needed before definite conclusions about long-term effects can be made.

Longitudinal structured surveillance, therefore, provides a way to assess the therapeutic success of drugs that are too expensive or too risky to be used in all patients who might benefit. Several guidelines for available treatment options are currently in use, produced by both professional organisations[135] and national authorities. Figure 8 provides an example of how such guidelines could be implemented in an individual patient.

The algorithm shown in figure 8 is based on the following treatment strategy. (1) Early intervention assures the best outcomes: administer DMARDs in the earliest possible phase of the disease to intervene within the window of opportunity. (2) Treat to target: whether the doctor uses DAS28, HAQ, or another disease activity or functional score, the target—at every clinical assessment point along the way—is remission, no evidence of disease, or normal functional status. (3) Define the extent of joint damage: plain hand radiographs are taken at baseline and every year to

identify presence of new erosions, joint-space narrowing, or both. Ultrasound or MRI can be used at therapeutic branch points when clinical status is worsening and plain radiographs are normal or unchanged. The finding of interval damage is, along with clinical variables, a clear sign of poor disease control. (4) Optimise the treatment regimen: changes in treatment—ie, addition of or switch to a new DMARD regimen—should accompany recorded continued disease activity and progressive damage.

Concluding remarks

Despite making major progress in rheumatoid arthritis research, important work still lies ahead of us. Already, new insights into the various molecular pathways have been used to develop new and very efficient treatment approaches for patients. However, we still need to find out how to best target these drugs to the right individuals at the right time. Some environmental risk factors for rheumatoid arthritis have been identified—mainly smoking—but we have not used this knowledge enough in clinical practice. Moreover, we have not worked sufficiently to identify and modify additional environmental and lifestyle factors that could affect onset and progression of the disease. Furthermore, we have not been able to change permanently the destructive behaviour of the immune system, despite the fact that this system can be regulated and disease cured, as seen by experimental animal models of arthritis. We, thus, have every reason to believe that we are only at the beginning of a process whereby the disorder we call rheumatoid arthritis will be subject to further change, treatment, cure, and prevention.

Contributors

All authors contributed ideas to and wrote the Seminar.

Conflict of interest statement

LK has no shares or board memberships in any relevant companies. During the past 5 years, he has received research funding, honoraria, or speakers' fees from: Wyeth, Schering-Plough, Abbott, Roche, Bristol Mayer Squibb, AstraZeneca, Amgen, Centocor, and BioCon. AIC has no shares or board memberships in any relevant companies. During the past 5 years, she has received research funding, honoraria, or speakers' fees from: Centocor, Abbott, and Roche. SP has no shares or board memberships in any relevant companies. During the past 5 years, he has received research funding, honoraria, or speakers' fees from: Pfizer, Abbott, Amgen, Genentech, Centocor, Medarex, and Rigen.

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