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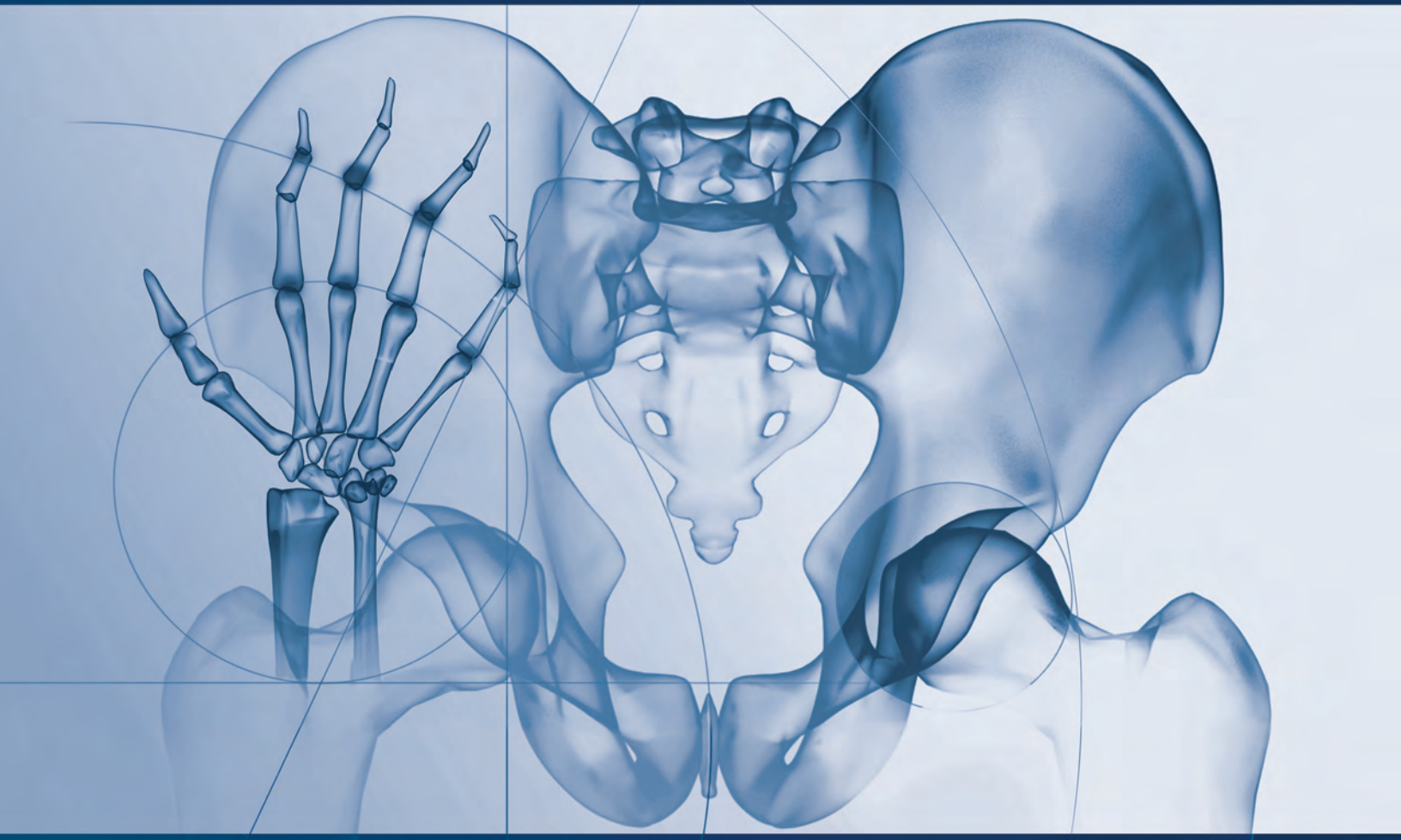



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# Contents

LEADING ARTICLE

# The Economics of Rheumatoid Arthritis Management

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**Evaluating the cost-effectiveness of therapies in rheumatoid arthritis (RA) has become increasingly important as the costs of medications rise. Such analyses present many methodological challenges. These include how to value non-medical costs, the time horizon of analyses, the differences between trial measures of efficacy and real-world effectiveness, and future drug costs with the potential for generic biologics. The authors of this article review the current state of pharmacoeconomics in RA.**
*Int J Adv Rheumatol* 2008;**6**(1):2–5.

Rheumatologists are skilled at recognizing the clinical manifestations of rheumatoid arthritis (RA), but the economic burdens may not always be as apparent. The direct and indirect medical expenditure for RA accounts for a portion of its costs, but work disability is also a major part of its expense [1]. The reduced work ability of patients with RA is an extremely important issue when considering the increasing cost of pharmacotherapy for RA. While biological disease-modifying antirheumatic drugs (DMARDs) typically cost US$10 000–20 000 per year in the US, their potential for reducing morbidity and disability may offset these costs. Although RA may not be the most prevalent condition in the general population, the growing cost of treatment has forced many healthcare payers to examine the pharmacoeconomics of RA management.

## Cost-effectiveness methods

Calculating the cost-effectiveness of RA management is complex and necessarily includes many assumptions. The methods for such analyses are well developed and much of the necessary inputs are available in the literature [2]. A cost-effectiveness analysis typically requires a decision analysis model evaluating the outcomes and costs of relevant management strategies, i.e. non-biological versus biological DMARDs in early or established RA. An appropriate model explicitly represents typical clinical decision-making addressing the uncertainty in outcomes through probabilistic simulation, and the uncertainty in evidence through adequate sensitivity analysis. The value attached to specific outcomes, and the probability of these outcomes, generates estimates of the cost and effect of treatment. These values are compared in a cost-effectiveness analysis to estimate the incremental cost-effectiveness of one strategy versus another.

The effectiveness of treatments in RA is typically estimated with response criteria, such as the American College of Rheumatology (ACR) Responder Index or the Disease Activity Score. While these can be used in cost-effectiveness models (i.e. probability of reaching an ACR50 response), analysts often opt for the more generic quality-adjusted life year (QALY), which is recommended because it allows comparison across diverse conditions [2]. The QALY assumes that a year of life may have a different value based on a given health state or utility. In other words, the value of a given health state can range from 0 (no quality of life) to 1 (perfect quality of life) and this value is multiplied by the number of years lived. A perfect health state contributes a full year for every year lived. For example, an RA patient may report that spending 10 years with RA is equivalent to spending 7 years in full health, in other words 10 years with RA are worth approximately 7 QALYs [3]. Gains in QALYs are used to summarize the incremental benefits of new interventions.

Estimating costs also has important methodological subtleties. Different types of costs are included when developing economic models of pharmacotherapy (Table 1). Direct medical costs comprise the cost of care directly related to RA, such as treatments, clinical visits for RA, and RA surgeries. Non-medical items that directly relate to the care

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**Table 1.** Components of the cost of RA.

| Types of cost | Definition | Examples |
|---|---|---|
| Direct medical costs | Resources directly related to the care of RA | Costs of drug treatments, laboratory tests, visits to physicians or nurses, hospitalizations, surgical procedures, durable medical equipment, rehabilitation services |
| Direct non-medical costs | Resources related to non-medical issues arising because of RA | Costs of child care during a physician visit or hospitalization |
| Productivity costs* | Resources related to lost wages because of RA | Costs of disability (temporary, partial, or permanent), costs of missed work because of treatments |

RA: rheumatoid arthritis.
*These costs are sometimes termed "indirect" costs. It is recommended that they be subtracted from quality of life, but they also can be included separately as costs.

**Table 2.** Methodological considerations in pharmacoeconomic analyses of RA.

| Consideration | Issues/difficulties |
|---|---|
| Estimation of indirect costs | • Measurement of lost productivity among persons working solely within the home<br>• Measurement of on the job productivity ("presenteeism")<br>• Whether to include it at all, or assume that it is part of the utility estimate |
| Long-term perspective on benefits and risks of treatments | • No adequate long-term data from RCTs<br>• Observational studies need to be large enough to include rare outcomes |
| Estimation of treatment costs | • Acquisition costs are likely to change in the future with increased options and the availability of "generic equivalents" |
| RCT versus observational data | • RCTs contain less biased data with respect to comparative outcomes but may not represent typical patients |

RA: rheumatoid arthritis; RCT: randomized controlled trial.

of RA are included as direct non-medical costs. For example, the cost of modifying a home to make it more accessible to a person with disabilities might be counted in direct non-medical costs. Productivity costs might be considered under indirect costs. However, the calculation of these costs is highly dependent on the methods and the estimates [4]. Thus, there is a recommendation that indirect costs be excluded from economic evaluations and included only as a decrement in the utility of RA [2]. Thus, decision makers need to be aware of the potential variation in total direct and indirect RA costs, and the proportion of the costs that may be offset by the high acquisition costs of new interventions.

## The cost of RA

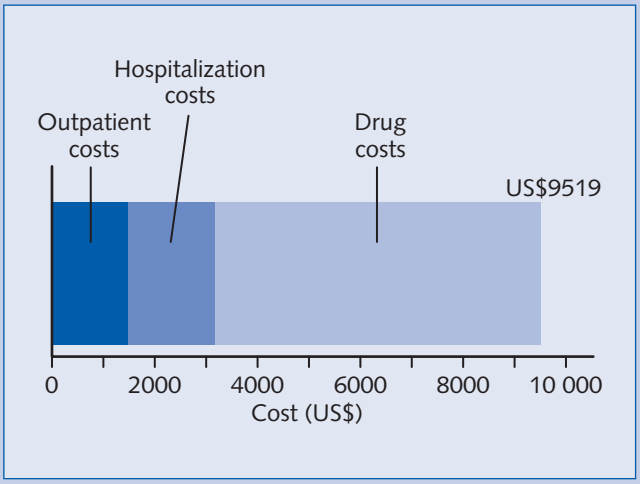
Pharmacoeconomic analyses are used to evaluate the extent to which specific management strategies offset the cost of caring for the disease. Thus, an understanding of the cost of illness (COI) is critical. Several COI studies have been conducted over the past 20 years to estimate the annual cost of RA [4–8]. These studies inform policy-makers about the size of the potential economic impact that a disease may have at a national level. Several challenges have been identified with COI studies (see Table 2), including:

- Disease definition and sampling of patients for studies.
- Comprehensiveness of data capture.
- Attribution of costs to target disease and other comorbid conditions.
- Valuation of productivity losses (as noted above).

Several COI studies in RA have used consecutive samples recruited from healthcare providers. The University of California–San Francisco (San Francisco, CA, USA) RA Panel Study has followed >1100 patients with RA recruited from random samples of Northern California rheumatologists for up to 14 years [6]. A total of 511 patients provided information for an economic evaluation in 1996 through comprehensive interviews. Annual 1996 medical costs were, on average, US$8500, of which US$5900 could be attributed to RA. A recent systematic review estimated the average annual direct costs of RA to be US$5800 (also in 1996 US$) [4]. Estimates for the proportion of total medical costs attributable to RA vary between 55% and 70%. In addition, national forecasts of the total economic burden of RA must account for the role of comorbidities among the total costs.

A recent COI study for RA was conducted by the US National Data Bank of Rheumatic Diseases [8]. Semi-annual questionnaires were returned by >7000 patients with RA.

**Figure 1.** Cost of rheumatoid arthritis. These data are from the National Data Bank of Rheumatic Diseases in the US [8]. Over 7000 patients with rheumatoid arthritis answered semi-annual questionnaires and their direct medical costs were calculated from these. Each resource was assigned a cost and a total direct medical cost was calculated and expressed as 2001 US$. The average cost was >US$9000 with approximately two-thirds of the cost attributable to drug treatments. For patients using biological DMARDs, the average cost was US$19 016, while those not receiving biological DMARDs had an average cost of US$6164.




DMARDs: disease-modifying antirheumatic drugs.

Direct medical costs were calculated from these questionnaires. Resource use was assigned a cost and direct medical costs were calculated in 2001 US dollars. For patients using biological DMARDs, the average cost was US$19 016, while those not receiving biological DMARDs had average costs of US$6164. The average cost was >US$9000, with approximately two-thirds of the cost attributable to drug treatments (Fig. 1).

## Cost-effectiveness of drug treatment in RA

Driven in large part by the growing popularity of biological DMARDs, there is an increasing interest in the potential cost-effectiveness of treatments for RA [9–22]. As we have noted, several methodological considerations are critical to the evaluation of these analyses (Table 2). Major drivers of cost include the loss of work capacity, hospitalizations related to the disease, and acquisition costs of treatments. Work capacity is typically measured by counting days of work missed. This does not take into account decreased work ability. Thus, the overall economic impact of RA may be incompletely reflected by employment.

Most economic models must incorporate relevant data from epidemiological studies as well as clinical trials. Since methods vary across studies, comparing economic analyses across treatments can be very difficult. The RA population being studied can have dramatic effects on the outcomes of models. For example, patients with early RA who have tried fewer treatments tend to respond to therapies to a greater extent than those with more established disease. Thus, it is critical to take into account the populations involved in these studies. Moreover, differences between patients enrolled in trials and typical RA patients will likely affect the results of economic models. Trials often provide the least biased data source but the information may not be as generally representative as data from observational studies.

Economic models attempt to provide a long-term perspective; however, there are few data sources that provide relevant long-term information. For example, hospitalizations related to joint replacement surgery are important and expensive sequelae of poorly controlled RA. While they are not common, they must be included in economic analyses. Uncommon toxicities (i.e. opportunistic infections and cancer) that may relate to treatment could be expensive, and must be part of any credible economic model. These events require long-term databases that can be problematic to interpret.

We now focus on actual cost-effectiveness estimates of RA treatment. Many of the biological DMARDs have shown substantial clinical efficacy and it is plausible based on analyses that they may have an incremental cost within the range of generally accepted medical interventions for selected populations. Many of these data come from follow-up of patients participating in clinical trials of infliximab, etanercept, and adalimumab in RA, and extend the time horizon through modeling. Studies using distinct populations and agents have reached similar estimates. Treatment of patients with established RA with biological agents costs approximately US$30 000 per discounted QALY gained [9,13,14,16,17]. Notably, an analysis that did not use clinical trial data but rather used information from patients in a national registry of RA patients treated with TNF inhibitors, as well as traditional DMARDs, found comparable results, with a cost per QALY of GB£23 882 (approximately US$47 000) [18].

Several further methodological issues will arise with the advent of new biological DMARDs and the increased use of biologics in patients with early RA [22]. If early RA patients achieve significant incremental or sustained efficacy with biological DMARDs, these treatments may have favorable cost-effectiveness ratios compared with standard strategies. However, the need for longer term, expensive therapies and the longer term implications of potential toxicity could make them less cost-effective. Nonetheless, if treatment paradigms include an "induction–consolidation" approach,

this might translate into a shorter period of treatment with highly effective and sustained benefits. This could favorably impact upon the cost-effectiveness of biological DMARDs or future therapies. An additional factor that will likely impact the health–economic implications of biological DMARDs is their literal cost. As more agents come on to the market and generics become available, these forces will both drive down drug acquisition costs.

## Conclusions

As drug treatments for RA evolve, so does the field of pharmacoeconomics. The methods are constantly refined and gaps in the evidence-base are filled. Biological DMARDs are generally not approved (or used) as first-line agents, but clearly have a role in the treatment of patients who fail to respond to other DMARDs. Thus, the incremental cost-effectiveness of new DMARDs can be evaluated as the only DMARD or as part of a sequence of DMARDs for RA management. The cost-effectiveness of a given agent may be influenced by the combination and role of the other DMARDs. Many of the clinical trials examining new biological DMARDs use "partial responders" – patients with an inadequate response to their current DMARD – as the eligible study population. Since partial responders have a low likelihood of improvement, it is not clear that these trials appropriately capture the real clinical decision. A study design that would more closely mimic clinical practice would compare two new treatments, for example, abatacept and infliximab in methotrexate partial-responders. Not only would this comparison be valuable for clinical decision-making, but it would also provide valuable data for comparing the cost-effectiveness of relevant treatment strategies.

Long-term follow-up of patients taking biological DMARDs will provide data for more precise estimates of the relative rates of their potential beneficial and adverse effects. It is possible that new agents result in greater longevity through reducing important comorbidities, such as myocardial infarctions and osteoporotic fractures. On the other hand, these newer drugs may result in significant increases in rare side effects, such as atypical infections and uncommon cancers. The clinical and economic implications of such beneficial and adverse outcomes will help clarify the role of these agents.

Most clinicians have learned pharmacoeconomics the hard way, through filling in "prior authorization" forms and petitioning pharmaceutical benefits programs to add these agents to the formulary. While the published data suggest that biological DMARDs may have favorable incremental cost-effectiveness ratios, not all new agents will be similar in their economics. As the proportion of healthcare budgets devoted to drugs continues to grow, prescribing physicians will be increasingly asked to make difficult decisions about which medications to prescribe to which patients. The science of pharmacoeconomics helps payers, clinicians, patients, and society at large to understand the value of a given medication.

## Disclosures

The authors have no relevant financial interests to disclose.

## References


1. Barrett EM, Scott DG, Wiles NJ et al. The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. *Rheumatology (Oxford)* 2000;**39**:1403–9.
2. Gold MR, Siegel JE, Russel LB et al. Cost-effectiveness in health and medicine. New York, NY: Oxford University Press, 1996.
3. Marra CA, Marion SA, Guh DP et al. Not all "quality-adjusted life years" are equal. *J Clin Epidemiol* 2007;**60**:616–24.
4. Cooper NJ. Economic burden of rheumatoid arthritis: a systematic review. *Rheumatology (Oxford)* 2000;**39**:28–33.
5. Clarke AE, Penrod J, St Pierre Y et al. Underestimating the value of women: assessing the indirect costs of women with systemic lupus erythematosus. Tri-Nation Study Group. *J Rheumatol* 2000;**27**:2597–604.
6. Yelin E, Wanke LA. An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. *Arthritis Rheum* 1999;**42**:1209–18.
7. Newhall-Perry K, Law NJ, Ramos B et al. Direct and indirect costs associated with the onset of seropositive rheumatoid arthritis. Western Consortium of Practicing Rheumatologists. *J Rheumatol* 2000;**27**:1156–63.
8. Michaud K, Messer J, Choi HK et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. *Arthritis Rheum* 2003;**48**:2750–62.
9. Wong JB. Cost-effectiveness of anti-tumor necrosis factor agents. *Clin Exp Rheumatol* 2004;**22**(5 Suppl 35):S65–70.
10. Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. *Am J Med* 2002;**113**:400–8.
11. Choi HK, Seeger JD, Kuntz KM. A cost-effectiveness analysis of treatment options for patients with methotrexate-resistant rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:2316–27.
12. Choi HK, Seeger JD, Kuntz KM. A cost effectiveness analysis of treatment options for methotrexate-naive rheumatoid arthritis. *J Rheumatol* 2002;**29**:1156–65.
13. Kobelt G, Jönsson L, Young A et al. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. *Rheumatology (Oxford)* 2003;**42**:326–35.
14. Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. *Ann Rheum Dis* 2004;**63**:4–10.
15. Welsing PM, Severens JL, Hartman M et al. Modeling the 5-year cost effectiveness of treatment strategies including tumor necrosis factor-blocking agents and leflunomide for treating rheumatoid arthritis in The Netherlands. *Arthritis Rheum* 2004;**51**:964–73.
16. Brennan A, Bansback N, Reynolds A et al. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK. *Rheumatology (Oxford)* 2004;**43**:62–72.
17. Bansback NJ, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. *Ann Rheum Dis* 2005;**64**:995–1002.
18. Brennan A, Bansback N, Nixon R et al. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. *Rheumatology (Oxford)* 2007;**46**:1345–54.
19. Kavanaugh A, Han C, Bala M. Functional status and radiographic joint damage are associated with health economic outcomes in patients with rheumatoid arthritis. *J Rheumatol* 2004;**31**:849–55.
20. Yelin E, Trupin L, Katz P et al. Association between etanercept use and employment outcomes among patients with rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:3046–54.
21. Fleurence R, Spackman E. Cost-effectiveness of biologic agents for treatment of autoimmune disorders: structured review of the literature. *J Rheumatol* 2006;**33**:2124–31.
22. Hallert E, Husberg M, Jonsson D et al. Rheumatoid arthritis is already expensive during the first year of the disease (the Swedish TIRA project). *Rheumatology (Oxford)* 2004;**43**:1374–82.

LEADING ARTICLE

# Anti-Citrullinated Protein Antibodies as a Risk Factor for Rheumatoid Arthritis

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**It has recently been discovered that anti-citrullinated protein antibodies (ACPA) are present in the majority of patients with rheumatoid arthritis (RA). Assays for detecting ACPA, which generally use cyclic citrullinated peptides (CCP) as targets, have been shown to have very good diagnostic and predictive characteristics, and may facilitate the identification of patients with early arthritis who need aggressive treatment. In addition to their function as diagnostic and predictive markers, ACPA have provided new insights into the pathophysiology of RA. The specific association of certain genetic and environmental risk factors with ACPA-positive versus ACPA-negative disease has led to new concepts regarding the underlying pathogenetic mechanisms. The fact that ACPA-positive patients have a more severe disease course with greater joint destruction has also fueled the hypothesis that ACPA themselves may be pathogenic. Although there is presently no direct proof for this last theory, it is clear that ACPA allow the classification of RA patients into two different disease subsets that are associated with distinct pathophysiological mechanisms and clinical outcomes.** *Int J Adv Rheumatol* 2007;**6**(1):6–10.

Rheumatoid arthritis (RA) is a chronic, potentially destructive arthritis that has a significant impact on patients' quality of life [1]. It has become clear that in order to prevent disease progression and joint destruction, RA needs to be diagnosed early; this requires diagnostic markers that can reliably predict disease development and progression [2]. Some of the most attractive diagnostic markers are autoantibodies.

Rheumatoid factor (RF) has long been known to be a marker of future RA development [3]. Owing to its predictive characteristics and high incidence among RA patients (60–70%), it has been included in the diagnostic criteria for RA that were developed by the American College of Rheumatology in 1987. However, the predictive ability of immunoglobulin M (IgM)-RF is limited by its relatively modest specificity (85%), which means that many patients who are IgM-RF-positive will not develop RA [4]. Recently, a better diagnostic and predictive marker has emerged in the form of anti-citrullinated protein antibodies (ACPA).

## Development of anti-citrullinated protein immunity

ACPA were first described as anti-perinuclear factor and anti-keratin antibodies, both of which bind to filaggrin [5–7]. It was not until several years later that recognition of this antigen was found to be exclusively dependent on the presence of citrulline residues [8]. The same was the case for citrullinated vimentin, which was discovered to be the target of the RA-specific anti-Sa antibodies that had been described many years before [9,10]. Based on these findings, several commercial assays that test for the presence of antibodies to cyclic citrullinated proteins (CCP) have been developed and successfully introduced into clinical practice [11].

Several studies have investigated the time-point at which patients develop ACPA [12,13]. By making use of pre-disease samples from blood-bank donors who later developed RA, these reports were able to demonstrate that ACPA can be detected many years before disease manifestation. Furthermore, ACPA titers were found to increase up to the point of disease onset. Once present, ACPA almost never disappear, but tend to persist in the vast majority of patients in whom they have developed [14].

The fact that ACPA appear during the preclinical phase of RA, together with the finding that ACPA can exacerbate arthritis in mice, suggest that anti-citrulline immunity may play a role in the pathogenesis of the disease [15]. This has prompted investigations into risk factors that may be associated with the emergence of anti-citrullinated protein immunity.

## Genetic risk factors for ACPA

The risk of developing RA is known to be influenced by several genetic risk factors, of which the human leukocyte

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antigen-DRB1 (*HLA-DRB1*) shared epitope (SE) alleles confer the highest risk [16]. After the first descriptions of ACPA, it soon became clear that the SE alleles were solely associated with, and thus only predisposed to, ACPA-positive RA. One study investigating the binding of citrullinated peptides to SE-encoded major histocompatibility complex (MHC) molecules was able to demonstrate that citrullination results in higher peptide–MHC binding affinity, providing a biological explanation for the association between ACPA and the SE alleles [17].

In view of the fact that ACPA can be detected before disease onset, the question arose as to whether SE alleles were truly a risk factor for developing RA or rather for developing an anti-citrullinated protein immune response. In order to answer this question, the influence of the SE alleles and ACPA on the progression from recent-onset, undifferentiated arthritis (UA) to RA was determined in 570 UA patients in a population-based inception cohort, the Leiden Early Arthritis Clinic cohort [18]. A total of 177 patients with UA developed RA during the first year of follow-up, while the remaining 393 patients either received other diagnoses or remained classified as UA. The SE alleles correlated with the presence of ACPA and, in both SE-positive and SE-negative patients with UA, the presence of ACPA was significantly associated with the development of RA. More intriguingly, however, was the fact that no apparent contribution of the SE alleles to the progression to RA could be identified when the analyses were stratified for the presence of anti-CCP antibodies. Thus, the SE alleles do not independently contribute to the progression to RA from UA, but rather predispose to the development of ACPA.

Similar data have been reported with regards to other known genetic risk factors for RA such as protein tyrosine phosphatase, non-receptor 22 (*PTPN22*) gene variants, although studies have thus far been underpowered to prove that *PTPN22* is a risk factor for the occurrence of the ACPA response rather than for the occurrence of ACPA-positive RA [19]. The recently described complement component 5-tumor necrosis factor receptor-associated factor (*C5-TRAF*) risk factor has also been reported to be predominantly associated with ACPA-positive RA [20].

Conversely, there are other genetic risk factors that have been described as exclusively associated with ACPA-negative RA, such as *HLA-DR3* and interferon regulatory factor (*IRF*) haplotypes [21]. As there are no markers available that are specific for this disease subset, it is impossible to determine whether these genetic risk factors predispose to ACPA-negative RA or to specific immunological alterations in these patients at present.

## Environmental risk factors for ACPA

In addition to genetic aspects, environmental risk factors are known to contribute to the etiology of RA. Many epidemiological studies have shown an association between cigarette smoking and the development of RA [22,23]. Smoking has been found to interact with the *HLA* SE alleles in the predisposition to RF-positive RA [24]. However, recent data from Sweden have shown a striking interaction between smoking and the SE alleles in conferring risk for ACPA-positive, rather than RF-positive, RA [25]. They also demonstrated an association between smoking and the development of citrullinated antigens in bronchoalveolar lavage fluid cells, thereby providing a possible pathogenetic link between smoking and the development of ACPA-positive RA.

## Pathophysiological model of RA

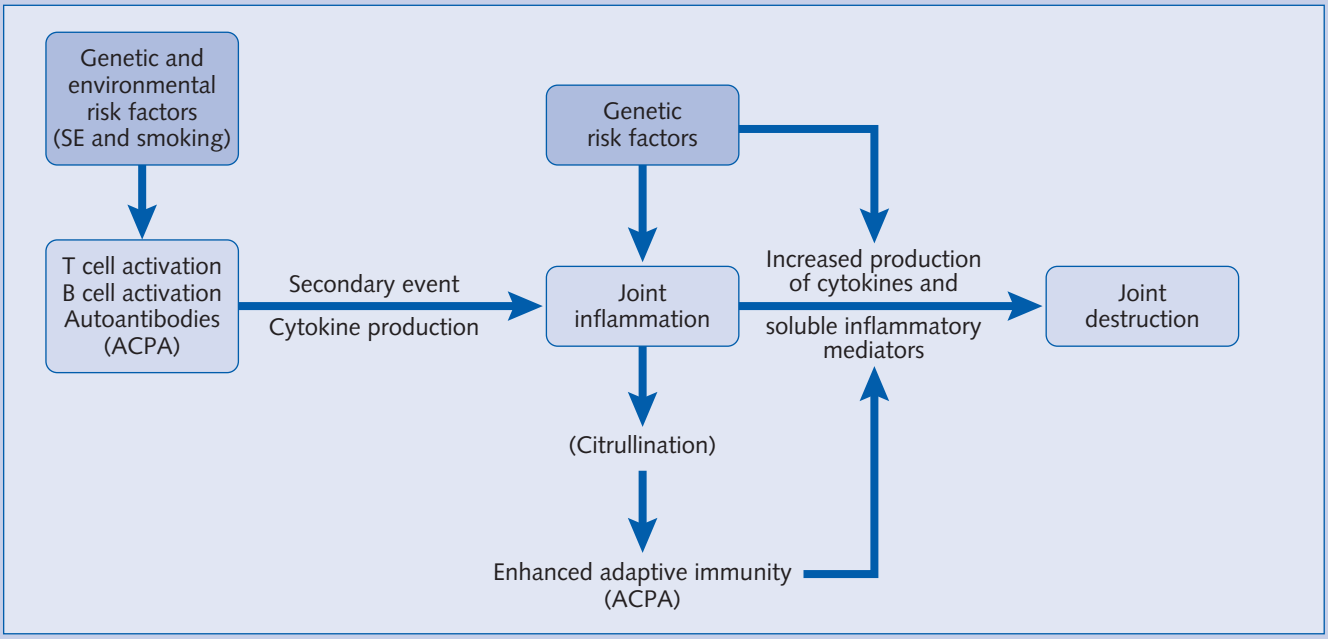
Recent findings that have elucidated the differences in risk factors between ACPA-positive and ACPA-negative RA have important consequences for the understanding of the pathophysiology of RA. These new insights have been incorporated into a hypothesis, which postulates that the pathogenesis of RA can be viewed as a multistage process. A schematic representation of this multistep model is depicted in Fig. 1.

In the first stage, genetic predisposition along with environmental factors result in an adaptive immune response with the production of autoreactive T cells, B cells, and autoantibodies. In the case of ACPA-positive RA, the SE alleles together with smoking may lead to the development of an anti-citrullinated protein immune response. A nonspecific environmental trigger could function as a secondary event leading to joint inflammation, which manifests as UA. Other genetic risk factors involved in, for example, cytokine regulation, play a role in determining the extent and duration of joint inflammation. The inflammatory process itself can subsequently further stimulate the adaptive immune response through the generation of new epitopes by, among other processes, citrullination, which has been shown to occur more readily in inflamed joints [26]. In individuals who have previously developed an adaptive immune response (possibly with production of ACPA), the immune cells that now gain access to the joints can enhance the inflammation and lead to the increased production of cytokines and soluble inflammatory mediators. This could cause perpetuation of the synovial inflammation and progression of UA to RA and erosive disease.

## Diagnostic characteristics of ACPA

After the discovery of anti-citrullinated protein immunity, many studies have investigated the exact diagnostic properties of ACPA in different rheumatological conditions.

**Figure 1.** Pathophysiology of RA: a multi-stage process.




ACPA: anti-citrullinated protein antibodies; RA: rheumatoid arthritis; SE: shared epitope.

Most of these studies have made use of the first- and second-generation tests based on the recognition of CCP, while some have used additional targets such as mutated citrullinated vimentin (MCV) [11,27]. In view of the fact that the anti-CCP assays are the most widely used tests in clinical practice, the following discussion will be limited to the diagnostic characteristics of these tests.

A recent meta-analysis provided a comprehensive overview of the anti-CCP and RF tests for the diagnosis of RA [4]. The findings of this study are summarized in Table 1. The most important difference between the two tests was the increased specificity of the anti-CCP assay compared with that of IgM-RF (95% vs. 85%). The sensitivity of CCP2 was similar to that of IgM-RF (67%), whereas CCP1 was markedly less sensitive. The diagnostic characteristics of IgG-RF and IgA-RF, which had previously been reported to be more accurate than IgM-RF, proved in fact to be similar to IgM-RF; thus, these measurements do not provide additional information.

In view of these data, it is necessary to re-examine how serological markers can be used most effectively in the diagnostic strategy for RA. Determination of anti-CCP2 antibodies, which have a high specificity and a reasonable sensitivity, is a good first option in patients presenting with inflammatory arthritis. However, CCP assays are still considerably more expensive than measurements of RF in most countries. Whether it is worthwhile to also determine IgM-RF depends on the interpretation of the results. Requiring a positive result on both tests leads to a loss of sensitivity, because fewer patients have both antibodies than have either RF or anti-CCP alone. On the other hand, considering a positive result on one test as sufficient for a diagnosis of RA would lead to a considerable reduction in specificity (especially when only using the RF test) in exchange for a small gain in sensitivity. This balance between sensitivity and specificity needs to be kept in mind when deciding whether to measure IgM-RF in addition to anti-CCP2.

It is important to note that in studies of cohorts of patients with longstanding RA, approximately one-third of patients do not have ACPA [28]. These ACPA-negative patients are characterized not only by a different set of genetic risk factors, but also by markedly less radiographic destruction than ACPA-positive patients, as will be discussed in detail below. The presence of ACPA may therefore distinguish separate disease entities with different putative pathophysiological mechanisms and distinct disease outcomes [29].

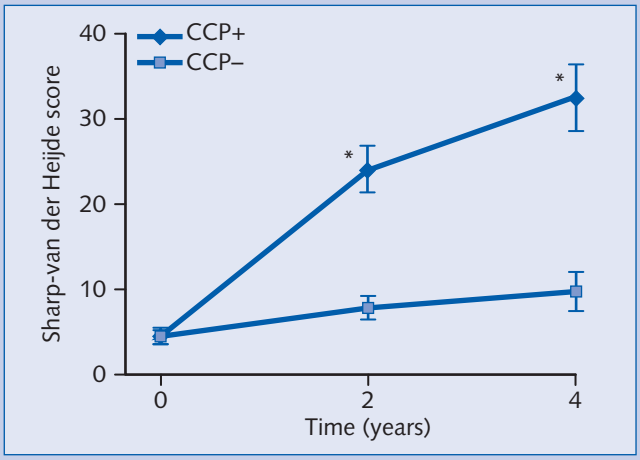
Despite the high specificity of 95%, there have been reports of other diseases that may be associated with ACPA, most notably psoriatic arthritis (PsA). In several cohorts of patients with psoriasis, PsA was associated with anti-CCP antibodies in 7–10% of patients, but cutaneous psoriasis was not associated with anti-CCP antibodies [30,31]. Furthermore, there has been one report of increased titers of anti-CCP antibodies in serum samples from 15 patients with active pulmonary tuberculosis [32]. However, in other

**Table 1.** Diagnostic accuracy of anti-CCP antibodies and RF for rheumatoid arthritis. Results from a meta-analysis [4].

| | Anti-CCP (95% CI) | IgM RF (95% CI) |
|---|---|---|
| Pooled positive likelihood ratio* | 12.46 (9.72–15.98) | 4.86 (3.95–5.97) |
| Pooled negative likelihood ratio** | 0.36 (0.31–0.42) | 0.38 (0.33–0.44) |
| Pooled sensitivity | 67% (65–68%) | 69% (68–70%) |
| Pooled specificity | 95% (95–96%) | 85% (84–86%) |

*Positive likelihood ratio = sensitivity/(1–specificity) **Negative likelihood ratio = (1–sensitivity)/specificity
CCP: cyclic citrullinated proteins; CI: confidence interval; IgM: immunoglobulin M; RF: rheumatoid factor.

**Figure 2.** Radiological joint destruction in 228 anti-CCP-positive RA patients and 226 anti-CCP-negative RA patients. Total Sharp-van der Heijde scores at inclusion and at 2 and 4 years of follow-up in RA patients with and without anti-CCP antibodies.




*p<0.001.
ACPA: anti-citrullinated protein antibodies; CCP: cyclic citrullinated protein; RA: rheumatoid arthritis. Redrawn with permission from [40].

rheumatic and non-rheumatic diseases known to be associated with RF, such as in hepatitis C virus infection and cryoglobulinemia, ACPA have been shown to be specific for RA [33].

## Predictive characteristics of ACPA

In addition to their function as a diagnostic marker for RA, ACPA have been extensively investigated with regard to their predictive abilities. As mentioned above, the awareness that early aggressive treatment of RA can best prevent joint destruction has increased the demand for markers that can reliably predict disease development and progression. Studies of patients who present with early arthritis have revealed that while only 20% of patients can be classified as having RA at their initial presentation, the majority of patients (35–55%) have UA [34,35]. The disease course of patients with UA is variable, with approximately half of all patients experiencing spontaneous remission, one-third of patients progressing to RA, and the remainder developing different diseases or remaining classified as having UA [36]. Owing to the toxicity associated with the current treatments for RA, it is of particular importance to be able to distinguish those UA patients who will probably develop RA from those who will not, in order to treat only the individuals who are likely to benefit from early therapy.

The presence of ACPA is currently the best predictive marker for the progression of UA to RA. As was shown in a study of 318 UA patients, 93% of ACPA-positive UA patients developed RA compared with 25% of ACPA-negative UA patients [37]. In multivariate logistic regression analysis that accounted for other predictive variables, anti-CCP2 positivity was associated with an odds ratio of 8.1 (95% confidence interval 4.2–15.8; p<0.001) for the development of RA in UA patients [38]. Based on these findings, a prediction rule for calculating the risk of developing RA in a patient who presents with UA has been developed [38,39]. Using anti-CCP and eight other variables that are routinely assessed in the outpatient clinic, this model determined negative and positive predictive values of 91% and 84%, respectively. This model can easily be applied in daily practice and can facilitate treatment decisions in UA patients.

The observations regarding the predictive ability of ACPA have also prompted investigations into the role of ACPA after disease development. A comparison of 228 anti-CCP-positive RA patients with 226 anti-CCP-negative RA patients revealed that there were no differences in type, location, or duration of symptoms at disease onset [40]. However, after 4 years of follow-up, ACPA-positive patients had significantly more swollen joints and more severe radiological destruction (Fig. 2). Despite these differences in severity, the distribution of swollen joints and of radiological joint space narrowing and erosions did not differ between anti-CCP-positive and anti-CCP-negative patients. Thus, ACPA do not appear to be associated with a distinct clinical phenotype, but may instead enhance inflammation once it is present and thereby contribute to the development of chronicity and exacerbation of the disease.

## Conclusion

The discovery of the RA-specific anti-citrullinated protein immune response has had a significant impact, not only on diagnosis and disease prediction, but also on the way we think about the pathophysiology of the disease. Recognition of the distinct genetic and environmental risk factors involved in ACPA-positive versus ACPA-negative disease, has allowed us to view RA in a more differentiated way. Although there is no conclusive proof as yet that ACPA themselves are pathogenic, they allow a useful distinction of disease subsets, each with associated risk factors and prognosis. With regard to the ability to serologically confirm the diagnosis of RA, in addition to our pathophysiological understanding of the disease, ACPA represent a great step forward.

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## Disclosures

The authors have no relevant financial interests to disclose.

## References


1. Suurmeijer TP, Waltz M, Moum T et al. Quality of life profiles in the first years of rheumatoid arthritis: results from the EURIDISS longitudinal study. *Arthritis Rheum* 2001;**45**:111–21.
2. Lard LR, Visser H, Speyer I et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001;**111**:446–51.
3. Visser H, Gelinck LB, Kampfraath AH et al. Diagnostic and prognostic characteristics of the enzyme linked immunosorbent rheumatoid factor assays in rheumatoid arthritis. *Ann Rheum Dis* 1996;**55**:157–61.
4. Nishimura K, Sugiyama D, Kogata Y et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007;**146**:797–808.
5. Nienhuis RL, Mandema E. A new serum factor in patients with rheumatoid arthritis; the antiperinuclear factor. *Ann Rheum Dis* 1964;**23**:302–5.
6. Young BJ, Mallya RK, Leslie RD et al. Anti-keratin antibodies in rheumatoid arthritis. *Br Med J* 1979;**2**:97–9.
7. Simon M, Girbal E, Sebbag M et al. The cytokeratin filament-aggregating protein filaggrin is the target of the so-called "antikeratin antibodies," autoantibodies specific for rheumatoid arthritis. *J Clin Invest* 1993;**92**:1387–93.
8. Schellekens GA, de Jong BA, van den Hoogen FH et al. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest* 1998;**101**:273–81.
9. Despres N, Boire G, Lopez-Longo FJ et al. The Sa system: a novel antigen-antibody system specific for rheumatoid arthritis. *J Rheumatol* 1994;**21**:1027–33.
10. Vossenaar ER, Despres N, Lapointe E et al. Rheumatoid arthritis specific anti-Sa antibodies target citrullinated vimentin. *Arthritis Res Ther* 2004;**6**:R142–50.
11. Coenen D, Verschueren P, Westhovens R et al. Technical and diagnostic performance of 6 assays for the measurement of citrullinated protein/peptide antibodies in the diagnosis of rheumatoid arthritis. *Clin Chem* 2007;**53**:498–504.
12. Rantapaa-Dahlqvist S, de Jong BA, Berglin E et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:2741–9.
13. Nielen MM, van Schaardenburg D, Reesink HW et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* 2004;**50**:380–6.
14. Kastbom A, Strandberg G, Lindroos A et al. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). *Ann Rheum Dis* 2004;**63**:1085–9.
15. Kuhn KA, Kulik L, Tomooka B et al. Antibodies against citrullinated proteins enhance tissue injury in experimental autoimmune arthritis. *J Clin Invest* 2006;**116**:961–73.
16. Kallberg H, Padyukov L, Plenge RM et al. Gene–gene and gene–environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. *Am J Hum Genet* 2007;**80**:867–75.
17. Hill JA, Southwood S, Sette A et al. Cutting edge: the conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1*0401 MHC class II molecule. *J Immunol* 2003;**171**:538–41.
18. van der Helm-van Mil AH, Verpoort KN, Breedveld FC et al. The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. *Arthritis Rheum* 2006;**54**:1117–21.
19. Feitsma AL, Toes RE, Begovich AB et al. Risk of progression from undifferentiated arthritis to rheumatoid arthritis: the effect of the PTPN22 1858T-allele in anti-citrullinated peptide antibody positive patients. *Rheumatology (Oxford)* 2007;**46**:1092–5.
20. Kurreeman FA, Padyukov L, Marques RB et al. A candidate gene approach identifies the TRAF1/C5 region as a risk factor for rheumatoid arthritis. *PLoS Med* 2007;**4**:e278.
21. Verpoort KN, van Gaalen FA, van der Helm-van Mil AH et al. Association of HLA-DR3 with anti-cyclic citrullinated peptide antibody-negative rheumatoid arthritis. *Arthritis Rheum* 2005;**52**:3058–62.
22. Hazes JM, Dijkmans BA, Vandenbroucke JP et al. Lifestyle and the risk of rheumatoid arthritis: cigarette smoking and alcohol consumption. *Ann Rheum Dis* 1990;**49**:980–2.
23. Symmons DP, Bankhead CR, Harrison BJ et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. *Arthritis Rheum* 1997;**40**:1955–61.
24. Padyukov L, Silva C, Stolt P et al. A gene–environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum* 2004;**50**:3085–92.
25. Klareskog L, Stolt P, Lundberg K et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006;**54**:38–46.
26. Makrygiannakis D, af Klint E, Lundberg IE et al. Citrullination is an inflammation-dependent process. *Ann Rheum Dis* 2006;**65**:1219–22.
27. Bang H, Egerer K, Gauliard A et al. Mutation and citrullination modifies vimentin to a novel autoantigen for rheumatoid arthritis. *Arthritis Rheum* 2007;**56**:2503–11.
28. van Gaalen FA, Visser H, Huizinga TW. A comparison of the diagnostic accuracy and prognostic value of the first and second anti-cyclic citrullinated peptides (CCP1 and CCP2) autoantibody tests for rheumatoid arthritis. *Ann Rheum Dis* 2005;**64**:1510–2.
29. van der Helm-van Mil AH, Huizinga TW, de Vries RR et al. Emerging patterns of risk factor make-up enable subclassification of rheumatoid arthritis. *Arthritis Rheum* 2007;**56**:1728–35.
30. Alenius GM, Berglin E, Rantapää DS et al. Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without joint inflammation. *Ann Rheum Dis* 2006;**65**:398–400.
31. Candia L, Marquez J, Gonzalez C et al. Low frequency of anticyclic citrullinated peptide antibodies in psoriatic arthritis but not in cutaneous psoriasis. *J Clin Rheumatol* 2006;**12**:226–9.
32. Elkayam O, Segal R, Lidgi M et al. Positive anti-cyclic citrullinated proteins and rheumatoid factor during active lung tuberculosis. *Ann Rheum Dis* 2006;**65**:1110–2.
33. Wener MH, Hutchinson K, Morishima C et al. Absence of antibodies to cyclic citrullinated peptide in sera of patients with hepatitis C virus infection and cryoglobulinemia. *Arthritis Rheum* 2004;**50**:2305–8.
34. van Aken J, van Bilsen JH, Allaart CF et al. The Leiden Early Arthritis Clinic. *Clin Exp Rheumatol* 2003;**21**(5 Suppl 31):S100–5.
35. Hulsemann JL, Zeidler H. Undifferentiated arthritis in an early synovitis out-patient clinic. *Clin Exp Rheumatol* 1995;13:37–43.
36. van Aken J, van Dongen H, le Cessie S et al. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. *Ann Rheum Dis* 2006;**65**:20–5.
37. van Gaalen FA, Linn-Rasker SP, van Venrooij WJ et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004;**50**:709–15.
38. van der Helm-van Mil AH, le Cessie S, van Dongen H et al. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum* 2007;**56**:433–40.
39. van der Helm-van Mil AH, Huizinga TW. Diagnostic and therapeutic opportunities in undifferentiated arthritis. *Int J Adv Rheumatol* 2007;**5**:34–9.
40. van der Helm-van Mil AH, Verpoort KN, Breedveld FC et al. Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. *Arthritis Res Ther* 2005;**7**:R949–58.

LEADING ARTICLE

# A Question and Answer Approach to Rheumatoid Arthritis Disease Activity

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**Disease activity is a pivotal term when considering the treatment of chronic, inflammatory, rheumatic diseases. As the modifiable component of chronic inflammatory (chronic "active") events, disease activity is central to therapeutic decision-making. Rheumatoid arthritis (RA) is the most frequent of such disorders, and thus often serves as a model of a chronic disease in which "activity" is a major factor. Furthermore, many methods and instruments used to assess disease activity in other rheumatic diseases have been borrowed from RA. For these reasons, disease activity issues related to RA are discussed in this review. However, the authors deviate from the traditional approach of presenting the measures systematically, one by one. Rather, they address the issue of disease activity in RA by raising and addressing a number of central questions that are relevant to rheumatologists and other physicians caring for patients with this, and other, diseases.** *Int J Adv Rheumatol* 2008;**6**(1):11–5.

## Why measure disease activity?

**In other words:** Is it not sufficient to measure "hard" endpoints, such as joint destruction or functional disability?

**Provocative statement:** Joint destruction and functional disability are the most important outcomes of RA. It should be sufficient to assess these attributes, and not disease activity, which is only a small snapshot and fluctuates considerably over time.

**Evidence:** In chronic rheumatic diseases, there is a temporal sequence linking disease activity to destruction. In these conditions, damage is a consequence of the active inflammatory process and both are related to disability. Earlier in the course of disease, impairment of physical function is primarily related to disease activity, while later on, this association of impairment with activity is partly superseded by, or occurs concurrently with (hitherto irreversible) damage. This sequence is probably best established for RA [1–4], but conceptually it clearly also applies to psoriatic arthritis (PsA), anklyosing spondylitis (AS), and other disorders. As a consequence, functional scores cannot distinguish between active components of the disease, which are treatable, and inactive components with irreversible damage that are not amenable to therapy. The goal of all therapies, however, is the prevention of structural damage and, ultimately, of persistent disability.

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The sequence of events described above also reveals that damage and irreversible disability are a consequence of time, and lag behind the actual processes reflected by disease activity. Thus, reacting to active disease with appropriate therapy will allow for real-time intervention with the prospect of preventing a poor outcome, rather than interventions aimed at repair of damage, which (orthopedic surgery aside) are not available at present.

Indeed, targeting disease activity is the most effective method to control the sequelae of chronic inflammation [5]. Thus, to be successful in achieving the main goal – prevention of destruction and disability – disease activity needs to be reduced. This can be undertaken most effectively if structured approaches are in place that demand rapid treatment changes if specific disease activity goals have not been reached [6–8]. In other words, functional capacity is one of the most important outcomes and should certainly be assessed in every patient with RA, but disease activity is the most important mediator between therapeutic intervention and improving functional ability. Without disease activity assessment, the physician would be blind to the usefulness of the employed therapies, resulting in a perpetual lack of effective feedback regarding treatment effects on functional ability.

**Conclusion:** Disease activity is the target of therapeutic interventions. Radiographic and functional assessments, although partly influenced by disease activity, measure disease outcome rather than the disease process. These are arguments against purely functionally oriented assessments

in chronic inflammatory diseases, and demand the attainment of measures of the active disease process.

## Why perform joint counts in RA?

**In other words:** Given the many facets of RA disease activity, why is it necessary to count affected joints?

**Provocative statement:** It is not reasonable to require laborious joint counts, which take time and/or personnel, if other measures that relate well to joint counts and require less effort are available.

**Evidence:** The many facets of RA allow for measurement and collection of data on various attributes of the disease. The typical disease activity measures include joint swelling, joint tenderness, and pain scores, in addition to global scores by the patient and the physician. Also, some measure of the acute phase response (APR) is usually collected. This is reflected by the definition of core sets of disease activity measures published in the 1990s [9–11]. Joint counts are included among these core sets because RA is primarily a joint disease and, therefore, joint assessment has construct and criterion validity, aside from face validity. Moreover, one can think of many therapies that would change pain and patient global scores, such as analgesic drugs or drugs against depression, which would not affect RA disease activity, and especially not affect the joint components of the disease. Such drugs would hardly be considered effective disease-modifying agents.

It is often argued that global scales provide a good and much simpler general tool to assess disease activity, and that therefore, the cumbersome evaluation of joint activity might not be necessary. Indeed, a global estimation of disease activity by the *physician* is a reasonable approach, as it is informed by all available measures at the time. However, the use of global scores is limited, in all settings, where patients are followed by more than one physician over time as the evaluation of various disease activity measures varies considerably between different physicians [12]. In contrast, when employing the *patient* global assessment of disease activity, such intra-observer variability would clearly not be a problem in the longitudinal follow-up. However, the limitation of patient global assessments of disease activity is that they vary considerably between patients based on their prior experiences of the disease, with their physicians, or other factors. This high inter-observer variability makes comparisons of effects between patients complicated, a fact that became apparent from an analysis that mapped objective disease activity measures to a "patient acceptable symptom state" [13]. In addition, as mentioned previously, it is highly possible that interventions affect the global score by the patient without treating disease activity. Thus, although patient-centered measures are desirable and should be reinforced given their important reflection of wellbeing [14], for the reasons discussed, their isolated use might not be ideal. In particular, instruments based on the Health Assessment Questionnaire Disability Index (HAQ), which measure disease activity only indirectly through its effects on physical function, should not be considered in isolation. Another group of variables frequently regarded as reflecting disease activity are those measuring the APR. However, the APR is only an indirect reflection of the joint events, correlates with joint counts only moderately to weakly, may be influenced by many factors other than the underlying disease, and thus cannot replace joint counts [2,15]. The need to measure disease activity more directly in the process of following patients with RA has been emphasized in the earlier section of this review: "why measure disease activity".

**Conclusion:** For a state-of-the-art follow-up of RA patients, there appears to be no way of avoiding joint assessments. In fact, in a disease that primarily manifests with arthritis it would be paradox to omit the assessment of the major target organ, the joints. This would be analogous to treatment of hypertension based on the severity of headaches or wellbeing, rather than the measurements of blood pressure.

## Is it sufficient to *only* look at joints in RA?

**In other words:** Do we need to make other assessments in addition to performing joint counts?

**Provocative statement:** If, as discussed above, joint assessment is key, then why cannot we limit our efforts in the evaluation of RA disease activity to joint assessment only?

**Evidence:** Although joint assessment is the central analysis in patients with RA, the sole evaluation of swelling and tenderness is generally less sensitive to change than if combined with other measures of disease activity [16,17]. Specific therapeutic effects can be better captured if measures are combined. In clinical trials, combined measures (criteria, scores, and indices) increase the power to discriminate treatment effects from placebo effects, and thus reduce sample size requirements. As a consequence, the number of patients that will be treated with placebo or comparator drug is also reduced [18].

In clinical practice, it is easier for patients to understand the doctor's benchmarks of disease activity if they are provided with a single score. Over the course of the disease, the patient will feel much more involved in the treatment decisions and their condition if clear definitions based on a particular index are provided to them. This should strengthen the compliance of the patient to therapy, relative to that achieved with a more descriptive communication of disease activity levels by the physician to the patient, which involves a semi-quantitative combination of various aspects of RA (a more traditional approach). This more structured approach

(from the aspect of the physician and patient) will likely improve outcomes of the patients in the longer term [6].

**Conclusion:** Indices including joint counts are the state-of-the-art method to implement new strategies in the treatment of RA, in addition to improving patient compliance and outcomes.

## Why are there so many different disease activity indices?

**In other words:** As there are a number of disease activity indices available for RA, what is the benefit of newer indices over traditional ones?

**Provocative statement:** The first widely accepted composite index, the Disease Activity Score (DAS) was developed approximately 15 years ago [19]. A plethora of additional indices have since been described, but their incremental benefits are unclear. In fact, they create confusion among users.

**Evidence:** Formerly, the most commonly used disease activity index was, in fact, not the original DAS, but rather a derivation of this index – the Disease Activity Score based on 28 joint assessments (DAS28) [20]. It was developed to overcome major limitations of the DAS that restricted its use in clinical practice, and also in trials of RA. These limitations included a complex joint assessment that was based on the graded evaluation of joint tenderness (the Ritchie index) [19], and a more comprehensive swollen joint count. Specifically, the graded Ritchie index led to a greater inter-rater variability [21], and its omission improved the properties of the index. For all of these reasons, the original DAS is not generally used in clinical practice and trials nowadays.

Like the DAS, the DAS28 is a summation of four disease attributes, the swollen and tender 28 joint count, the erythrocyte sedimentation rate (ESR), and a global health score (by the patient). The variables were transformed to reach normal distribution (using logarithms or square roots), and were weighted in the formula so that the additive score best predicted a rheumatologist's decision to change therapy in a patient with RA. Given this complexity, computer or online applications or calculators have been developed in the more recent past. Without these tools, a DAS28 is not feasible.

In an effort to facilitate disease activity assessment in RA, the Simplified Disease Activity Index (SDAI) has also been developed [22]. The SDAI is the linear sum of five core set variables (swollen and tender joints, 0–28; C-reactive protein [CRP] levels, mg/dL; patient and physician global disease activity, on a 0–10 cm visual analogue scale). With this index, there is no need for a calculator, and it is very easy to determine the meaning of a given score, because no transformation has taken place. This also supports the understanding of the score by the patient, which has been outlined as an important element of effective therapy in the previous section of this review. Arguments that the simplification processes leading to the development of the SDAI could jeopardize the validity of the score can be countered with evidence from a number of studies and trials from different parts of the world that convincingly shows otherwise [23–30].

In addition, it has been suggested that the validity of DAS28 may be compromised in the elderly and in pregnant women, as the global health scores and ESR, but not CRP, appear to increase independently from RA activity in these patients [31]. The unweighted nature of the SDAI and the incorporation of a physician global assessment in addition to a patient global assessment in the determination of disease activity may therefore be of advantage when following certain patient groups. Finally, when assessing remission, the SDAI appears to be the most stringent index, approaching the quest for no or minimally active disease most closely [32].

**Conclusion:** Every stage in the evolution of disease activity indices has been justified by simplifications that improved the applicability, and historically also the acceptance, of the subsequent index. These simplifications included the involved assessments (DAS → DAS28) or the method used to calculate the index (DAS28 → SDAI). In addition, the stringency and apparent validity of the term "remission" has become a relevant feature of an index in more recent times (DAS/DAS28 → SDAI).

## Is *measuring* disease activity enough?

**In other words:** What are the implications of quantifying RA disease activity?

**Provocative statement:** Measuring disease activity, and assessment of its changes, is helpful from a psychological point of view, but does not have any impact on disease outcomes.

**Evidence:** Therapeutic strategies have become a mainstay of modern therapy of RA. In earlier years, the intuition or "gut feeling" of rheumatologists was often the gold standard for any treatment consideration; however, this approach has been criticized. A recent survey found that physicians tend to be satisfied with an improvement, even if it is small and high disease activity levels persist; furthermore, physicians have implicit and unknown weights that they assign to different attributes of RA disease activity [12]. In addition, physicians tend to tolerate worsening in single attributes of the disease, so long as others have improved. Therefore, more standardized ways to reach therapeutic decisions have been suggested.

Randomized, controlled, strategic trials from the past 10 years have shown that it is important to have a clear-cut

treatment goal, which should be based on a defined disease activity level (or so-called disease activity "states"). The achievement of the targeted activity state should be checked periodically, ideally every 2–3 months. If the goal is not achieved, there should be no delay in an adequate treatment change. Two studies need to be mentioned in this context, the TICORA (Tight Control for Rheumatoid Arthritis) and the BeSt (Behandel Strategieen) trials [6,7]. Algorithms to implement these strategies in clinical practice have also been suggested [8]. These algorithms and the 3-monthly intervals of assessment have a scientific basis – after this period of time a prediction of a longer term response can be effectively established [33]. Importantly, and as already mentioned in the first section of this review ("why measure disease activity?"), periods of active disease may translate into damage and irreversible disability, and the TICORA and BeSt trials have shown that if active disease prevails, adaptation of therapy significantly improves outcomes.

**Conclusion:** Assessment of disease activity is the key element of each clinical visit of patients with RA, as it serves as the anchor for immediate treatment decisions and the general short- and long-term benefit of the patient.

## What is the usefulness of a purely clinical index?

**In other words:** Can indices that omit laboratory variables be preferentially used in disease activity assessment of RA?

**Provocative statements:** Acute phase reactants are important measures of the disease process in RA. They correlate with radiographic progression [1,34,35] and, as objective measurements, are not subject to observer bias. They should be an integral part of every disease activity index.

**Evidence:** All indices discussed thus far include laboratory measures (either ESR or CRP assessments). Without these acute phase measures, no meaningful score can be obtained. To alleviate this pressure and to provide physicians with an index than can be employed at any time and place, the Clinical Disease Activity Index (CDAI) has been developed as a minor modification of the SDAI (Table 1) [2].

The CDAI is a purely clinical score, omitting the CRP assessment that is needed to calculate the SDAI. The validity of the CDAI has already been shown in the original publication describing the SDAI [22], and the scientific basis and arguments why exclusion of CRP from the formula is reasonable has been detailed in the subsequent initial publication on the CDAI [2]. Acute phase reactants can be evaluated independently from the clinical index, and might even be used to "double-check" the therapeutic decisions made based on the index, but they do not need to be assessed for calculation of the index. At the present authors' clinics, the use of the CDAI has considerably facilitated structured management of patients with RA, and has, in fact, allowed implementation of index-based treatment decisions while the patient is being assessed. Although laboratory test results are usually available on the next day (following the patient visit), there remains the need to recall the clinical status of the patient, contact the patient by telephone, or mail prescriptions to the patient. This is an inherent problem of employing a score that includes assessment of an acute phase reactant, and leaves much room for error. However, it should also be mentioned that instructing the patient to attend a clinic with a laboratory report in hand is also often limited, simply by the failure of the patient to do so.

**Table 1.** Disease activity states according to the SDAI and CDAI. Cutoff values for SDAI are based on the recent rating of 32 patient profiles by 35 experts [37]. CDAI cutoffs were derived by using a strategy identical to the one in the study on the SDAI cutoff points [36].

| | Remission | Low DA | Moderate DA | High DA |
|---|---|---|---|---|
| SDAI* | ≥3.3 | ≥11 | ≥26 | >26 |
| CDAI* | ≥2.8 | ≥10 | ≥22 | >22 |

CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DA: disease activity; SDAI: Simplified Disease Activity Index.
*Calculations: SDAI = swollen joint count (0–28) + tender joint count (0–28) + patient global assessment of disease activity (on a 0–10 cm visual analogue scale) + evaluator (physician) global assessment of disease activity (0–10 cm) + CRP (mg/dL); CDAI = SDAI – CRP (mg/dL).

In any case, it should be emphasized that acute phase reactants are important elements of RA disease activity evaluation, which cannot and must not be omitted. However, as shown in the study validating the CDAI [2], this does not imply that they need to be an integral part of an index, and render the index useless if missing. Whenever they are available, acute phase reactants need to be considered alongside a clinical index, but their integration into the index may not significantly alter its validity.

As mentioned previously, patient awareness of disease activity measures and its beneficial consequences can be conceptualized [36], and the current authors have implemented a credit card shaped document that the patient brings along to every clinic visit. On this card, the current disease activity is documented using the CDAI, and the goal is to encourage the patient to come forward with a request regarding the current disease activity level at every such visit. We used the high grade of patient awareness about hemoglobin A1c levels in diabetes as an example of how patient understanding of the doctor's assessments and measurements can improve compliance and, as a consequence, disease outcomes.

**Conclusion:** Disease activity can be assessed reliably by a purely clinical index. Clinical disease activity based on the index should be evaluated alongside acute phase measures in clinical practice; however, the latter do not necessarily need to be an integral part of the index.

## Summary

Disease activity in RA is the mediator of poor long-term outcome, such as disability. Joint counts should be an integral part of disease activity assessment, as the joints are the major site of the pathogenetic process of this immune-mediated disease. Joints need to be assessed in conjunction with other clinical variables to increase the responsiveness to change and the reliability of the overall assessment of disease activity. Laboratory measures are also needed, but not necessarily as part of an index, because these measures often become the limiting factors of calculation. Therefore, a purely clinical index has been proposed – this can be calculated at any time, which allows tighter disease activity follow-up, and will eventually improve the long-term consequences of RA.

## Disclosures

The authors have no relevant financial interests to disclose.

## References


1. van Leeuwen MA, van Rijswijk MH, van der Heijde DM et al. The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: a prospective study during the first three years of the disease. *Br J Rheumatol* 1993;**32** (Suppl 3):9–13.
2. Aletaha D, Nell VP, Stamm T et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005;**7**:R796–806.
3. Welsing PM, Landewé RB, van Riel PL et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. *Arthritis Rheum* 2004;**50**:2082–93.
4. Drossaers-Bakker KW, de Buck M, van Zeben D et al. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. *Arthritis Rheum* 1999;**42**:1854–60.
5. van Leeuwen MA, van der Heijde DM, van Rijswijk MH et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. *J Rheumatol* 1994;**21**:425–9.
6. Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;**364**:263–9.
7. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;**52**:3381–90.
8. Smolen JS, Sokka T, Pincus T et al. A proposed treatment algorithm for rheumatoid arthritis: aggressive therapy, methotrexate, and quantitative measures. *Clin Exp Rheumatol* 2003;**21**(5 Suppl 31):S209–10.
9. Felson DT, Anderson JJ, Boers M et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* 1993;**36**:729–40.
10. Boers M, Tugwell P, Felson DT et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. *J Rheumatol Suppl* 1994;**41**:86–9.
11. Scott DL, Panayi GS, van Riel PL et al. Disease activity in rheumatoid arthritis: preliminary report of the Consensus Study Group of the European Workshop for Rheumatology Research. *Clin Exp Rheumatol* 1992;**10**:521–5.
12. Aletaha D, Machold KP, Nell VP et al. The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey. *Rheumatology (Oxford)* 2006;**45**:1133–9.
13. Heiberg T, Kvien TK, Mowinckel P et al. Identification of disease activity and health status cut points for the symptom state acceptable to rheumatoid arthritis patients. *Ann Rheum Dis* 2007; [Epub ahead of print]
14. Pincus T, Swearingen C, Wolfe F. Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. *Arthritis Rheum* 1999;**42**:2220–30.
15. Wolfe F, Michaud K. The clinical and research significance of the erythrocyte sedimentation rate. *J Rheumatol* 1994;**21**:1227–37.
16. Goldsmith CH, Smythe HA, Helewa A. Interpretation and power of a pooled index. *J Rheumatol* 1993;**20**:575–8.
17. Boers M, Verhoeven AC, Markusse HM et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997;**350**:309–18.
18. Tugwell P, Bombardier C. A methodologic framework for developing and selecting endpoints in clinical trials. *J Rheumatol* 1982;**9**:758–62.
19. van der Heijde DM, van 't Hof MA, van Riel PL et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990;**49**:916–20.
20. Prevoo ML, van 't Hof MA, Kuper HH et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:44–8.
21. Hart LE, Tugwell P, Buchanan WW et al. Grading of tenderness as a source of interrater error in the Ritchie articular index. *J Rheumatol* 1985;**12**:716–7.
22. Smolen JS, Breedveld FC, Schiff MH et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)* 2003;**42**:244–57.
23. Leeb BF, Andel I, Sautner J et al. Disease activity measurement of rheumatoid arthritis: Comparison of the simplified disease activity index (SDAI) and the disease activity score including 28 joints (DAS28) in daily routine. *Arthritis Rheum* 2005;**53**:56–60.
24. Soubrier M, Zerkak D, Gossec L et al. Which variables best predict change in rheumatoid arthritis therapy in daily clinical practice? *J Rheumatol* 2006;**33**:1243–6.
25. American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. *Arthritis Rheum* 2007;**57**:193–202.
26. Wong AL, Harker JO, Park GS et al. Longitudinal measurement of RA disease activity in a clinical practice setting: ssefulness of the SDAI (abstract). *Arthritis Rheum* 2004;**50**(Suppl):S386–7.
27. Lissiane K, Guedes N, Kowalski SC et al. The new indices SDAI and CDAI in early arthritis: similar performance to the DAS28 index (abstract). *Arthritis Rheum* 2006;**54**(Suppl):S206–7.
28. Burmester GR, Ferraccioli G, Flipo RM et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. *Arthritis Rheum* 2008;**59**:32–41.
29. Cuomo G, Molinaro G, La Montagna G et al. [A comparison between the Simplified Disease Activity Index (SDAI) and the Disease Activity Score (DAS28) as measure of response to treatment in patients undergoing different therapeutic regimens]. *Reumatismo* 2006;**58**:22–5. In Italian.
30. Gülfe A, Geborek P, Saxne T. Response criteria for rheumatoid arthritis in clinical practice: how useful are they? *Ann Rheum Dis* 2005;**64**:1186–9.
31. de Man YA, Hazes JM, van de Geijn FE et al. Measuring disease activity and functionality during pregnancy in patients with rheumatoid arthritis. *Arthritis Rheum* 2007;**57**:716–22.
32. Mierau M, Schoels M, Gonda G et al. Assessing remission in clinical practice. *Rheumatology (Oxford)* 2007;**46**:975–9.
33. Aletaha D, Funovits J, Keystone EC et al. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. *Arthritis Rheum* 2007;**56**:3226–35.
34. Dawes PT, Fowler PD, Clarke S et al. Rheumatoid arthritis: treatment which controls the C-reactive protein and erythrocyte sedimentation rate reduces radiological progression. *Br J Rheumatol* 1986;**25**:44–9.
35. Plant MJ, Williams AL, O'Sullivan MM et al. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:1473–7.
36. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;**23**(5 Suppl 39):S100–8.
37. Aletaha D, Ward MM, Machold KP et al. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005;**52**:2625–36.

CASE STUDY

# Adalimumab Therapy for Childhood Uveitis: A Case Report

**Case Study presented by: Alexa B Adams, MD[1] and Thomas JA Lehman, MD[2]**

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A 9-year-old Caucasian female had previously been diagnosed with pauciarticular juvenile idiopathic arthritis (JIA) at the age of 18 months elsewhere. She had initially presented with complaints of frequent falls and intermittent right knee swelling. During subsequent years there were occasional complaints of left ankle and wrist pain. She had not required medication during the 2 years prior to the current presentation. She was antinuclear antibody (ANA)-positive (titer 1:40), with an erythrocyte sedimentation rate (ESR) of 56 mm/h. The patient had experienced one previous episode of JIA-associated anterior uveitis, which was easily controlled with topical corticosteroids. At the time of the current presentation, her only complaint was of recurrent knee swelling.

A review of the patient's history (by organ systems) was noteworthy only for osteochondritis dessicans of the right knee. There was no involvement of other joints, systemic symptoms, or rash (except for a brief rash following the administration of naproxen, leading to its discontinuation). Nothing on the review of systems suggested an alternative diagnosis to JIA. Her past medical history was unremarkable for preceding hospitalizations, surgeries, or serious illness. The patient was adopted and no family history was available.

Physical examination of the subject was remarkable for swelling and limitation of motion of the right knee. She had tenderness at the tendon insertions around the wrists and in the plantar fascia bilaterally. There was no evidence of ocular inflammation on slit-lamp examination. Radiographs of the involved knee confirmed a moderate synovial effusion. An evaluation of laboratory tests showed normal complete blood count, renal and liver function tests, persistently low-titer positive ANA, negative rheumatoid factor (RF), and a normal ESR. The overall assessment was consistent with a diagnosis of JIA with enthesitis, and the patient was placed on tolmetin 600 mg twice daily. Aspirin was discontinued.

She responded well to tolmetin and this treatment was discontinued after 1 year. However, arthritis in the right knee recurred 6 months later. An arthrocentesis was performed and synovial fluid was culture-negative (for bacterial, fungal, and acid-fast organisms). The ESR was moderately elevated at 41 mm/h. Nonsteroidal anti-inflammatory drugs (NSAIDs) were resumed, but improvement was slow, necessitating intra-articular corticosteroid injection and the addition of sulfasalazine (1 g twice daily, equivalent to 40 mg/kg/day). Sulfasalazine was eventually discontinued because of an allergic reaction. She responded to diclofenac (50 mg three times daily, 3 mg/kg/day) and physical therapy. After 2 years the patient discontinued her medications, but again had a subsequent disease flare involving the left knee. This responded to intra-articular corticosteroid injection and piroxicam 20 mg daily. She did well for 2 years.

When her joint complaints recurred, subcutaneous etanercept (Enbrel®, Immunex Corporation, Thousand Oaks, CA, USA) 25 mg twice weekly was started. She had a good response and required only occasional NSAID use. At 1 year after starting etanercept, she experienced a flare of her bilateral anterior uveitis, treated initially with topical corticosteroid (Pred Forte®, Allergan, Irvine, CA, USA) and mydriatic eye drops. She failed to respond and was started on oral prednisone 30 mg twice daily and weekly methotrexate (with folic acid). She tolerated high-dose prednisone poorly, experiencing emotional disturbance, difficulty sleeping, and a fainting episode. Poor medication compliance and residual intraocular inflammation persisted for several months, and she ultimately required a subtenon corticosteroid injection. Owing to the fact that active eye disease continued, she was switched from etanercept to subcutaneous adalimumab (40 mg weekly). Her uveitis improved dramatically. The patient was weaned from prednisone, and methotrexate was tapered to dosing every other week, except for a brief period of weekly administration for a mild uveitis flare. She experienced a uveitis

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flare 1 year later; this was related to noncompliance and quickly resolved when adalimumab therapy was resumed. Her disease remained well-controlled for nearly 3 years with prednisone (5 mg daily), adalimumab (40 mg weekly), subcutaneous methotrexate (20 mg weekly), and diclofenac (3 mg/kg/day).

In 2007, she again became noncompliant and experienced a severe anterior uveitis flare. Weekly adalimumab and subcutaneous methotrexate with low-dose prednisone and diclofenac again brought the inflammation under control.

## Discussion

Although the majority of childhood uveitis is idiopathic, the most commonly associated disease is JIA [1]. Uveitis is one of the most serious complications of JIA. It is a chronic, non-granulomatous inflammation, most often affecting the anterior chamber of the eye. JIA-associated uveitis is clinically subtle, often asymptomatic, and requires the use of a slit-lamp examination for diagnosis. In the absence of adequate screening, it is typically the development of visual impairment or synechiae that brings the condition to the attention of the patient or caregiver. In the evaluation of uveitis patients, it is important to determine whether there is an underlying systemic disease that may accompany or cause the ocular inflammation, or if there is an infectious etiology. The presence of posterior or panuveitis with accompanying arthritis should raise the possibility of alternate diagnoses. The most common infectious etiology of uveitis in children is parasitic [1].

Occasionally, JIA-associated uveitis may be detected prior to the onset of arthritis, but in the absence of synechiae it can only be recognized by ophthalmological examination with slit-lamp microscopy [2]. Signs of uveitis include the presence of inflammatory cells and protein (termed "flare") in the aqueous humor of the anterior chamber. Overall, 15–20% of such patients may develop uveitis [3,4]. ANA-positive young girls with oligoarticular JIA have the greatest frequency of JIA-associated uveitis [5,6]. Uveitis is observed less often in polyarticular-course JIA and is an atypical finding in systemic-onset disease. Owing to the well-documented association between JIA, ANA positivity, and uveitis, recommendations for screening have been well-established. Frequency of screening is based upon risk stratification by age at onset of arthritis, subtype of JIA, disease duration, and ANA status [7].

Sequelae of chronic uveitis may include synechiae, band keratopathy, cataracts, glaucoma, and, ultimately, blindness [8]. Treatment of uveitis has typically followed a stepwise approach, beginning with topical corticosteroid preparations [9]. A topical mydriatic agent may be added to induce pupillary dilation and prevent the development of posterior synechiae. Uveitis refractory to topical steroids may require oral or even intraocular corticosteroid therapy. However, the use of corticosteroids carries a risk of cataracts and glaucoma, in addition to a myriad of extraocular complications, making alternate, steroid-sparing immunosuppressive therapies preferable. A number of steroid-sparing regimens have been utilized, including methotrexate, cyclosporine, azathioprine, mycophenolate mofetil, cyclophosphamide, chlorambucil, and daclizumab [9,10]. None of these agents has demonstrated consistent success.

Recent evidence suggests that tumor necrosis factor-α (TNF-α) plays a role in the pathogenesis of uveitis. The sera and aqueous humor of patients with uveitis has been shown to contain high levels of TNF-α, with the highest levels present in the sera [11]. Serum TNF-α levels correlate with uveitis, suggesting a greater systemic than local role for TNF-α [11]. Although this has been borne out with TNF inhibition using a p55 TNF-α receptor protein in experimental models of ocular inflammation [12], similar success has not been consistently observed with the use of etanercept or infliximab for childhood uveitis [13–19]. However, of the two agents, infliximab appears to be more effective in certain patients [20,21]. A 2001 study of 10 children with JIA-associated uveitis failed to show efficacy of etanercept compared with placebo [14].

Adalimumab is a recombinant human immunoglobulin 1 (IgG1) monoclonal antibody specific for human TNF-α. It binds circulating TNF-α and blocks its interaction with the p55 and p75 cell surface TNF-α receptors. The patient described in this report was treated with weekly dosing of adalimumab, which may provide more consistent inhibition of TNF-α than intermittent administration of infliximab [22]. A 2006 case series from our institution of 14 children with refractory JIA-associated and idiopathic uveitis treated with adalimumab showed improvement of intraocular inflammation in 80% of eyes, with 15% remaining stable, and only one patient with worsening disease over an 18-month follow-up period [23]. No adverse events were encountered [23]. Additional reports support the increased efficacy of adalimumab [24,25].

With the use of all immunosuppressive therapies, infection- and medication-related complications must be monitored. Rigorous screening for infection (including tuberculosis), and monitoring of laboratory parameters, is essential for patients on these medications. As with any chronic illness, the care of children and adolescents with uveitis presents a challenge to treating physicians. Because uveitis flares may be asymptomatic, the need for medication, including occasional corticosteroids with their undesirable cosmetic side effects, can be difficult to impress upon patients, particularly in the adolescent population. Among adolescents with chronic disease, the course is often complicated by patient fatigue and medication noncompliance. Even in the best

patient–physician partnership, the adolescent may fail to comply with medical instructions. This is a particular risk with uveitis, which may be difficult to get back under control following a medication "holiday". The need for effective steroid-sparing agents is of particular importance for this population in which body image issues often take priority.

Our experience indicates that adalimumab is potentially a more useful therapy for childhood uveitis than either etanercept or infliximab. However, larger, placebo-controlled studies will be needed to fully demonstrate the efficacy of adalimumab for idiopathic and JIA-associated uveitis. Comparisons with the other anti-TNF-α agents will need to be made in a blinded fashion. The case presented indicates the difficulty of dealing with the chronic nature of this illness, patient compliance, and the dramatic response of refractory JIA-associated uveitis to adalimumab therapy.

## Disclosures

Dr Lehman is a member of the speakers bureau for Abbott. Dr Adams has no relevant financial interests to disclose.

## References


1. BenEzra D, Cohen E, Maftzir G. Uveitis in children and adolescents. *Br J Ophthalmol* 2005;**89**:444–8.
2. Kanski JJ. Anterior uveitis in juvenile rheumatoid arthritis. *Arch Ophthalmol* 1911;**95**:1794–7.
3. Cassidy JT, Brody JL, Martel W. Monoarticular juvenile rheumatoid arthritis. *J Pediatr* 1967;**70**:867–75.
4. Bywaters EG, Ansell BM. Monoarticular arthritis in children. *Ann Rheum Dis* 1969;**24**:116–22.
5. Cassidy JT, Levinson JE, Bass JC et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. *Arthritis Rheum* 1986;**29**:274–81.
6. Cassidy JT, Sullivan DB, Petty RE. Clinical patterns of chronic iridocyclitis in children with juvenile rheumatoid arthritis. *Arthritis Rheum* 1977;**20**(Suppl):224–7.
7. Cassidy J, Kivlin J, Lindsley C et al. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics* 2006;**117**:1843–5.
8. Rosenberg KD, Feuer WJ, Davis JL. Ocular complications of pediatric uveitis. *Ophthalmol* 2004;**12**:2299–306.
9. Jabs DA, Rosenbaum JT, Foster CS et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000;**130**:492–513.
10. Papaliodis GN, Chu D, Foster CS. Treatment of ocular inflammatory disorders with daclizumab. *Ophthalmology* 2003;**110**:786–9.
11. Santos Lacomba M, Marcos MC, Gallardo Galera JM et al. Aqueous humor and serum tumor necrosis factor-alpha in clinical uveitis. *Ophthalmic Res* 2001;**33**:251–5.
12. Dick AD, Duncan L, Hale G et al. Neutralizing TNG alpha activity modulates T cell phenotype and function in experimental autoimmune uveoretinitis. *J Autoimmun* 1998;**11**:255–64.
13. Joseph A, Raj D, Dua HS et al. Infliximab in the treatment of refractory posterior uveitis. *Ophthalmology* 2003;**110**:1449–53.
14. Reiff A, Takei, S, Sadeghi S et al. Etanercept therapy in children with treatment-resistant uveitis. *Arthritis Rheum* 2001;**44**:1411–5.
15. Falappone PC, Iannone F, Scioscia C et al. The treatment of recurrent uveitis with TNF alpha inhibitors. *Reumatismo* 2004;**56**:185–9.
16. El-Shabrawi Y, Mangge H, Hermann J. Anti-tumor necrosis factor alpha treatment in chronic recurrent inflammation of the anterior segment of the eye in patients resistant to standard immunomodulatory treatment. *Ann Rheum Dis* 2003;**62**:1243–4.
17. Mangge H, Heinzl B, Grubbauer HM et al. Therapeutic experience with infliximab in a patient with polyarticular juvenile idiopathic arthritis and uveitis. *Rheumatol Int* 2003;**23**:258–61.
18. Smith JR, Levinson RD, Holland FN et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthrits Rheum* 2001;**45**:252–7.
19. Smith JA, Thompson DJ, Whitcup SM et al. A randomized, placebo controlled, double masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005;**53**:18–23.
20. Foeldvari I, Nielsen S, Kummerle-Deschner J et al. Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. *J Rheumatol* 2007;**34**:1146–50.
21. Rajaraman RT, Kimura Y, Li S et al. Retrospective case review of pediatric patients with uveitis treated with infliximab. *Ophthalmology* 2006;**113**:308–14.
22. Nestorov I. Clinical pharmacokinetics of TNF antagonists: how do they differ? *Semin Arthritis Rheum* 2005;**34**(Suppl 1):12–8.
23. Vazquez-Cobian LB, Flynn T, Lehman TJ. Adalimumab therapy for childhood uveitis. *J Pediatr* 2006;**149**:572–5.
24. Biester S, Deuter C, Michels H et al. Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007;**91**:319–24.
25. Gallagher M, Quinones K, Cervantes-Castaneda RA et al. Biological response modifier therapy for refractory childhood uveitis. *Br J Ophthalmol* 2007;**91**:1341–4.

# CLINICAL REVIEWS

## Commentary and Analysis on Recent Key Papers

**Clinical reviews were prepared by Tom Huizinga, MD, Peter Nigrovic, MD, Eric Ruderman, MD, and Hendrik Schulze-Koops, MD**

## EPIDEMIOLOGY

### Hospitalizations and mortality in systemic sclerosis: results from the Nationwide Inpatient Sample

Chung L, Krishnan E, Chakravarty EF.
*Rheumatology (Oxford)* 2007;**46**:1808–13.

While in-hospital mortality in scleroderma patients is both age- and gender-related, the presence of pulmonary fibrosis has an impact across all categories.

Recent advances in the management of scleroderma patients, including the use of angiotesin-converting enzyme inhibitors to treat renal crisis, cyclophosphamide to treat early alveolitis, and multiple agents to treat pulmonary arterial hypertension, have led to improvements in survival rates. It seems likely that these same treatments have also resulted in changes in hospitalization patterns, but the last large study of hospitalization patterns in this disease used data from 1995 [1], prior to the impact of many of these advances.

The authors of the current study used data from a 2002 and 2003 nationwide inpatient survey to study the causes and patterns of hospitalization and mortality in scleroderma patients. They selected patients with a discharge diagnosis of limited or diffuse scleroderma (International Classification of Disease 9 [ICD 9] code 710.1) and excluded those with a concomitant diagnosis of rheumatoid arthritis or systemic lupus erythematosus.

Patients admitted with a diagnosis of scleroderma had an in-hospital mortality rate of 6.3%. Mortality rates increased with age, but were lower for women than for men of comparable age. Scleroderma was the most common principal diagnosis for both hospitalization and for those patients who died. Pulmonary fibrosis was the most common secondary diagnosis for admission, and respiratory failure was the second most common diagnosis in those who died. The presence of pulmonary fibrosis led to an increased length of stay in hospital, and increased the risk of in-hospital death by nearly three-fold.

The findings of this study highlight the importance of pulmonary fibrosis as a predictor of poor hospital outcome in patients with scleroderma, suggesting the possibility that more effective therapies for this particular complication of disease will have a positive impact on mortality.

1. Nietert PJ, Silverstein MD, Silver RM. Hospital admissions, length of stay, charges, and in-hospital death among patients with systemic sclerosis. *J Rheumatol* 2001;**28**:2031–7.

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### The widening mortality gap between rheumatoid arthritis patients and the general population

Gonzalez A, Maradit Kremers H, Crowson CS et al.
*Arthritis Rheum* 2007;**56**:3583–7.

Patients with rheumatoid arthritis (RA) are at an increased risk of mortality compared with the population as a whole. The present authors investigated whether declining mortality rates in the general population have translated into improved survival in RA patients. In fact, they found that the mortality rate in patients with RA remained constant among patients diagnosed between 1955 and 2000, resulting in an expanding "mortality gap" between patients with RA and the rest of the population.

To examine whether improving overall mortality rates among the general population is reflected in patients with rheumatoid arthritis (RA), the present authors examined an inception cohort of 822 adult patients who received a diagnosis of RA in Olmsted County, MN, USA, between 1955 and 2000. Mortality was assessed through to January 1, 2007, by longitudinal tracking using a variety of publicly available data sources. Mortality rates adjusted for age, sex, and disease duration were compared with expected rates of death for the local population as a whole, obtained from statistics compiled by a government agency. While the population mortality

declined strikingly from 1965 to 2000 (in women, from 1.0 to 0.2 per 100 person-years; in men, from 1.2 to 0.3 per 100 person-years), mortality among patients with RA remained roughly constant at 2.4 per 100 person-years for women and 2.5 per 100 person-years for men. The causes of death are not described in the article. Since much of the improved survival in the general population resulted from declining rates of cardiovascular death, and patients with RA are known to be at elevated cardiovascular risk, the authors speculate that improvements in cardiovascular care may not have been as effective in RA patients as in the general population.

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### Five-year outcome of a primary-care-based inception cohort of patients with inflammatory polyarthritis plus psoriasis

Morgan C, Lunt M, Bunn D et al.
*Rheumatology (Oxford)* 2007;**46**:1819–23.

Results from this analysis of a primary care-based inception cohort of patients with inflammatory arthritis suggest that psoriasis patients with inflammatory arthritis have similar outcomes to other rheumatoid factor-negative, inflammatory arthritis patients.

From the time that psoriatic arthritis (PsA) was first recognized as a distinct entity from rheumatoid arthritis (RA), rheumatologists have speculated as to whether this disease has a worse prognosis than RA. The recent development of the Classification of Psoriatic Arthritis (CASPAR) criteria for the diagnosis of PsA will enable better outcome and prognostic studies of a defined population of patients, which will have obvious implications for therapy. In the meantime, the authors of this article have used an existing primary cohort of inflammatory arthritis patients to examine the outcomes of those with concomitant psoriasis.

The Norfolk Arthritis Register (NOAR) is a primary care-based inception cohort of patients with new inflammatory arthritis treated by both general practitioners and rheumatologists. Patients were initially evaluated by a research nurse, who collected baseline demographics, laboratory test results, and health assessment questionnaires (HAQs), and performed a structured joint examination. Patients were assessed annually for 5 years, and then had a follow-up joint examination, radiographs, and completed questionnaires at 5 years. During the period 1990–1994, 834 patients with inflammatory arthritis were enrolled in the cohort, 79 of whom had psoriasis and formed the basis of the current analysis.

Overall, the patients with psoriasis were more likely to be male and were younger at symptom onset than those who did not have psoriasis, although the latter was not statistically significant. They were also more likely to be rheumatoid factor (RF)-negative. At the 5-year follow-up assessment, the patients with psoriasis remained more likely to be RF negative, although a similar proportion of psoriasis and non-psoriasis subjects fulfilled 1987 American College of Rheumatology criteria for RA. There was no difference between the two groups in the number of tender, swollen, or deformed joints, or in the proportion with radiographic erosions, although the patients who did have erosions had lower Larsen scores. Those with psoriasis were statistically just as likely to be receiving disease-modifying antirheumatic drug (DMARD) therapy, but the delay to receiving the first DMARD was longer (18 months vs. 9 months).

When the analysis was restricted to the 58 psoriasis patients and the 475 others who were RF-negative, the results were similar, including the finding of relatively less damage in the patients with erosive disease. After adjustment for age, gender, and treatment, the patients with psoriasis remained less likely to be RF-positive and had lower Larsen scores. The authors concluded that patients with inflammatory arthritis plus psoriasis have similar outcomes to other RF-negative inflammatory arthritis subjects. Pending the results of large studies using the CASPAR criteria to define PsA, this type of data suggests that these patients should be treated similarly to other inflammatory arthritis patients.

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## PROGNOSIS AND ASSESSMENT

### Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies

Svenson M, Geborek P, Saxne T et al.
*Rheumatology (Oxford)* 2007;**46**:1828–34.

Specific and neutralizing anti-infliximab antibodies can develop in rheumatoid arthritis patients treated with infliximab. The current investigators found that the presence of these antibodies is associated with low trough levels of functional infliximab. This suggests that in patients who experience a disease flare on infliximab, measurement of anti-infliximab antibodies could be used to preclude inappropriate use of the drug.

A disease flare in patients treated with an anti-tumor necrosis factor (TNF) agent poses the problem of whether treatment adaptation (e.g. switching to another anti-TNF drug), changing to an agent with another mechanism of action, or continuation of the drug alongside a treatment for the flare (e.g. with local steroids), would be the best option. With regard to infliximab, it is possible that assessment of its bioavailability and immunogenicity could be used to guide treatment decisions.

Infliximab is a mouse–human immunoglobulin G1 (IgG1)/κ chimeric antibody, and it is known that anti-infliximab antibodies may develop during treatment. These anti-infliximab antibodies are predominantly IgG and, in this analysis, 36% were of the IgG4 subclass. Antibody titers were associated with inhibition of TNF binding to the drug, and low trough levels of infliximab were most frequent in anti-infliximab antibody-positive sera. Cross-binding to two other anti-TNF drugs, etanercept and adalimumab, was not observed.

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## Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers

Young-Min S, Cawston T, Marshall N et al.
*Arthritis Rheum* 2007;**56**:3236–47.

The process of joint destruction is, in theory, reflected by the presence in body fluids of breakdown products of collagen or cartilage, and synovial and immune cell metabolism. Indeed, in this longitudinal study involving 118 rheumatoid arthritis (RA) patients who were followed for 2 years, levels of matrix metalloproteinase-3 (reflecting breakdown of collagen) and C-telopeptide of type II collagen (reflecting collagen cleavage in cartilage) predicted radiographic outcome in RA. It is to be expected that models consisting of biomarker concentrations will eventually help clinicians in chosing treatment options for patients with RA.

In this study, the performance of biochemical and traditional markers in the prediction of radiographic progression was evaluated in 132 patients with early rheumatoid arthritis (RA). Serum levels of matrix metalloproteinase-1 (MMP-1), MMP-13, and MMP-3 (all enzymes that digest collagen), tissue inhibitor of metalloproteinases-1 (TIMP-1; the local inhibitor of MMPs), and cartilage oligomeric matrix protein (COMP; a breakdown product of cartilage) were assessed. The presence of pyridinoline (Pyr) and deoxypyridinoline (both markers of collagen breakdown), glycosylated Pyr (a marker of synovial metabolism), and C-telopeptide of type II collagen (CTX-II) in urine was assessed. Radiographic damage worsened during the 2-year assessment period in 50 patients, while 68 patients had no radiographic progression. Levels of a variety of biochemical markers, such as MMP-3, CTX-II, COMP, TIMP-1, Pyr, and glycosylated Pyr correlated significantly with radiographic progression. In a multivariate analysis, a model including MMP-3 and CTX-II was identified as providing the best prediction of radiographic progression at entry, while a combination of MMP-3, CTX-II, and swollen joint count formed the best longitudinal area under the curve model for analyzing the parameters measured at fixed time points during the first 2 years.

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## Evidence for a different anatomic basis for joint disease localization in polymyalgia rheumatica in comparison with rheumatoid arthritis

Marzo-Ortega H, Rhodes LA, Tan AL et al.
*Arthritis Rheum* 2007;**56**:3496–501.

Magnetic resonance imaging of rheumatoid arthritis (RA) and polymyalgia rheumatica (PMR) shows similar synovial changes in both diseases, but more prominent extra-capsular soft tissue inflammation was observed in PMR than in RA.

Rheumatoid arthritis (RA) and polymyalgia rheumatica (PMR) are both believed to be diseases of chronic synovial inflammation, yet the former is associated with progressive joint destruction while the latter is characterized by the absence of joint destruction and a good prognosis. The authors put forward that these clinical differences may suggest a difference in the anatomical location of the disease process, and that magnetic resonance imaging (MRI) may be useful in identifying and evaluating this difference.

The investigators recruited patients from an early arthritis clinic and compared 10 patients who had meta-carpophalangeal (MCP) synovitis and who met 1987 American College of Rheumatology criteria for RA with 10 patients who had newly diagnosed PMR and MCP swelling. The groups were balanced for gender, with five men and five women in each group. Each patient underwent both conventional MRI and dynamic contrast-enhanced MRI of the affected joints.

Upon review of the MRI scans, no significant differences were seen in the volume of synovitis, the degree of flexor tenosynovitis, the degree of bone edema, or in the extent of periarticular erosions. However, extra-capsular soft tissue

enhancement was seen in 100% of the PMR patients, but only in 50% of the RA patients, suggesting that inflammation is more prominent in these tissues in the former condition.

The finding of prominent extra-capsular inflammation in PMR is perhaps not unexpected given the symptomatic presentation of this disease, with prominent muscle stiffness and pain, but the presence of erosive change and bone marrow edema comparable to that seen in RA is somewhat surprising. The authors suggest that the fact that these changes do not progress to radiographic erosions may be due to the exquisite sensitivity of PMR to corticosteroids, with a rapid resolution of the inflammatory process that might otherwise lead to erosions. Nonetheless RA is also quite sensitive to corticosteroids, and yet most RA patients do progress to develop radiographic erosions; thus, there may be other factors at work as well.

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## Finger tendon disease in untreated early rheumatoid arthritis: a comparison of ultrasound and magnetic resonance imaging

Wakefield RJ, O'Connor PJ, Conaghan PG et al.
*Arthritis Rheum* 2007;**57**:1158–64.

Both ultrasound and magnetic resonance imaging are useful tools for assessing tendon sheath inflammation in early rheumatoid arthritis (RA) although, as determined in this assessment of 50 patients with RA, the latter is more sensitive.

Most clinical rheumatologists have encountered rheumatoid arthritis (RA) patients who, despite control of erosive disease, develop progressive deformities and disability due to ligament and tendon changes in the hands. As treatment to prevent erosive damage improves, the relative clinical importance of tendon involvement in RA is likely to increase.

In this, the first comparative study using ultrasound and magnetic resonance imaging (MRI) to evaluate tendon pathology in early RA, 50 patients with RA underwent both ultrasound and MRI examinations of their second through fifth metacarpophalangeal (MCP) joints. Their results were compared with the ultrasound scans of 20 healthy control subjects.

None of the controls had tenosynovitis on ultrasound. Among the 50 RA patients, 28.5% of 200 joints in 24 patients had flexor tenosynovitis on ultrasound, compared with 64% of 200 joints in 41 patients on MRI. As might be expected in early RA, extensor tenosynovitis was less common, being present in 7% of the joints in nine patients on ultrasound and 40% of the joints in 36 of the patients on MRI. The second and third MCP joints were the most frequently involved joints in both studies.

Data on the prevalence of tenosynovitis in RA vary widely, and there are few data on the prevalence in early disease. The authors conclude that both ultrasound and MRI may be useful methods of assessing tendon disease in early RA, with MRI being the more sensitive methodology.

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## Rheumatoid arthritis bone erosion volumes on CT and MRI: reliability and correlations with erosion scores on CT, MRI and radiography

Døhn UM, Ejbjerg BJ, Hasselquist M et al.
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The authors of this study investigated bone erosion volumes in the metacarpophalangeal joints of patients with rheumatoid arthritis. The results reveal high intra- and intermodality agreement between computed tomography and magnetic resonance imaging methods, and good correlation with erosion scores.

In recent years, magnetic resonance imaging (MRI) has evolved as a new method for diagnosing and monitoring rheumatoid arthritis (RA). There is some evidence to suggest that quantitative assessment of bone erosion volumes with MRI is helpful in documenting destructive changes in the joints of RA patients. Since only sparse information is available on the evaluation of bone erosion volumes using MRI compared with an external reference, new data comparing MRI with computed tomography (CT) and correlating volume measurements with erosion scores are needed to clarify the diagnostic value of MRI-based erosion volume quantification.

In this prospective study, 17 RA patients and four healthy control subjects underwent MRI, CT, and radiography of the second through fifth metacarpophalangeal (MCP) joints of one hand. The volumes of the erosions detected on MRI and CT were measured after manual outlining by a blinded expert using the OSIRIS imaging software (Digital Imaging Unit, Radiology Departmemt, University of Geneva, Geneva, Switzerland) with a 1-week interval between assessments. The results were compared with erosion scores obtained by standard measures, e.g. the Outcome Measures in Rheumatology Clinical Trials/Rheumatoid Arthritis Magnetic

Resonance Imaging Score (OMERACT RAMRIS) grading system. Radiographs were scored according to the Sharp/van der Heijde method.

Whereas no erosion was seen in control subjects, CT, MRI, and radiography detected 77, 62, and 12 erosions, respectively, in the MCP joints of RA patients. The mean volume per erosion was 30 $mm^3$ (median 18 $mm^3$, range 1–163 $mm^3$) on MRI and 26 $mm^3$ (10 $mm^3$, 0–248 $mm^3$) on CT. The total erosion volumes per patient were 90 $mm^3$ (46 $mm^3$, 0–389 $mm^3$) on MRI and 97 $mm^3$ (29 $mm^3$, 0–485 $mm^3$) on CT. Spearman correlation coefficients calculated between CT and MRI erosion volumes and corresponding OMERACT RAMRIS erosion scores showed a close correlation for single erosion volumes (MRI 0.99, CT 0.97; both $p<0.01$) as well as for total erosion volumes (MRI 0.91, CT 0.98; both $p<0.01$). Radiographic Sharp/van der Heijde erosion scores of the MCP joints also correlated, although to a lesser extent, with the volume of erosions measured by MRI and CT (0.63 and 0.65, respectively; both $p<0.01$). For single and total erosion volumes, high intramodality agreement for MRI (0.95–0.98) and CT (0.96–0.99) as well as high intermodality agreements for MRI versus CT were demonstrated (0.89–0.64).

The authors concluded that erosion volume measurements on CT and MRI are highly reproducible and closely correlated. This, and the good correlation with the well-validated OMERACT RAMRIS score, supports the reliability of MRI in estimating sizes of bone erosions; thus it may be potentially valuable in longitudinal studies as an outcome measure of structural joint damage.

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## Microscopic measurement of inflammation in synovial tissue: inter-observer agreement for manual quantitative, semiquantitative and computerised digital image analysis

Rooney T, Bresnihan B, Andersson U et al.
*Ann Rheum Dis* 2007;**66**:1656–60.

Quantitative, semiquantitative, and computerized digital image analysis of microscopic measurement of inflammation in synovial tissue from rheumatoid arthritis patients showed strong interobserver agreement in the present multicenter study.

The microscopic measurement of inflammation in synovial tissue can be used to examine various parameters such as cell populations and cytokines, which relate to disease activity, severity, and outcome in rheumatoid arthritis (RA). Thus, several techniques have been employed to assess these parameters, namely semiquantitative analysis, quantitative analysis, and digital image analysis. To standardize and validate these three methods, the authors performed a study involving six international centers, with paired tissue sections from 12 patients with active RA. T lymphocytes and macrophages infiltrating the synovial sub-lining layer were quantified by staining for CD3 and CD68. Quantitative scores were derived by counting the absolute number of positively stained cells, while semiquantitative analysis was calculated on a five-point scale and computerized digital analysis was performed using AnalySIS software (Soft Imaging Systems, Denver, CO, USA). Validation of the three methods in the different centers was performed by correlation statistics (Spearman's Rho) and single-measure intraclass correlation coefficients (ICCs). A range of interobserver r-values was observed for quantitative (r=0.66–0.97; mean ICC 0.73 for both $CD3^+$ and $CD68^+$), semiquantitative (r=0.64–0.97; mean ICC 0.83 for $CD3^+$ and 0.78 for $CD68^+$), and digital image (r=0.49–0.92; mean ICC 0.79 for $CD3^+$ and 0.58 for $CD68^+$) analysis. Almost all intercenter r-values were highly significant for both $CD3^+$ and $CD68^+$ cell infiltration except the correlation coefficient for digital image analysis of sub-lining $CD68^+$ cell infiltration of one reader pair. ICCs for all three methods derived from scores generated by all participating centers were highly significant, irrespective of the method used or the tissue marker assessed. Furthermore, digital analysis agreed well with both manual techniques, and the observed r-values were again highly significant. The strong interobserver agreement demonstrated for all three analysis techniques for microscopic measurement of synovial inflammation in RA supports further development of these methods as outcome measures in the disease.

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## Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus

Roman MJ, Crow MK, Lockshin MD et al.
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In systemic lupus erythematosus (SLE), atherosclerosis is usually attributed to traditional risk factors. However, some observations in recent years indicate that the presence of SLE itself might be primarily responsible for the genesis and the progression of atherosclerosis.

The goal of the present investigators was to determine whether atherosclerosis, once it is established, progresses

more rapidly in pathients with systemic lupus erythematosus (SLE) than in those without, and whether traditional risk factors such as age at the time of diagnosis, disease duration, or typical biochemical laboratory parameters influence the progression of atherosclerosis.

The study population consisted of 158 patients participating in a longitudinal trial of cardiovascular disease in SLE. All patients met the American College of Rheumatology diagnostic criteria for SLE. Patients were tested for cardiovascular disease risk factors according to the study protocol at baseline and 2–3 years later (the repeat examination was performed at a mean of 34±9 months). The presence of traditional risk factors such as hypertension, diabetes, smoking history, family history of premature myocardial infarction, and fasting lipid profile were determined. At the clinic visits, the patients underwent carotid ultrasonography and echocardiography using a standardized protocol. The presence and extent of atherosclerotic plaques was assessed. Between baseline and follow-up assessments, 77 patients (49%) had no atherosclerosis, 36 (23%) had atherosclerosis without any changes, and 45 (28%) had progressive atherosclerosis. Multivariate determinants of atherosclerosis progression were age at diagnosis (odds ratio [OR] 2.75, 95% confidence interval [CI] 1.67–4.54 per 10 years; p<0.001), duration of SLE (OR 3.16, 95% CI 1.64–6.07 per 10 years; p<0.001), and baseline homocysteine concentration (OR 1.24, 95% CI 1.06–1.44 per µmol/L; p=0.006). SLE patients with stable plaques and progressive plaques differed only in terms of baseline homocysteine concentrations. Atherosclerosis progression was increased across tertiles of homocysteine concentrations (16.2%, 36.4%, and 56.1%; p=0.001), and homocysteine tertile was independently related to progression of atherosclerosis (OR 3.14, 95% CI 1.65–5.95 per tertile; p<0.001). Less aggressive immunosuppressive therapy and lower average prednisone dose were associated with progression of atherosclerosis in univariate, but not multivariate, analyses. Inflammatory markers and lipids were not related to atherosclerosis progression. The study demonstrated that atherosclerosis develops or progresses in SLE (10% per year on average); however, this was only in a minority of patients, and subjects were followed for just the first 3 years after diagnosis. An older age at diagnosis, longer duration of SLE, and higher homocysteine concentrations are independently related to the progression of atherosclerosis. These findings show that aggressive control of SLE and lowering of homocysteine concentrations are potential means of retarding the development and progression of atherosclerosis in SLE.

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## Risk factors for the development of cataract requiring surgery in uveitis associated with juvenile idiopathic arthritis

Sijssens KM, Rothova A, Van De Vijver DA et al.
*Am J Ophthalmol* 2007;**144**:574–9.

The present authors examined a population of patients with uveitis secondary to juvenile idiopathic arthritis (JIA) with the aim of identifying factors associated with an elevated risk of requiring cataract surgery. The principal risk factor was found to be advanced disease at initial examination, manifested by posterior synechia.

Uveitis remains a potentially devastating complication of juvenile idiopathic arthritis (JIA). Recent large surveys have demonstrated that 13–46% of patients with JIA-associated uveitis experience meaningful vision loss, while many require surgery to address complications including glaucoma and cataracts [1,2].

The authors of this study reviewed the records of 53 patients treated for JIA-associated uveitis at one center in The Netherlands from 1990 to 2006. Of this group of patients, 23 required surgery to correct vision-limiting cataracts; this is a high proportion and likely reflects a subset referred for tertiary care. Patients who underwent surgery were compared with those who did not require surgery, with the aim of identifying risk factors for the development of cataract requiring surgery. Posterior synechia at the time of uveitis diagnosis was the strongest risk factor for needing subsequent surgery (hazard ratio [HR] 4.55, 95% confidence interval 1.82–11.11). The onset of uveitis prior to JIA was also a risk factor (HR 2.44) but became non-significant when corrected for the presence of synechia – an expected result because pre-arthritic uveitis is problematic precisely due to the structural injury that may occur before diagnosis. Gender and antinuclear antibody (ANA) status were non-significant as risk factors. Treatment with methotrexate was associated with a reduced risk of requiring surgery and a longer lag time between diagnosis of uveitis and corrective surgery, while treatment with periocular (injected) steroids correlated with an increased need for surgery, but in neither analysis could a causal relationship be inferred, due to obvious potential confounders. The authors do not comment on anti-tumor necrosis factor therapy in their patients.

Together, these data support the importance of aggressive screening for uveitis in patients with JIA before damage occurs, but they shed little light on optimal therapeutic choices.

1. Saurenmann RK, Levin AV, Feldman BM et al. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. *Arthritis Rheum* 2007;**56**:647–57.
2. Heiligenhaus A, Niewerth M, Ganser G et al.; German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology (Oxford)* 2007;**46**:1015–9.

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## Comparison of *in vitro*-specific blood tests with tuberculin skin test for diagnosis of latent tuberculosis before anti-TNF therapy

Sellam J, Hamdi H, Roy C et al.; RATIO (Research Axed on Tolerance of Biotherapies) Study Group.
*Ann Rheum Dis* 2007;**66**:1610–5.

Owing to the possible reactivation of latent tuberculosis infection (LTBI) in patients with RA who are treated with tumor necrosis factor blockers, screening for the presence of LTBI is mandatory prior to the initiation of therapy. To date, the tuberculin skin test (TST) is the only generally accepted test for LTBI detection. However, as the TST has a relatively poor specificity, the authors investigated two *in vitro* blood assays with TB-specific antigens.

The tuberculin skin test (TST) often results in false-positive results in subjects who have previously been vaccinated with Bacille Calmette-Guérin (BCG) and those with environmental mycobacterial exposure. In subjects with autoimmune diseases, the TST may often give false-negative results because of the underlying immunosuppressive therapy. This represents a subsequent risk of tuberculosis (TB) reactivation during anti-tumor necrosis factor (anti-TNF) therapy. The recent identification of genes in the *Mycobacterium tuberculosis* genome that are absent in BCG and in most environmental mycobacteria offers an opportunity to develop more specific tests to investigate *M tuberculosis* infection, in particular latent TB infection (LTBI). Two antigens, culture fibrate protein-10 (CFP-10) and early secretory antigen target-6 (ESAT-6), have been shown to induce a strong cellular immune response in TB patients. Thus, in the present study, the authors aimed to investigate the performance of the anti-CFP-10 and anti-ESAT-6 proliferative and enzyme-linked immunosorbent spot (ELISPOT) assays in the detection of LTBI in patients with autoimmune diseases.

A total of 68 patients (29 rheumatoid arthritis, 25 spondylarthropathy, and 14 Crohn's disease patients) were enrolled in the study before starting anti-TNF therapy. The patients were grouped into those with LTBI (n=35) and those without (n=33) according to the TST result. Radiographic examination confirmed the LTBI diagnosis in six TST-positive patients and detected LTBI in five patients with a negative TST. Mononuclear cells were isolated from the peripheral blood of the patients and the capacity to react to the CFP-10 and/or ESAT-6 was tested by proliferation and the ELISPOT assay. Among the 13 patients with LTBI that was diagnosed independently of TST results, only two demonstrated a negative blood assays result (15.4%) while five had a negative TST result (38.5%). These five LTBI patients with negative TST results all had positive blood assay results. In CFP-10 and ESAT-6 ELISPOT assays, and in the CFP-10 proliferation assay, the results of 10 patients without LTBI but with intermediate TST results (size 6–10 mm) did not differ from those of patients with a TST result ≤5 mm ($p>0.3$), and were lower than the results in those with LTBI ($p<0.05$).

Therefore, anti-TB blood assays are beneficial for LTBI diagnosis in autoimmune diseases. Compared with TST, they showed better sensitivity, giving positive results in five patients with confirmed LTBI and a negative TST. They also demonstrated better specificity, as confirmed by negative blood assay results in the majority of patients who were classed as having a diagnosis of LTBI according to an intermediate TST result. In the absence of radiographic findings of LTBI, blood assays could replace TST in deciding whether anti-TNF treatment can be started.

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# PATHOGENESIS

## Tophaceous joint disease strongly predicts hand function in patients with gout

Dalbeth N, Collis J, Gregory K et al.
*Rheumatology* 2007;**46**:1804–7.

Although gout is a common disorder, its functional consequences have not received a great deal of attention. In this study, it was found that the presence of tophaceous disease strongly predicted impairment of hand mobility and function. This suggests that intensive treatment to lower serum urate levels to <0.36 mmol/L (to achieve tophus regression and to prevent tophaceous disease), may prevent the functional consequences of gout.

Twenty unselected patients with gout were recruited into this study. None of these subjects had an acute gout flare at assessment. Clinical characteristics of gout, including the site and number of tophi, were correlated with hand function as

assessed by the Sollerman hand function test (this measures 20 everyday hand functions such as picking up coins and doing up a zip). The number of joints of the hand with overlying tophi (hand tophus joint count) was the strongest single predictor of the hand function test ($r^2$=0.59), and also predicted the other measures of hand mobility and function. A regression model that included hand tophus joint count, sex, number of gout flares in the preceding 6 months, gout disease duration, and hand tender joint count was found to be a better predictor of the hand function test than hand tophus joint count alone ($r^2$=0.81). Thus, measures of chronic and poorly controlled disease predict hand function in patients with gout, thereby indicating the need for early treatment with urate-lowering drugs.

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## Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists

Curtis JR, Kramer JM, Martin C et al.
*Rheumatology (Oxford)* 2007;**46**:1688–93.

The use of tumor necrosis factor (TNF) blockade in patients with established congestive heart failure (CHF) has been associated with worsening of CHF in some patients. These authors queried a US health insurance claims database to identify patients with rheumatoid arthritis (RA) or Crohn's disease who developed CHF before the age of 50 years in order to assess a possible contributory effect of TNF blockade. No significant effect was discovered, but patient numbers were small.

Tumor necrosis factor (TNF) blockade has been linked to the onset or exacerbation of congestive heart failure (CHF) in patients with systemic inflammatory diseases, but such series cannot provide estimates of incidence or of risk compared with TNF inhibitor-naïve patients. To address this concern with respect to younger patients who are typically at lower risk of CHF, the authors examined a medical and pharmacy administrative claims database from a multistate US healthcare organization to identify patients with rheumatoid arthritis (RA) or Crohn's disease aged <50 years who had received anti-TNF therapy (the authors refer to etanercept and infliximab only) or another immunosuppressive drug (n=4018). Using claims data followed by a multistep medical record review, patients were further screened to identify nine who developed CHF (0.2% of the starting population). Within RA patients, exposure to TNF blockade was associated with a cumulative incidence of CHF of 4.4 per 1000 persons over a mean follow-up of 18 months, compared with one per 1000 for the TNF blocker-unexposed subjects (relative risk [RR] 4.3), but the confidence intervals for these figures overlap widely. In no case does the CHF appear to have come "out of the blue". Associated conditions in the five identified cases of CHF in RA patients treated with TNF blockade include:

- Hypertension, diabetes, or sleep apnea.
- Coronary artery bypass grafting and angioplasty.
- Rheumatoid carditis.
- Pulmonary hypertension and acute myocardial infarction.
- Pre-TNF-blockade therapy with furosemide.

In the Crohn's disease group, the RR of CHF with anti-TNF exposure was 1.2 (also non-significant). In both diseases, patients treated with TNF blockade were clearly more severely affected by their disease than untreated controls, resulting in potential confounding by indication, as the authors highlight. Assuming that the absolute difference in CHF due to TNF blockade in RA is 3.4 cases per 1000, the authors calculate that one additional case of CHF would result from the treatment of 294 patients with TNF blockade (i.e. the number needed to harm [NNH] is 294); however, given the wide confidence intervals and likely confounding in the incidence figures, there can be little confidence in this NNH. Rather, these data suggest that *de novo* CHF is an uncommon complication of TNF blockade in patients under 50 years of age.

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## Systemic autoimmune disease mortality and occupational exposures

Gold LS, Ward MH, Dosemeci M et al.
*Arthritis Rheum* 2007;**56**:3189–201.

Twin studies have implicated environmental as well as genetic factors in the pathogenesis of autoimmune diseases. In this study, the authors examined the contribution of occupational exposures to rheumatic disease using death certificate data. Individuals in whom a rheumatic disease was listed as a contributing cause of death were compared with matched controls. Potentially interesting associations emerged, but the authors caution that these can be regarded only as hypotheses for further investigation given the limitations of the research methodology.

Identical twins are frequently discordant in terms of systemic rheumatic diseases, suggesting that environmental triggers contribute fundamentally to the genesis of autoimmunity. Previous studies have implicated different exposures, such as silica or cigarette smoke, as potentially important environmental stimuli. These authors set out to identify additional occupational or environmental contributors to rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and other systemic rheumatic diseases. An ideal study of such associations would include a large cohort of patients with well-documented occupational and exposure histories (both "on" and "off the job"), and would compare patients with a conclusive diagnosis of a rheumatic disease with control subjects to identify exposures that occurred at a higher than expected frequency prior to the onset of illness. In the current study, these ideal conditions are approximated only incompletely. Occupation data were limited to the single "usual" occupation listed on the death certificate. Exposure to specific candidate agents (e.g. asbestos or silica) was imputed from expected exposures for a given occupation. Recreational exposures could not be assessed. The presence of a rheumatic disease could be identified only if it was listed as a contributor to death and was not otherwise confirmed or excluded. The timing of exposure relative to disease onset could not be ascertained. Each case of a death to which a rheumatic disease was thought to contribute was compared with five controls matched for age, sex, year of death, and geographic region. Almost 53 000 cases were compared with >260 000 controls to assess odds ratios (ORs) for any systemic rheumatic disease, RA, SLE, or SSc across 509 occupations and at least 16 imputed exposures (e.g. silica, pesticides, and contact with the public); that is, at least 2100 separate comparisons.

In this context, the authors report that farming (crop, not livestock) was associated with an increased risk of death from RA (OR 1.4, 95% confidence interval [CI] 1.3–1.5) or SLE (OR 1.3, 95% CI 1.0–1.6). Firefighters were at elevated risk of death from SSc (OR 2.3, 95% CI 1.2–4.5), as were garage or service station employees. Teachers (but not teachers' aides) were at a higher risk of death from autoimmune disease. Imputed exposure to pesticides and animals was associated with an increased risk of death, while silica and solvents were not. Given the multilayered approximations and assumptions underlying these findings, the authors' caution that the results serve simply to generate hypotheses for further investigation is amply justified.

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## Overexpression of human decoy receptor 3 in mice results in a systemic lupus erythematosus-like syndrome

Han B, Moore PA, Wu J et al.
*Arthritis Rheum* 2007;**56**:3748–58.

To explore the possible role of human decoy receptor 3 (DcR3) in the pathogenesis of systemic lupus erythematosus (SLE), transgenic mice with actin promoter-driven expression of human DcR3 were generated in this study. Beyond 5–6 months of age, these DcR-transgenic mice manifested a SLE-like syndrome with various features of the disease.

Decoy receptor 3 (DcR3) is a secreted protein that belongs to the tumor necrosis factor receptor (TNFR) family. It can inhibit apoptosis mediated by Fas, herpes virus entry mediator (HVEM) protein, lymphotoxin β receptor (LTβR), and the death domain-containing receptor DR3 by binding to their ligands, thereby blocking the ligand–receptor interaction.

To examine the role of DcR3 in the pathogenesis of systemic lupus erythematosus (SLE), transgenic mice were generated that expressed human DcR3 driven by the human β-actin promoter. Beyond the age of 4–6 months, transgenic mice developed lymphadenopathy, splenomegaly, and an SLE-like syndrome, with a higher penetrance in females compared with males. Evaluation of immunological parameters revealed abundant autoantibodies against self tissue, antinuclear antibodies, and anti-double stranded DNA antibodies in transgenic mouse serum. Kidney pathology characterized by immunoglobulin G and complement C3 deposition, leukocyturia, proteinuria, and hematuria, as well as liver pathology with periarterial lymphocyte infiltration, was observed. Furthermore, transgenic females showed a higher frequency of leukocytopenia, thrombocytopenia, and anemia, as well as partly developed skin lesions beyond the age of 12 months. As abnormal T cell activation-induced cell death (AICD) is believed to be one of the factors involved in the pathogenesis of SLE, the role of DcR3 in T cell survival after activation was assessed in an *in vitro* model of AICD. This revealed impaired apoptosis in $CD4^+$ and $CD8^+$ transgenic cells. Moreover, resting transgenic $CD4^+$ and $CD8^+$ cells showed reduced Fas ligand (FasL)-induced apoptosis compared with wild-type cells. After addition of exogenous recombinant DcR3 to wild-type cells, a protective dose-dependent effect against FasL-induced apoptosis could be observed. Compatible with these results, the percentage of previously activated $CD4^+$ cells was elevated in the peripheral blood of transgenic mice.

These findings demonstrate that DcR3 overexpression results in a lupus-like syndrome in mice and suggest that DcR3

might promote the survival of CD4+ cells that could be at the core of SLE pathogenesis.

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### Exacerbation of collagen-induced arthritis by oligoclonal, IL-17-producing cells

Roark CL, French JD, Taylor MA et al.
*J Immunol* 2007;**179**:5576–83.

The authors of this study found that a Vγ4/Vδ4 subset of γδ T cells is enhanced in collagen-induced arthritis in mice and strongly contributes to interleukin-17 production and disease progression. Further detailed investigation of the pathogenic role of these cells during chronic autoimmune inflammation might be important for the development of new therapeutic strategies targeting γδ T cells.

The functional importance of γδ T cells (T cells bearing T cell receptors [TCR] composed of γ and δ chains) has been proposed following observations in various disease models. However, the precise role of γδ T cells during autoimmune inflammation remains largely unknown. In this study, the authors investigated the contribution of two main γδ T cell peripheral subsets, Vγ1+ and Vγ4+ cells, to collagen-induced arthritis (CIA), a mouse model of chronic autoimmune inflammation. CIA was induced in DBA/1 mice by two injections of bovine collagen type II (CII). Expansion, activation, and cytokine production of Vγ1+ and Vγ4+ γδ T cells in lymph nodes and affected joints of CIA mice were determined by flow cytometric analysis. Additionally, the disease outcome in mice depleted of either Vγ1+ or Vγ4+ γδ T cells using anti-Vγ1 or anti-Vγ4 immunoglobulins, respectively, was examined.

Mirroring the total increase of γδ T cells in CIA, Vγ4+ γδ T cells were increased in the draining lymph nodes and diseased joints of CIA mice compared with naïve mice. In addition, Vγ4+ γδ T cells showed an activated phenotype ($CD62L^{low}$, $CD44^{high}$, $CD45^{RBlow}$) and up to 60% of Vγ4+ γδ T cells in lymph nodes and 80% of Vγ4+ γδ T cells in diseased joints expressed interleukin-17 (IL-17; a cytokine associated with inflammatory damage in CIA). The number of Vγ4+ IL-17 producers in CIA mice was similar to the number of CD4+ αβ T cells that produced IL-17, suggesting that Vγ4+ γδ T cells are an important source of IL-17 in CIA. In contrast, although increased in lymph nodes (but not in diseased joints) of CIA mice, Vγ1+ γδ T cells did not express activation markers and did not produce IL-17, indicating a specific response of Vγ4+ γδ T cells to CII immunization, in contrast to Vγ1+ γδ T cells. Interestingly, the majority of CIA-elicited Vγ4+ γδ T cells coexpressed Vδ4 and, in contrast to naïve mice, showed limited TCR junctions, suggesting an antigen-driven oligoclonal response. However, the Vγ4/Vδ4 γδ T cells that were expanded in the CIA model were not specific for collagen as in the control mice, and sham immunization with phosphate-buffered saline resulted in a similar increase of activated Vγ4+/Vδ4+ γδ T cells. Importantly, depletion of Vγ4+, but not Vγ1+, γδ T cells reduced CIA disease activity and incidence, and inhibited late production of anticollagen antibodies.

In conclusion, Vγ4+, but not Vγ1+, γδ T cells are pathogenic in CIA and may contribute to disease development. Thus, subsets of γδ T cells might represent an interesting therapeutic target, although more detailed delineation of their role in autoimmune inflammation is necessary.

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## TREATMENT STRATEGIES

### Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up

Ardoin SP, Kredich D, Rabinovich E et al.
*Am J Ophthalmol* 2007;**144**:844–9.

Pediatric rheumatologists commonly use infliximab to treat juvenile idiopathic arthritis (JIA)-associated uveitis, although supportive data remain limited. In this article, the authors report a series of 16 children treated with infliximab for uveitis, many of whom had no underlying autoimmune diagnosis. Infliximab appears to have been effective and well tolerated in the majority of patients.

Infliximab has assumed a prime position among medications used to control severe juvenile idiopathic arthritis (JIA)-associated uveitis, although data to support this practice remain at the case series level. These authors report another such case series – but with a twist.

Among 16 children with chronic non-infectious uveitis (median age 11 years), only five had associated JIA (including one with juvenile psoriatic arthritis). The remaining children had no clear systemic inflammatory disease, yet were started on infliximab after adequate control of ocular inflammation could not be obtained without intolerable doses of systemic steroids. Therapy was typically initiated at 5 mg/kg at weeks 0 and 2, followed by infusions every 4 weeks; 81% were on background methotrexate treatment. The infliximab dose was escalated

at each infusion until the disease was controlled, at which time infusions were spaced as tolerated. After an average 2-year follow-up period, the median dose was 8.2 mg/kg (range 2–12.9 mg/kg) and the median interval between infusions was 5.6 weeks. At 1 year, 64% of patients had no detectable ocular inflammation and another 15% exhibited a substantial decline in inflammation. Almost 70% were able to discontinue topical glucocorticoids. Three patients did not improve with infliximab and received intraocular or systemic steroids. Recurrence of uveitis was relatively common (16 recurrences in 56% of children), and often (in nine out of 16) followed decreases in infliximab dose or interval. Visual acuity remained stable in all children.

These observations continue the encouraging news about infliximab in severe non-infectious uveitis, whether associated with JIA or not.

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## Limited effects of high-dose intravenous immunoglobulin (IVIG) treatment on molecular expression in muscle tissue of patients with inflammatory myopathies

Helmers SB, Dastmalchi M, Alexanderson H et al.
*Ann Rheum Dis* 2007;**66**:1276–83.

Inflammatory myopathies are generally treated with prednisone, azathioprine, methotrexate, cyclosporine, or cyclophosphamide. In open studies involving patients resistant to these treatments, beneficial effects of intravenous immunoglobulin (ivIg) have been reported. The most impressive effect of ivIg has been observed in vasculitis disorders, suggesting that one of its modes of action may be to reduce endothelial cell activation. This small study of treatment-resistant inflammatory myositis patients who underwent muscle biopsies before and after ivIg treatment did not identify any histological correlates with clinical effects of ivIg.

The present study authors aimed to identify a possible mechanism of action of high-dose intravenous immunoglobulin (ivIg) in the treatment of inflammatory myopathies by correlating muscle function with immunological molecules in the skeletal muscle of patients with polymyositis (PM), dermatomyositis (DM), or inclusion body myositis (IBM).

Thirteen treatment-resistant patients – six with PM, four DM, two IBM, and one juvenile DM – were treated with 2 g/kg of ivIg at monthly intervals for 3 months. Improved muscle function was observed in three patients and creatinine kinase levels decreased in five. Analysis of biopsies before and after ivIg treatment found similar levels of T cells, macrophages, major histocompatibility complex (MHC) class I antigen on muscle fibers, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) expression, and membranolytic attack complex (MAC) deposits on capillaries. No correlation between the clinical responses observed and molecular changes was found, which suggests that the clinical effects of high-dose ivIg on muscle function is not mediated by an effect on the infiltrate in the muscle tissue itself.

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## Role of raloxifene as a potent inhibitor of experimental postmenopausal polyarthritis and osteoporosis

Jochems C, Islander U, Kallkopf A et al.
*Arthritis Rheum* 2007;**56**:3261–70.

Sex hormones, specifically the estrogen hormone pathways, are clearly involved in the pathogenesis of rheumatoid arthritis as illustrated by the female:male ratio of the disease being 3:1. Hormone replacement therapy increases the risk of breast and uterine cancer, stroke, and deep-vein thrombosis. An alternative method of interfering in this hormone pathway is through the use of selective estrogen receptor modulators (SERMs) such as raloxifene and its analogues. In the present murine study, the raloxifene analogue LY117018 was found to potently inhibit the progression of arthritis and the associated development of osteoporosis in both a prophylactic and a therapeutic regimen. This illustrates that SERMs may have the potential to become a new class of anti-arthritic drugs.

Estrogen deficiency and rheumatoid arthritis (RA) itself can contribute to the development of generalized osteoporosis in postmenopausal women. Using a murine model of human RA, the effects of a selective estrogen receptor modulator (SERM) – the raloxifene analogue LY117018 – was evaluated in the present study. Treatment with raloxifene dramatically decreased the frequency and severity of arthritis. Effective preservation of bone and cartilage was seen in raloxifene-exposed mice, as demonstrated by increased bone mineral density and decreased serum levels of cartilage breakdown products. Decreased levels of messenger RNA for both tumor necrosis factor-α and receptor activator for nuclear factor-κB ligand (RANKL) in spleen cells from raloxifene-treated arthritic mice indicated

an additional immunosuppressive action of this SERM. These data indicate that raloxifene represents a potential adjuvant treatment for postmenopausal RA.

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### The effects of vigorous exercise training on physical function in children with arthritis: a randomized, controlled, single-blinded trial

Singh-Grewal D, Schneiderman-Walker J, Wright V et al.
*Arthritis Rheum* 2007;**57**:1202–10.

Children with juvenile idiopathic arthritis (JIA) are often deconditioned compared with age-matched controls. In this thoughtfully designed trial, patients with JIA were randomized to high- versus low-intensity exercise programs; fitness and clinical parameters were assessed after 12 weeks. Both regimens were well tolerated. No differences were noted between the groups, but adherence to the high-intensity program – despite every effort by the investigators – was marginal.

Children with juvenile idiopathic arthritis (JIA) are often less physically active than their peers, and may suffer accordingly from deconditioning. Trials in adults with rheumatoid arthritis have identified benefits in strength, endurance, and potentially quality of life, gained from aerobic training. To determine whether there are similar benefits in childhood arthritis, the authors randomly assigned 80 JIA patients aged 8–16 years to a thrice-weekly, 30-min, cardio-karate program with a target heart rate >75% of maximal, versus a control, non-aerobic program based on qigong (a relaxation program similar to tai chi). To optimize adherence, only one weekly session was held with an instructor at a fixed location, while two were performed at home using videotaped instructions. Instructors remained in close contact with subjects to encourage completion of the home program; heart rate monitors were periodically loaned, and small prizes were given for compliance – measures derived from adherence difficulties observed in an earlier pilot trial. Improvement in conditioning was assessed by formal peak oxygen uptake ($VO_{2peak}$) and higher oxygen requirement ($VO_{2submax}$) measurement, and clinical outcome was assessed by validated questionnaires. No adverse effects were observed. No differences in conditioning or health status could be observed between groups after the 12-week duration of the trial. However, subjects assigned to the high-intensity group completed an average of only two sessions per week, and the target heart rate was attained in little more than half of sessions. Both groups experienced a small improvement in physical function, but whether either exercise program accounted for this change could not be determined.

This well-conducted trial highlights the difficulty inherent in motivating subjects to complete an exercise program, but the findings do suggest that moderate exercise is safe in this patient population.

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## MISCELLANEOUS

### The health status of retired American football players: Super Bowl III revisited

Nicholas SJ, Nicholas JA, Nicholas C et al.
*Am J Sports Med* 2007;**35**:1674–9.

In this specific cohort of retired professional American football players, arthritis was common, but no other detrimental impact of their careers on mental or physical health was identified.

Participation in high-impact professional sports, such as American football, has often been presumed to have deleterious effects on health outcomes, including arthritis, although the supporting data for this is limited. The authors of the present study, who have a long history of involvement with professional American football players, use their experience to examine the long-term health outcomes of the players on the winning team from the 1969 Super Bowl American football game.

There were 41 players on the roster for this Super Bowl game, 36 of whom were contacted 35 years after the event (three had died and contact information was not available for two subjects). Those who were contacted completed a short form-36 (SF-36) questionnaire and a medical history questionnaire. They were not examined for this study. Each player's history of American football-related injuries prior to the game was documented from his medical records.

The subjects included in this study had played professional American football for a mean of 8.3±3.8 years. Overall, their physical and mental health scores on the SF-36 were not different from age-matched, US population-based controls. In terms of medical conditions, 24 of the 36 subjects reported arthritis, 13 reported hypertension, and 13 reported chronic low back pain. Those players not reporting arthritis had SF-36 physical health scores that were above normal, while those with arthritis had scores that were no different from population norms. Seven of the 36 players had had a total knee arthroplasty, an outcome that

was statistically more likely in those with a history of major ligamentous knee injuries prior to the Super Bowl game. The overall reported health of this subset, however, was no different from the other subjects. The authors conclude that, in this group of professional American football players, their careers had rendered them prone to arthritis, but had no long-term detrimental effects on their mental or physical health.

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## Smoking and the risk of psoriasis in women: Nurses' Health Study II

Setty AR, Curhan G, Choi HK.
*Am J Med* 2007;**120**:953–9.

Lifestyle modifications associated with improvements in health are more easily achieved if specific data regarding the ensuing benefits are available. The current large analysis of the US Nurses' Health Study II shows that smoking increases the risk of developing psoriasis, and that cessation of smoking leads (albeit with a delay of 10–20 years) to a reduction in this risk. In addition to the well-established positive effects of smoking cessation, this study provides evidence of specific benefit for patients with psoriasis.

In order to prospectively evaluate the risk of smoking on the development of psoriasis, the relationship of smoking status, duration, intensity, cessation, and exposure to secondhand smoke with incident psoriasis was examined over a 14-year time period (1991–2005) in 78 532 women from the US Nurses' Health Study II. A total of 887 incident cases of psoriasis were documented. Compared with those who had never smoked, the multivariate relative risk (RR) of psoriasis was 1.8 (95% confidence interval [CI] 1.5–2.2) for current smokers and 1.4 (95% CI 1.2–1.6) for past smokers. Compared with non-smokers, the multivariate RR of psoriasis was 1.6 (95% CI 1.4–2.0) for those who had smoked 11–20 pack-years and 2.1 (95% CI 1.7–2.5) for those who had smoked ≥21 pack-years. Compared with never-smokers, the multivariate RR of psoriasis was 1.6 for those who quit smoking <10 years ago, 1.3 for 10–19 years ago, and 1.2 for ≥20 years ago. In addition, prenatal and childhood exposure to passive smoke was associated with an increased risk of psoriasis.

In summary, this study provides clear evidence of the association between smoking and the development of psoriasis.

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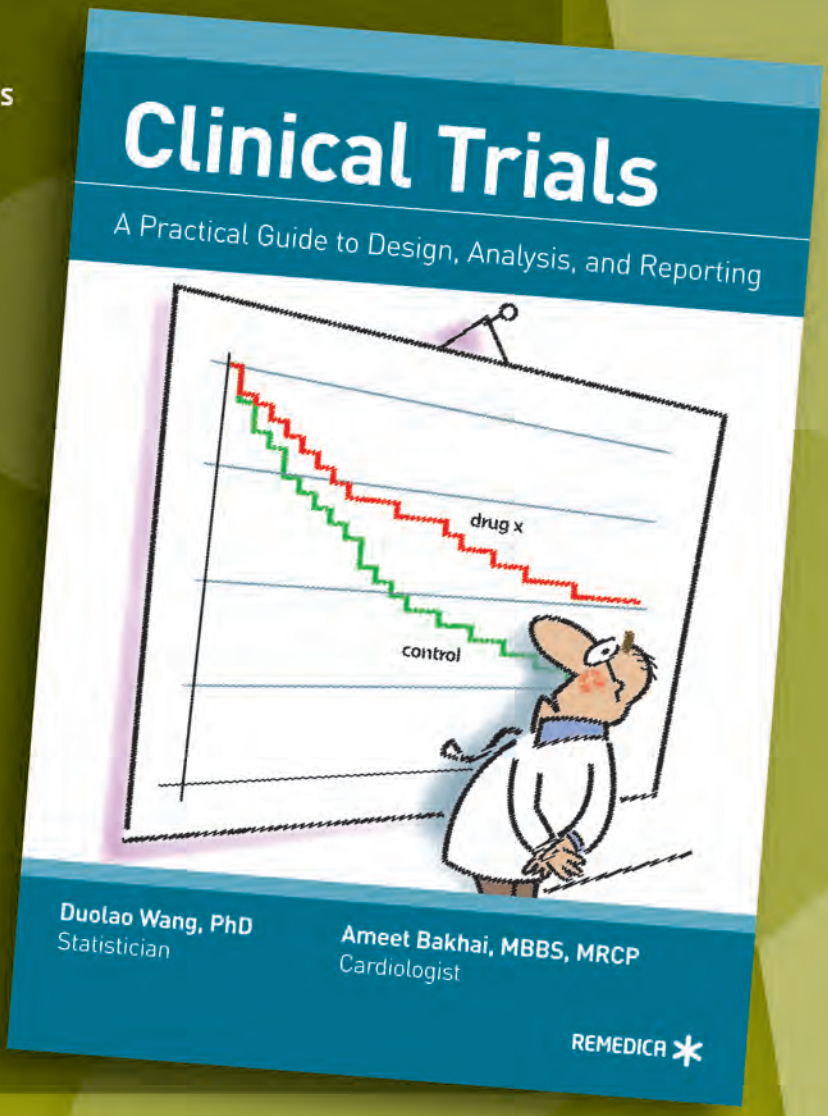


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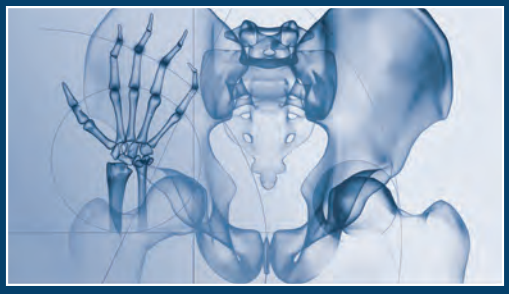

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