Published in final edited form as:
Best Pract Res Clin Rheumatol. 2012 April ; 26(2): 251–261. doi:10.1016/j.berh.2012.03.001.

Advances in the treatment of inflammatory arthritis

David S. Pisetsky[a,b,*] and **Michael M. Ward**[c,1]

[a]Medical Research Service, Durham VA Hospital, 151G Durham VAMC, 508 Fulton Street, Durham, NC 27705, USA

[b]Department of Medicine, Duke University Medical Center, Durham, NC 27705, USA

[c]NIH/NIAMS/IRP, Bethesda, MD 20892, USA

Abstract

The inflammatory arthritides are a diverse group of conditions characterised by joint inflammation which can lead to pain, deformity and disability. Of these diseases, rheumatoid arthritis (RA) and spondyloarthritis are two of the most common. While the clinical and demographic features of these diseases differ, the central role of inflammation in their pathogenesis has allowed the development of highly effective treatment strategies with wide applicability. These strategies include the use of biological agents which target the cytokine tumour necrosis factor (TNF), a key mediator of inflammation. With the advent of effective agents, therapy has become more aggressive, reducing disease activity and allowing, at least in RA, remission in many patients. While the array of available effective treatments is extensive, the use of objective measures of disease activity can guide treatment decisions (treat to target) and lead to improved outcomes.

Keywords

Rheumatoid arthritis; Spondyloarthritis; Ankylosing spondylitis

Introduction

The inflammatory forms of arthritis are a diverse group of conditions characterised by inflammation of the joints and adjacent structures as well as systemic manifestations. Of these diseases, rheumatoid arthritis (RA) and spondyloarthritis are two of the most common. While the clinical and demographic features of these diseases vary, the central role of inflammation in their pathogenesis has allowed the development of highly effective treatment strategies with wide applicability. This article considers recent advances in the elucidation of disease mechanisms as well as innovations in therapy. Importantly, this article emphasises the role of objective measures of disease activity in making treatment decisions and the importance of a ‘treat to target’ strategy to reduce inflammation and damage.

Rheumatoid arthritis

RA is the most common form of chronic inflammatory arthritis. This disease affects women more than men and occurs in as much as 1–2% of the population [1]. As shown in large

*Corresponding author. Medical Research Service, Durham VA Hospital, 151G Durham VAMC, 508 Fulton Street, Durham, NC 27705, USA. Tel.: +1 9192866835; fax: +1 9192866891. dpiset@duke.edu (D.S. Pisetsky), wardm1@mail.nih.gov (M.M. Ward).
[1]Tel.: +1 3014967263; fax: +1 3014020012.

Conflict of interest
There are no conflicts of interest declared by the authors.

genome-wide association studies (GWAS), multiple genes can influence pathogenesis although genes in the major histocompatibility complex have the greatest impact [2]. As in the case of other autoimmune diseases, susceptibility genes likely determine both specific and non-specific immune responses, altering the poise of the immune system to promote autoreactivity. RA affects both large and small joints, the axial as well as peripheral skeleton and extra-articular organs that include the eyes, heart and skin among others. Like other chronic inflammatory diseases, RA is associated with a marked increase in the frequency of cardiovascular disease (CVD), with atherosclerosis becoming a major determinant of outcome [3].

Pathogenesis

While RA is classified as a form of inflammatory arthritis, synovial pathology suggests a complex process that transforms the joint into a site of persistent inflammation and tissue destruction. The normal synovial lining is ordinarily only a few cells thick and is comprised of fibroblastic cells called ‘synoviocytes’ along with macrophages. With RA, the synovial lining expands dramatically in association with disturbed synoviocyte growth to form a structure called ‘pannus’. In this setting, the synovial fibroblast in RA becomes destructive and produces mediators that degrade cartilage and joints [4].

In addition to synoviocyte proliferation, the joint, including the synovial fluid, displays intense inflammation that results from the interplay of B cells, T cells, macrophages and neutrophils, all operating locally to produce cytokines and other pro-inflammatory mediators. Among these mediators, the cytokine tumour necrosis factor (TNF), a product of macrophages and other immune populations, can orchestrate the activity of other cells in the joint, including stimulation of cytokines such as interleukin (IL)-1 [5].

Pointing to a role of autoreactivity in disease pathogenesis, two autoantibodies have major significance as markers for diagnosis and prognosis: rheumatoid factor (RF) and antibodies to citrullinated proteins (ACPAs). A RF is an immunoglobulin (Ig)M antibody to IgG. While considered an autoantibody, RFs may have a physiological function in host defence to potentiate the activity of IgG antibodies. RFs occur commonly in infectious and inflammatory diseases, likely reflecting non-specific immune activation. RFs occur in about 80% of patients with RA. Although sensitive markers for diagnosis, RFs are not specific for RA [1].

In contrast to RFs, ACPAs are highly specific for RA. These antibodies are directed to proteins containing citrulline, a post-translational modification of the amino acid arginine that is mediated by the enzyme peptidyl arginine deiminase (PAD). The role of citrullination is not known, although this modification may result from inflammation. While many citrullinated proteins are autoantigens, current assays involve a synthetic peptide antigen called ‘cyclic citrullinated peptide (CCP) ’ whose composition can be varied to increase the sensitivity of antibody detection. The term anti-CCP is therefore commonly applied to this serological finding since most assays involve antibody binding to the CCP antigen. Depending on the assay, the sensitivity of anti-CCP in diagnosing RA approaches that of RF [6,7].

Studies on the epidemiology of RA indicate a powerful relationship between genetic and environmental factors, with anti-CCP playing an important role. Thus, these studies indicate that smoking may be a trigger for disease, perhaps leading to protein citrullination in the lung because of chronic inflammation [8]. In the presence of certain genes (most prominently genes encoding the shared epitope in the HLA-DR molecule), citrullinated proteins may induce anti-CCP autoantibodies which form immune complexes to drive

immune cell activation and cytokine production. These cytokines can in turn stimulate fibroblasts to proliferate and activate osteoclasts to degrade bone.

Diagnosis of RA

Current treatment paradigms for RA are based on early therapy to decrease inflammation; improve patient quality of life; and reduce pain, disability and joint damage. Key to this paradigm is early diagnosis which, in the clinical setting, is based on the presence of synovitis, as exemplified by joint tenderness and swelling; the presence of RF and/or anti-CCP; and non-specific measures of systemic inflammation such as increased sedimentation rate or levels of C-reactive protein. X-ray evidence of joint destruction includes erosions and/or joint space narrowing and, while these findings can be characteristic of RA, they indicate established disease.

These findings form the basis of new criteria for classification which, interestingly, do not include X-ray findings to increase applicability to early stage disease (Table 1). Classification is based on a total score [9]. Of these findings, anti-CCP is notable since, in some patients, the anti-CCP antibodies can precede the development of arthritis, sometimes by several years [10]. Thus, while anti-CCP is an important diagnostic marker, interpretation of the finding must be made in the context of the overall clinic presentation.

Radiographs are important in documenting arthritis, with plain radiographs traditionally the main modality to evaluate joint damage in the routine clinical setting. Plain radiographs can reveal erosions, which are focal areas of bone loss, as well as joint space narrowing indicative of cartilage destruction. In early disease, however, radiographs may show only soft-tissue swelling and juxta-articular osteopenia. Two other radiographic techniques can provide information to assess arthritis. Magnetic resonance imaging (MRI) allows more complete visualisation of joint structures as well as adjacent bone marrow. Ultrasound imaging can also reveal events in soft tissue and bone and, using Doppler flow methodology, show vascularity of the synovial tissue [11,12].

Principles of RA treatment

The treatment of RA is ideally based on objective measures of disease activity with the goal of reducing, if not eliminating, inflammation to prevent tissue destruction [13,14]. This approach has been termed ‘treat to target’ by analogy with other conditions where the reduction of measures such as blood pressure or cholesterol to a set level is the goal. These measures are of two kinds: measures of disease activity based on joint counts along with laboratory markers of inflammation and questionnaires to assess patient functional status.

Of measures of disease activity, the disease activity scores (DAS) provides a simple score for the intensity of inflammation. While joint involvement of RA is extensive, a commonly used DAS format involves testing of only 28 joints for tenderness and swelling [15]. Joints in this count must allow palpation, eliminating from consideration joints such as the hip and the cervical spine. Furthermore, the 28-joint count does not include the feet, a common site of RA involvement, since swelling and pain in the lower extremity often occurs in the general population. To the joint count in the DAS are added a measure of inflammation (erythrocyte sedimentation rate or C-reactive protein) and a patient global assessment score. The values are introduced into a formula to provide a score.

In contrast to the DAS and related measures, indices such as the health assessment questionnaire (HAQ) rely rather on patient reports of functional ability for common activities of daily life [16]. Each activity receives a score from 0 to 3, with an average calculated. The HAQ and its derivative versions are easy to complete and encourage patient

participation in the process. While the HAQ can correlate with other activity measures, it can be limited with advanced disease when functional disability is fixed.

The range of anti-rheumatic drugs

The therapy of RA involves a wide variety of agents that exert either anti-inflammatory or immunomodulatory activity. These agents can be either small molecules or large molecules. The large molecules include biological agents such as monoclonal antibodies and soluble receptors. These agents can attenuate the signs and symptoms of RA and modify the course of disease as assessed by radiographic progression of bone erosion and joint space narrowing. Those agents that can slow or halt erosion are termed ‘disease-modifying anti-rheumatic drugs’ (DMARDs); sometimes, this term is used for the small molecules as opposed to the biological agents [17–19].

At present, the treatment of RA involves four classes of agents that can be used alone or in combination to reduce disease activity as indicated by the DAS (or related index) or the HAQ (or related index). In clinical trials, imaging is a key part of the assessment; in routine practice, however, imaging is less commonly used to assess treatment effects since quantitation of erosions and joint space narrowing can be difficult and requires special skill. The following are the agents used to treat RA.

(1) *Nonsteroidal anti-inflammatory agents (NSAIDs)*. These agents inhibit the cyclooxygenase (COX) enzymes and can reduce pain and swelling. Most available NSAIDs inhibit both COX I and COX II. According to current models, anti-inflammatory actions relate to the inhibition of COX II while gastrointestinal side effects relate to inhibition of COX I; an increase in CVD appears common among all of these agents. Celecoxib is the only NSAID available in the United States that is selective for COX II. Because of their cardio-renal effects, NSAIDs are used cautiously for prolonged therapy especially in older patients. Furthermore, among non-selective COX inhibitors, gastrointestinal (GI) side effects (bleeding and ulceration) can be significant and require adjunctive measures such as proton pump inhibitors or H2 blockers to reduce risk [20].

(2) *Glucocorticoids*. These agents, of which prednisone is the most commonly used, have broad anti-inflammatory and immunosuppressive activities that result from inhibition of key immune signalling systems such as nuclear factor kappa B (NF-κB). Glucocorticoids are used at widely varying doses both acutely and chronically to control disease activity. When prednisone is used chronically, doses usually are in the range of 5–7.5 mg daily. Some regimens for treating early RA prescribe much higher doses initially (up to 1 mg/kg) to achieve rapid disease control. In addition to the systemic use of glucocorticoids, intra-articular steroids can quell inflammation in single joints [21].

(3) *Small molecule DMARDs*. These agents differ in pharmacological action although they are all orally active and have immunomodulatory effects; in general, the actual mode of action of these drugs is not known [17,19]. Of the group, methotrexate (MTX) has emerged as the preferred orally active agent for initial DMARD therapy. MTX inhibits the enzyme tetrahydrofolate reductase, an essential enzyme for purine synthesis and cell growth and division, but it is used at low doses where expected side effects of cell cytotoxicity such as cytopenias are minimal. This observation has suggested that MTX reduces arthritis by another mechanism such as adenosine release from cells [22].

MTX has become a mainstay of RA treatment and is begun in patients with signs of persistent disease activity and evidence of poor prognosis such as the presence of erosions on radiographs. Doses used range from 7.5 mg to 25 mg each week on a single day although, for some patients, subcutaneous administration may be necessary to achieve adequate bioavailability. The major side effect of MTX is hepatic toxicity which can be associated with fibrosis and even cirrhosis. Frequent monitoring of liver function including albumin is necessary to assess hepatic toxicity and allow dose adjustment [22].

The other small-molecule DMARDs include leflunomide, sulphasalazine, hydroxychloroquine, azathioprine and cyclosporine. These agents can be used as adjuncts or substitutes for MTX, alone or in combination [17,19].

(4) *Biological or large-molecule DMARDs*. The advent of the biological agents has had a major impact on the treatment RA, with TNF blockers achieving widespread use frequently in combination with MTX. The TNF blockers include monoclonal antibodies (infliximab, adalimumab, certolizumab and golimumab) as well as a soluble receptor (etanercept). These proteins can all bind TNF, a potent pro-inflammatory mediator, and block its downstream effects. While these agents are ‘targeted’, the effects of TNF are broad and the step in pathogenesis that is blocked is not clear [17,19].

Well-performed clinical trials indicate that TNF blockers can improve the signs and symptoms of RA and can retard radiographic progression. In some studies, these effects are similar to those of MTX although the effects on radiographic progression appear to be greater and, depending on the agent, benefits can be achieved more rapidly. Importantly, the combination of a TNF blocker and MTX produces benefits greater than either alone, with this combination able to block radiographic progression almost entirely [21–26].

Since many patients with RA can respond well to MTX alone, this agent is still commonly used before a TNF blocker, reflecting cost considerations and greater experience. The major side effects of TNF blockers relate to susceptibility to infection, with tuberculosis (TB) a major concern. Screening for TB is necessary before institution of TNF blockade; for patients who show skin reactivity indicative of TB infection, evaluation for extent of disease and treatment with anti-TB therapy is required before beginning a TNF blocker.

At present, four other biological agents have been approved for the treatment of RA. Two act on cytokines. Anikinra or IL-Ra is a molecularly cloned form of a naturally occurring inhibitor of the pro-inflammatory cytokine IL-1. While blocking IL-1 should be effective in RA, the pharmacologic properties of IL-1Ra as a receptor blocker and the necessity for daily administration of high doses of protein have limited anikinra use; this agent, however, can be very effective in the treatment of auto-inflammatory syndromes and possibly gout. Tocilizumab is an antibody to the IL-6 receptor and can block the effects of IL-6, another potent pro-inflammatory mediator that plays a key role in the acute-phase response [18].

Abatacept is a molecularly cloned product which is a fusion protein of the cytotoxic T lymphocyte-associated (CTLA)-4 molecule with the Fc portion of IgG. Abatacept can block the interaction of the surface molecule CD28 on T cells with the surface molecules B7-1/B7-2, preventing an interaction of T cell with antigen-presenting cells called ‘co-stimulation’. By contrast, rituximab is a monoclonal antibody that can deplete B cells. Despite their different modes of action, both abatacept and rituximab are effective DMARDs and are usually used in patients who have not had an adequate response to other therapies including a TNF blocker, especially in combination with MTX [18].

Treatment paradigm of RA

Given the armamentarium of effective agents to treat RA and the ability to use multi-drug combinations, the number of possible treatments of RA is virtually limitless. In the face of this variety, head-to-head trials of adequate size have not been accomplished and treatment remains empiric. Nevertheless, the effectiveness of reducing disease activity by 'treating to target' appears well established [27–29]. In the application of these approaches, two key issues remain. The first concerns the relative merits of switching drugs as opposed to adding drugs in face of an inadequate response to a single agent (or even a combination). While combination therapy can work better than single agents in large clinical trials, this effect could relate to the benefits gained by the administration of effective agents to a greater number of patients as opposed to additive or synergistic effects of the combination in individual patients.

A second question relates to the continuation of therapy once remission is achieved. This situation is new but has become possible with the availability of so many effective agents. While in established disease (years duration), continued therapy may be needed to maintain a treatment response, early disease (less than a year or two) may have a different pattern of response. There has long been interest in the idea of a 'window of opportunity'; this theoretical window represents a time in which therapy can inhibit or even terminate pathogenetic pathways in RA such that continued therapy is no longer necessary or entails fewer agents or much lower doses. Perhaps, with early treatment, RA will show long-term disease quiescence following an initial intensive therapy [30].

Seronegative spondyloarthritis

Seronegative spondyloarthritis encompasses a family of conditions marked by enthesitis, sacroiliitis and axial inflammatory arthritis, all occurring with increased prevalence in people with the major histocompatibility marker *HLA-B27*. Ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis and arthritis associated with inflammatory bowel disease represent the four major defined diseases in this family, which together affect 0.3–0.6% of the population in Western countries [31,32]. An equally large proportion is thought to have undifferentiated spondyloarthritis, either as a *forme fruste*, with isolated or suggestive manifestations, or early disease not yet advanced enough to meet diagnostic criteria for one of the more specific conditions [32]. Recent genetic discoveries provide a basis for the commonalities among diseases in the spondyloarthritis family, and suggest targets for new treatments distinct from those operative in RA.

Diagnosis of spondyloarthritis

The modified New York criteria are often used in the diagnosis of AS, although they are formally classification criteria rather than diagnostic criteria. Definite AS by these criteria requires either unilateral sacroiliitis of grade 3 or 4 or bilateral sacroiliitis of grade 2 or higher on radiographs, and either inflammatory back pain, limited lumbar range of motion or reduced chest expansion [33]. Radiographic sacroiliac damage of this degree takes many years, often more than 10 years, to develop. Because the New York criteria emphasise chronic changes, they perform very well for classification, with a high specificity for AS. They perform less well in diagnosis, particularly in early disease, when symptoms of inflammatory back pain and enthesitis are present but radiographs are normal or minimally abnormal. The presence of sacroiliac joint inflammation or juxta-articular osteitis on MRI in many symptomatic patients provides evidence that radiographs can be falsely negative early in the course of disease, as do studies demonstrating that the severity of sacroiliac inflammation on MRI predicts subsequent progression to radiographically confirmed AS [34].

Recognition of the inadequacy of current classification criteria to describe the full spectrum of AS in evolution has led to the development of criteria for 'axial spondyloarthritis', which defines AS-spectrum disease without the requirement for radiographically evident sacroiliitis [35]. (Table 2). Using expert physician's diagnosis as the gold standard, the Assessment of Spondyloarthritis International Society (ASAS) criteria for axial spondyloarthritis had a sensitivity of 0.83 and specificity of 0.84. Testing in additional cohorts is needed. The clinical features of patients with early axial spondyloarthritis are generally comparable to those of patients with radiographically confirmed AS, supporting the view that these are phases of the same disease [36].

Inflammatory back pain is a cardinal feature of spondyloarthritis, and differentiating inflammatory from mechanical back pain is a key step to the correct diagnosis. In use since 1977, the Calin criteria for inflammatory back pain are met if at least four of the following features are present: onset before age 40, insidious onset, present for at least 3 months, morning stiffness and improvement with exercise [37]. In a re-evaluation of symptoms of inflammatory back pain, Rudwaleit and colleagues proposed the Berlin criteria, to include at least two of the following: morning stiffness of at least 30 min, improvement with exercise but not rest, awakening with pain in the latter half of the night and alternating buttock pain [38]. These criteria are only to be applied to persons aged 50 or younger who have had low back pain for at least 3 months. These criteria had a sensitivity of 0.70 and a specificity of 0.81 in distinguishing patients with established AS from those with mechanical back pain, although testing in an independent sample was not done. In addition, because the criteria are ultimately intended to be used to aide diagnosis, testing in a sample with early spondyloarthritis is needed to assess their true performance characteristics. A more recent criteria set, based on expert opinion of the presence of inflammatory back pain, and validated in an independent sample with a sensitivity of 0.80 and specificity of 0.72, included four of the following features: onset younger than 40 years, insidious onset, improvement with exercise, no improvement with rest and pain at night [39]. The large overlap among the criteria included in different sets suggests that the core features that characterise inflammatory back pain are agreed upon.

While the above criteria deal with axial disease, some patients with spondyloarthritis have peripheral arthritis, either predominantly or exclusively. Classification of peripheral arthritis as due to spondyloarthritis is improved if the onset is before age 45, if arthritis is asymmetric or involves lower extremity joints, if enthesitis or dactylitis is also present, or if uveitis, psoriasis, inflammatory bowel disease, preceding infection or *HLA-B27* is present [40]. The Classification Criteria for Psoriatic Arthritis (CASPAR) criteria have become widely accepted for the classification of psoriatic arthritis, requiring three or more points among the following for patients with inflammatory arthritis: current psoriasis (two points) or prior psoriasis (one point) or family history of psoriasis (one point); nail dystrophy (one point); absence of RF (one point); dactylitis (one point); or new bone formation on hand or foot radiographs (one point) [41]. The inclusion of the radiographic criteria may reduce the sensitivity of the criteria in early psoriatic arthritis [42]. Applying these criteria, fewer than 10% of patients with psoriasis develop psoriatic arthritis.

Pathogenesis of spondyloarthritis

Although the aetiologies of the different forms of spondyloarthritis are not known, reactive arthritis, in which an environmental exposure (e.g., infection with *Chlamydia trachomatis*) in a genetically susceptible (*HLA-B27* positive) individual leads to immune system activation as well as inflammation in skeletal and extra-skeletal locations, provides a relevant model. Potential inciting environmental exposures are less clear in AS and psoriatic arthritis, although gut or skin infections, perhaps aided by alterations in barrier functions, or abnormal innate immune responses to commensal microorganisms, are leading contenders. Focus on

the role of the gastrointestinal tract in the aetiology of AS is supported by the clinical identity between AS and the axial spondylitis of Crohn's disease or ulcerative colitis, and the high prevalence of subclinical inflammatory bowel disease in patients with AS [43]. Patients with AS not uncommonly also have inflammatory bowel disease-associated antibodies, further supporting the overlap between these conditions [44].

Recent genome-wide association studies (GWAS) in AS have identified 11 gene regions in addition to *HLA-B27* that are associated with susceptibility to AS [45]. The association of *ERAP1* with AS is particularly interesting. *ERAP1* encodes the enzyme endoplasmic reticulum aminopeptidase-1, which functions to trim intracellular peptides to the appropriate length for loading in the binding groove of HLA class I molecules, including HLA-B27, for display on the cell surface and presentation to the immune system. The finding that *ERAP1* is associated with AS supports the often-challenged theory that HLA-B27 is involved in the pathogenesis of AS because of its role in antigen presentation.

Three other genes identified in GWAS, *IL23R*, *IL12B* and *PTGER4*, are also interesting because they regulate molecules involved in the proliferation and survival of Th17 cells. Th17 cells are a unique class of T-helper cells, named for their ability to secrete IL-17, that function in host defence by drawing neutrophils to sites of infection; these cells stimulate the production of TNF-α, IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [46]. Serum levels of IL-17 have been reported elevated in patients with AS. Although more extensive study of the role of Th17 cells in the pathogenesis of AS is needed, the finding of multiple genetic associations suggests this pathway is likely intimately involved.

IL23R, *IL12B*, *PTGER4* and *LTBR-TNFRSF1A* genes are also associated with Crohn's disease, and *IL23R*, *IL12B* and *ERAP1* are susceptibility markers for psoriasis, providing a genetic explanation for the clinical associations between these diseases and AS [47,48]. Th17-associated pathology is abundant in psoriatic skin lesions and the intestines of patients with inflammatory bowel disease, indicating that the genetic associations have direct relevance to immune abnormalities and inflammation in these diseases [49,50].

Principles of spondyloarthritis treatment

As in RA, the goals of treatment in spondyloarthritis are to minimise symptoms, improve or maintain functioning and prevent long-term skeletal damage. Non-pharmacologic treatment includes education in self-management techniques, back exercises to lessen stiffness and improve posture and smoking cessation to reduce the chances of respiratory compromise. Pharmacologic treatment of AS or axial spondyloarthritis is centred on nonsteroidal anti-inflammatory medication for short-term symptom relief, with analgesics, muscle relaxants and sedatives used selectively as adjunctive treatments for residual pain, muscle spasm and sleep disturbance. TNF blockers can be very effective in improving symptoms in patients who do not respond to, or who are intolerant of, non-steroidal anti-inflammatory medications. Etanercept, infliximab, adalimumab and golimumab have been shown in clinical trials to improve symptoms and disease activity, and are approved for the treatment of AS in North America and Europe. No trials have directly compared the efficacy of different TNF blockers in axial spondyloarthritis. Some patients can discontinue treatment without prompt symptom recurrence, but most require reinstitution and continued treatment with TNF blockers long term. MTX is generally not effective in axial spondyloarthritis. Sulphasalazine has limited benefit for axial symptoms, but may help peripheral joint disease.

The treatment of psoriatic arthritis and reactive arthritis generally follows the approach taken for RA. One difference is avoidance of corticosteroids in patients with psoriatic arthritis, which can be associated with flares of psoriasis when they are discontinued. The role of antibiotics in the treatment of reactive arthritis remains controversial. Recent trials in

Chlamydia-related reactive arthritis suggested no benefit from a 4-month course of doxycycline, whereas a 6-month course of treatment with combinations of either doxycycline/rifampin or azithromycin/rifampin leads to improvement in most, and remission in some, patients [51,52].

Despite the widespread use and clinical benefits of MTX in psoriatic arthritis, evidence substantiating its disease-modifying ability is limited, and based on observational data [53]. By contrast, TNF blockers have been shown to reduce progression of peripheral joint damage relative to placebo. Effects on spinal damage have not been assessed in patients with psoriatic arthritis. In AS, the best available evidence suggests that treatment with TNF blockers for 2 years does not result in appreciable slowing of bone formation in the spine [54,55]. While these results may indicate that longer durations of treatment or more sensitive methods of measuring new bone formation are needed, they also raise questions about the linkage of inflammation and spinal fusion in AS.

Summary

RA and spondyloarthritis are two of the most common forms of inflammatory arthritis, representing major sources of pain and disability. Despite common features such as inflammatory arthritis, these diseases differ in serological findings; patterns of disease, including axial skeletal involvement; and demographic features. Nevertheless, certain therapeutic agents, in particular, the TNF blockers can be highly effective in both groups of conditions. In RA, current treatment strategies focus on early therapy with DMARDs, the regular assessment of disease activity, and the adjustment of therapy to minimise disease activity and induce remission (treat to target). Current research suggests that, as long as disease activity in RA is reduced, many different agents, alone or in combination, can reduce inflammation and decrease damage. In addition to clinical measures of disease activity, radiographs to assess bone erosion and joint space narrowing can help determine treatment efficacy and outcome. By contrast, while TNF blockers can effectively reduce symptoms in spondyloarthritis and increase mobility, a benefit on spinal fusion as measured by radiography has not yet been established. Future studies will determine biomarkers to allow selection of treatment strategies and to determine the approach to continued therapy in patients who achieve clinical remission.

Acknowledgments

These studies were supported by a VA Merit Review grant and NIH grant AI083923.

References

1. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet. 2010; 376:1094–108. [PubMed: 20870100]
2. Coenen MJH, Gregersen PK. Rheumatoid arthritis: a view of the current genetic landscape. Genes and Immunity. 2008; 77:1–11.
3. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Annals of the Rheumatic Diseases. 2011; 70:8–14. [PubMed: 21109513]
4. Ospelt C, Gay S. The role of resident synovial cells in destructive arthritis. Best Practice & Research in Clinical Rheumatology. 2008; 22:239–52.
5. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nature Reviews Immunology. 2007; 7:429–42.
6. Aggarwal R, Liao K, Nair R, Ringold S, Costenbader KH. Anti-citrullinated peptide antibody assays and their role in the diagnosis of rheumatoid arthritis. Arthritis Rheum. 2009; 61:1472–83. [PubMed: 19877103]

7. Prujin GJM, Wilk A, van Venrooij WJ. The use of citrullinated peptides and proteins for the diagnosis of rheumatoid arthritis. Arthritis Research & Therapy. 2010; 12:1–8.

8. Kallberg H, Ding B, Padyukov L, Bengtsson C, Rönnelid J, Lareskog L, et al. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis. 2011; 70:508–11. [PubMed: 21149499]

*9. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria. Arthritis Rheum. 2010; 62:2569–81. [PubMed: 20872595]

10. Majka DS, Deane KD, Parrish LA, Lazar AA, Baron AE, Walker CW, et al. Duration of preclinical rheumatoid arthritis-related autoantibody positivity increases in subjects with older age at time of disease diagnosis. Ann Rheum Dis. 2008; 67:801–7. [PubMed: 17974596]

11. Joshua F, Lassere M, Bruyn GA, Szkudlarek M, Naredo E, Schmidt WA, et al. Summary findings of a systematic review of the ultrasound assessment of synovitis. J Rheumatol. 2007; 34:839–47. [PubMed: 17407235]

12. Baillet A, Gaujoux-Viala C, Mouterde G, Pham T, Tebib J, Saraux A, et al. Comparison of the efficacy of sonography, magnetic resonance imaging and conventional radiography for the detection of bone erosions in rheumatoid arthritis patients: a systematic review and meta analysis. Rheumatology. 2011; 50:1137–47. [PubMed: 21278073]

*13. Smolen JS, Aletha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010; 69:631–7. [PubMed: 20215140]

14. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011; 70:404–13. [PubMed: 21292833]

15. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. 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. [PubMed: 7818570]

16. Pincus T, Bergman MJ, Yazici Y. RAPID3 – an index of physical function, pain, and global status as "vital signs" to improve care for people with chronic rheumatic diseases. Bulletin of NY Hospital for Joint Diseases. 2009; 67:211–25.

17. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. New England Journal of Medicine. 2004; 350:2591–602. [PubMed: 15201416]

18. Smolen JS, Aletha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet. 2007; 370:1861–74. [PubMed: 17570481]

19. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease- modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008; 59:762–84. [PubMed: 18512708]

20. Recommendations for use of selective and nonselective nonsteroidal anti-inflammatory drugs: an American College of Rheumatology white paper. Arthritis and Rheumatism. 2008; 59:1058–73. [PubMed: 18668613]

21. Hoes JN, Jacobs JWG, Buttgereit F, Bijlsma JWJ. Current view of glucocorticoid co-therapy with DMARDs in rheumatoid arthritis. Nature Reviews Rheumatology. 2010; 6:693–702.

22. Kremer JM. Toward a better understanding of methotrexate. Arthritis and Rheumatism. 2004; 50:1370–82. [PubMed: 15146406]

23. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000; 343:1586–93. [PubMed: 11096165]

24. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial iri rheumatoid arthritis with concomitant therapy study group. N Engl J Med. 2000; 342:1594–602. [PubMed: 11096166]

*25. van der Heijde D, Klareskog L, Landewé R, Bruyn GA, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and

methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2007; 56:3928–39. [PubMed: 18050208]

26. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The Premier Study: a multi-center, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006; 54:26–37. [PubMed: 16385520]
27. Landewé RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis. Arthritis Rheum. 2002; 46:347–56. [PubMed: 11840436]
*28. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single- blind randomized controlled trial. Lancet. 2004; 364:263–9. [PubMed: 15262104]
*29. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study). Arthritis Rheum. 2005; 52:3381–90. [PubMed: 16258899]
30. Klarenbeek NB, van der Kooij SM, Güler-Yuksel M, van Groenendael JH, Han KH, Kerstens PJ, et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the best study. Ann Rheum Dis. 2011; 70:315–9. [PubMed: 21068104]
31. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part 1. Arthritis Rheum. 2008; 58:15–25. [PubMed: 18163481]
32. Akkoc N. Are spondyloarthropathies as common as rheumatoid arthritis worldwide? A review. Current Rheumatology Reports. 2008; 10:371–8. [PubMed: 18817640]
33. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis and Rheumatism. 1984; 27:361–8. [PubMed: 6231933]
34. Bennett AN, McGonagle D, O'Connor P, Hensor EM, Sivera F, Coates LC, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. Arthritis Rheum. 2008; 58:3413–8. [PubMed: 18975311]
35. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of Spondyloarthritis International Society classification criteria for axial spondylarthritis (part II): validation and final selection. Ann Rheum Dis. 2009; 68:777–83. [PubMed: 19297344]
36. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Marker-Hermann E, Zeidler H, et al. The early disease: stage in axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum. 2009; 60:717–27. [PubMed: 19248087]
37. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. JAMA. 1977; 237:2613–4. [PubMed: 140252]
*38. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis. A reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis and Rheumatism. 2006; 54:569–78. [PubMed: 16447233]
*39. Sieper J, van der Heijde D, Landewe R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of Spondyloarthritis International Society (ASAS). Ann Rheum Dis. 2009; 68:784–8. [PubMed: 19147614]
40. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011; 70:25–31. [PubMed: 21109520]
41. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. Arthritis Rheum. 2006; 54:2665–73. [PubMed: 16871531]

42. D'Angelo S, Mennillo GA, Cutro MS, Leccese P, Nigro A, Padula A, et al. Sensitivity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. J Rheumatol. 2009; 36:368–70. [PubMed: 19208566]

43. Smale S, Natt RS, Orchard TR, Russell AS, Bjarnason I. Inflammatory bowel disease and spondyloarthropathy. Arthritis Rheum. 2001; 44:2728–36. [PubMed: 11762932]

44. de Vries M, van der Horst-Bruinsma I, van Hoogstraten I, van Bodegraven A, von Blomberg BM, Ratnawati H, et al. pANCA, ASCA, and OmpC antibodies in patients with ankylosing spondylitis without inflammatory bowel disease. J Rheumatol. 2010; 37:2340–4. [PubMed: 20810508]

*45. Reveille JD, Sims AM, Danoy P, Evans DM, Leo P, et al. Australo-Anglo-American Spondylitis Consortium (TASC). Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. Nat Genet. 2010; 42:123–7. [PubMed: 20062062]

46. Crome SQ, Wang AY, Levings MK. Translational mini-review series on Th17 cells: Function and regulation of human T-helper 17 cells in health and disease. Clinical and Experimental Immunology. 2009; 159:109–19. [PubMed: 19912252]

47. Franke A, McGovern DP, Barnett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nature Genetics. 2010; 42:1118–25. [PubMed: 21102463]

48. Genetic Analysis of Psoriasis Consortium Wellcome Trust Case Control Consortium 2. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nature Genetics. 2010; 42:985–90. [PubMed: 20953190]

49. Tonel G, Conrad C, Laggner U, et al. A critical functional role of IL-23 in psoriasis. Journal of Immunology. 2010; 185:5688–91.

50. Abraham C, Cho J. Interleukin-23/Th17 pathways and inflammatory bowel disease. Inflammatory Bowel Diseases. 2009; 15:1090–100. [PubMed: 19253307]

51. Putschky N, Pott HG, Kuipers JG, Zeidler H, Hammer M, Wollenhaupt J. Comparing 10- day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial. Ann Rheum Dis. 2006; 65:1521–4. [PubMed: 17038453]

52. Carter JD, Espinoza LR, Inman RD, Sneed KB, Ricca LR, Vasey FB, et al. Combination antibiotics as a treatment for chronic *Chlamydia*-induced reactive arthritis. A double-blind, placebo-controlled, prospective trial. Arthritis Rheum. 2010; 62:1298–307. [PubMed: 20155838]

53. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. Journal of Rheumatology. 2008; 35:469–71. [PubMed: 18085735]

*54. van der Heijde D, Landewe R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to 2 years of treatment with etanercept. Arthritis Rheum. 2008; 58:1324–31. [PubMed: 18438853]

*55. van der Heijde D, Landewe R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum. 2008; 58:3063–70. [PubMed: 18821688]

Practice points

- Remission or at least a state of low disease activity should be the goal of therapy in inflammatory arthritis.
- Therapy should be instituted as soon as possible in patients with evidence of persistent disease activity.
- There are many acceptable approaches to therapy as long as disease activity is monitored and maintained at a low level by ‘treating to target’.
- TNF blockers are effective in the treatment of RA as well as spondyloarthritis.
- Management of inflammatory arthritis requires attention to general health and evaluation and treatment of co-morbidities to prevent complications such as CVD and osteoporosis.

Research agenda

- Research should focus on personalised medicine approaches to determine the most effective treatment strategies for individual patients.
- Research should determine strategies for the reduction of therapy in patients in remission and identify biomarkers to assess likelihood of flare.
- In spondyloarthritis, research should determine mechanisms of spinal fusion and develop approaches to prevent this complication.

Table 1

The 2010 American College of Rheumatology/European league against rheumatism classification criteria for rheumatoid arthritis.[a]

Classification criteria for RA	Score
A. Joint involvement	
1 Large joint	0
2–10 Large joints	1
1–3 Small joints (with or without involvement of large joints)	2
4–10 Small joints (with or without involvement of large joints)	3
>10 Joints (at least 1 small joint)	5
B. Serology	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 Weeks	0
>6 Weeks	1

[a] A patient is classified as RA with a score of 6 or greater.

Table 2

Assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis (SpA, spondyloarthritis).

1. Chronic back pain
2. Age at onset < 45 years
3. Sacroiliitis on imaging (MRI or radiographs) and 1 SpA feature
Or
HLA-B27 positive and 2 SpA features
SpA features
Inflammatory back pain
Arthritis
Heel enthesitis
Dactylitis
Uveitis
Psoriasis
Ulcerative colitis or Crohn's disease
Good response to nonsteroidal anti-inflammatory medications
Family history of SpA
HLA-B27
Elevated C-reactive protein level