Inflammation is the major factor driving the progression of structural damage in rheumatoid arthritis (RA); therefore, it is critical to achieve rapid suppression of inflammation to maximize disease control. The severity of inflammation and progression of joint damage varies from patient to patient. Some patients have the propensity to change slowly over time and then progress in a more rapid and dynamic fashion. In those where inflammation is more severe, extensive damage can occur within only a few years of disease onset. The progress of joint destruction, as assessed radiographically, results in a decline in functional capacity and quality of life. Consequently, the challenge for clinicians is to identify and treat those patients who develop rapid, progressive disease. Several biological markers and clinical indicators have been identified to help predict or establish which of the patients have rapidly progressing disease or who are at most risk for rapid progression. Early diagnosis of patients with rapidly progressing RA enables immediate and intensive intervention (e.g. with biologic therapy) and a greater opportunity to change the course of disease.

KEY WORDS: Biologic therapy, Disease progression, Inflammation, Rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder, with inflammation implicated in pathogenesis at every disease phase. Furthermore, RA involves not only synovial inflammation associated with the pain, stiffness and swelling that are the cardinal features of RA, but also other compartments such as the bone marrow, cartilage and bone strongly associated with tissue destruction. Parallel involvement of blood vessels likely accounts for early cardiovascular morbidity and mortality in RA patients [1, 2]. Inflammation is a manifestation of the immune system’s response to events such as infection and injury/wound healing. It forms part of the normal immune response and is tightly regulated, particularly by pro- and anti-inflammatory cytokines. Pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-15, IL-18 and tumour necrosis factor-α (TNF-α), initiate a number of physiological changes that result in the characteristic signs of inflammation (redness, swelling, pain and the perception of surface and internal heat) [3]. Other cytokines such as IL-4 and IL-10 act to control these responses [4]. Inflammation has historically been considered a static condition. It is, however, a dynamic process driven by many factors including cytokines, and diseases that are subserved by inflammation should not be considered as being uniform or one-dimensional.

In RA, the balance between pro- and anti-inflammatory cytokines is tipped toward continued inflammation. The normally low levels of pro-inflammatory cytokines that maintain the balance during acute inflammation become chronically increased and cause prolonged disproportional inflammation. This persistent inflammation leads to connective tissue, cartilage and bone destruction, resulting in the progression of structural damage [5, 6]. Initially, it is inflammation and subsequent radiological progression that drive disability in RA [7]. Since inflammation is the major factor leading to structural damage, it is critical to achieve rapid suppression of inflammation to maximize disease control since ~90% of patients with RA suffer disability within 20 yrs of onset. Therefore, early diagnosis and treatment of RA is of paramount importance [8].

TNF-α is one of the pivotal pro-inflammatory cytokines responsible for inflammation and joint destruction in RA (Fig. 1) [6]. It is considered to play a more dominant role in inflammation than IL-1 and IL-6 [9]. In addition to its important direct role in inflammation, TNF-α acts as a potent paracrine inducer of other pro-inflammatory cytokines, including IL-1, IL-6 and IL-8. In doing so, TNF-α has a direct or indirect effect on the inflammatory response in RA and the mechanisms involved in the destruction of bone and cartilage [6, 9]. In the endothelium, TNF-α also stimulates expression of adhesion molecules that facilitate the transport of large numbers of leucocytes to areas of inflammation [9]. Furthermore, TNF-α promotes angiogenesis via its effect on endothelial growth factor [10]. The irreversible articular cartilage damage seen in RA largely results from the ability of TNF-α to stimulate the release of metalloproteinases by fibroblasts that destroy joint tissue [11].

Anti-TNF-α-targeted biologic agents (e.g. infliximab, etanercept or adalimumab) have been shown to reduce joint inflammation and, most significantly, slow radiographic progression of joint damage [12–16], resulting in improved physical functioning. Anti-TNF-α therapy, therefore, presents an opportunity to change the disease course in RA and represents a way forward for the management of the disease.

Disease progression in RA

There is pronounced variation in disease course, rate of progression and extent of joint damage between individual patients with RA [17, 18]. In some patients, the severity of inflammation and progression of joint damage is very slow, while in others inflammation is more severe and extensive damage can occur within only a few years of disease onset [17]. Both inflammation and radiographic progression can be linked to functional decline [7]. In some cases, inflammation is the main determinant of disability initially, with joint destruction more dominant later in disease (Fig. 2). However, not all patients with RA progress in a uniform way. Some patients have the propensity to slowly change over time and then progress in a more rapid and dynamic fashion. Patients seemingly doing well can, in a relatively short period of time, start to progress more rapidly [19].
It has been estimated that 60–90% of patients diagnosed with RA have a progressive disease course and that this is usually associated with considerable joint destruction [20–23]. The progress of joint destruction, as assessed radiographically, results in a decline in functional capacity and quality of life [19]. Consequently, the challenge is to identify and treat those patients who develop rapid, progressive disease [21, 24]. This is because these patients may be candidates for more intensive therapy rather than the conventional ‘step-up’ approach to RA treatment [21].

Intensive treatment, initiated immediately, may retard the destructive process and improve long-term functional outcomes in this at-risk group of patients [21].

Tracking RA progression

Tracking disease progression can be difficult and patients ‘at risk’ for disease progression may go undetected. Conventionally, radiographs of the hands and feet are used as the standard measure for joint damage and RA progression via observed changes in bone erosion/cartilage loss [24]. Radiographs, however, only reveal gross anatomical changes in calcified bone, and it usually takes considerable time (12 months) before relevant changes are observable [17]. Consequently, to avoid delays in predicting/identifying rapidly progressing patients, the use of more sensitive, rapid and reliable assessments of disease progression is necessary [17]. These assessments should ideally reflect structural damage measured by radiography and provide an accurate measure for the early prediction of future damage [24]. Many potential predictors of structural damage have been identified, most of which are based on clinical signs/disease activity and/or inflammation or radiographic damage [24]. They include both biological (markers of bone, cartilage and synovial tissue) and clinical indicators.

Potential biological markers of RA

RA affects the different tissues of the joint including bone, cartilage and the synovial membrane [24]. The use of markers for these joint tissues could be useful in evaluating joint damage in RA. Several types of biological markers have been used to assess disease activity/progression as well as treatment response in RA. These include genetic markers, auto-antibodies, inflammation markers, cartilage markers and bone markers (Table 1) [24, 25].

The genetic component of RA may be an important determinant of disease severity [1]. The presence of HLA-DR4 is strongly associated with RA in white, Japanese, Southern Chinese, black American and Native American populations. Patients homozygous for the arthritogenic subtypes appear to have more severe disease [25]. The HLA-DR4 subtypes associated with increased RA prevalence share a common amino acid sequence in the region of the so-called shared epitope (HLA–DR1/DR4/DR10). Prevalence of the shared epitope varies in different racial populations, with it being lower in Afro-Caribbeans and North American Indians [1]. However, HLA-DR4 in many studies has been a poor prognostic marker for the development of erosions. It is possible that patients with rapidly progressing disease may have a different genotype. It is not known which genes may be involved, but there are some candidates. The gene PTPN22 has been shown to predict which patients will have a poor prognosis, but considerable research is needed before clinical practice decisions can be made based on genotype [26].
**RA auto-antibodies.** Rheumatoid factor (RF), although non-specific for RA, is an important predictor of outcome in RA [1, 25], although its value is dependant on the stage of the disease. Early in the course of RA, RF seropositivity is associated with more active disease and the development of bone erosions [1, 25]. Later in RA, however,RF seropositivity is less predictive. Anti-perinuclear factor (APF) and anti-keratin (AK) are as specific to RA as RF, and like RF are sometimes present before the onset of disease [25]. APF and AK antibodies are present in 49–91% and 36–59% of RA patients, respectively [25, 27]. APF and AK antibodies have been shown to correlate with RA severity and activity [28, 29]. However, the tests used to determine their presence are difficult to perform and are not routinely available.

Perhaps even more predictive of disease course in RA is the appearance of anti-cyclic citrullinated peptide (anti-CCP) antibodies. In one study of 279 patients with early RA, a relationship between serum levels of anti-CCP antibodies and the course of disease was evaluated. Although anti-CCP-positive and -negative patients had similar disease activities at baseline, anti-CCP-positive patients experienced a worsening of their clinical presentation and greater radiological progression despite the administration of aggressive therapy. During the first 5 yrs of active RA, anti-CCP antibodies are stable, which suggests that the disease course before the onset of clinical symptoms is determined by the appearance of this antibody. Therefore, the presence of anti-CCP antibodies at the time of diagnosis is predictive of greater radiological progression in RA and changes in antibody levels are not predictive of changes in disease activity [30].

Even more predictive of the course of disease in patients with RA is the evaluation of the interrelationship between anti-CCP antibodies and antibodies to AK (AKAs) in the absence of RF. Kamali et al. [31] investigated the frequency of antibodies against CCP and AK in patients with RA. These patients may have also presented with RF-positive arthritis. AKAs, in the RF-negative RA group, were found to have a high frequency (55%) in comparison with anti-CCP (38%). In RA patients, seropositivity was found to be 87% for any one of the three auto-antibodies tested. The authors concluded that values for RA, anti-CCP antibodies and AKA are useful for providing a differential diagnosis of patients with RF-positive arthritis, provided that a higher specificity of testing is available, and that diagnostics may be improved with screening for all three antibodies [31].

**Markers of inflammation.** Inflammation plays a critical part in the pathophysiology of RA. Measurement of the acute-phase response is used as a surrogate marker of inflammation in RA. The acute-phase reactants C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most widely used biological markers for assessing disease activity and inflammation in RA. ESR is a marker of inflammation activity and correlates with disease severity, although its specificity as a sole indicator of disease progression is questionable because it is influenced by other unrelated factors such as anaemia [25]. CRP levels correlate significantly with RA disease activity, radiological progression and response to therapy [25, 32–34]. Consequently, CRP is considered to be a more specific biological marker for RA disease activity than ESR since the hepatic production of CRP is reflective of the effects of inflammatory cytokines on the liver [35, 36]. In addition, CRP status is predictive of functional disability, and suppression of elevated CRP levels is associated with improvement in functionality [37]. Significantly, normalization of CRP levels by drug therapy may minimize new joint damage, supporting the immediate introduction of inflammation-suppressing therapy before the onset of erosive damage [32, 38]. Assessments of CRP and ESR are easy to perform and are routinely available. Notably the direct link between cytokine synthesis, particularly TNF-α and IL-6, and CRP is exemplified in the rapid suppression of IL-6 and CRP following TNF-α blockade [39].

**Serological predictors of joint/cartilage damage.** Markers of joint and connective tissue destruction and erosion of articular cartilage may be useful for monitoring RA patients [25]. Concentration of serum biomarkers of cartilage/collagen breakdown (C1, 2C, C2C, C11-Cr and CS84-epitope) and proteoglycan turnover have been shown to be related to joint destruction and may be useful in assessing progression of joint damage [17]. Cartilage breakdown can also be monitored by measuring aggrecan and circulating cartilage oligomeric matrix protein (COMP). Both aggrecan and COMP are associated with rapid joint destruction in RA [25, 40, 41]. High aggrecan and COMP ratios are a strong predictor of joint destruction [25].

High levels of several markers of collagen degradation, including urinary glucosyl-galactosyl-pyridinoline (Glc-Gal-Pyd), urinary C-terminal cross-linking telopeptide of type II collagen (CTX-II) and serum matrix metalloproteinase-3 (MMP-3), have also been shown to be associated with increased risk of progression of joint destruction in early RA [34, 42]. Combining these molecular markers with radiological assessment of joint damage may be useful for identifying patients with RA who are at risk for rapid progression [42].

**Bone turnover markers.** Bone formation can be evaluated by measuring serum osteocalcin, bone-specific alkaline phosphatase and collagen I polypeptides (PINP) [25]. Serum of bone sialoprotein (BSP) and osteoblast-derived calcium-binding protein in synovial fluid have been shown to correlate with the degree of joint destruction [25, 40]. In addition, degradation of collagen I with the appearance of increased urine pyridinoline cross-links has also been shown to correlate with RA disease activity [25]. Bone turnover markers, however, reflect the overall rate of bone turnover, which can be affected by a number of conditions (e.g. menopausal status and bone disease such as osteoporosis). Therefore, it is unclear whether the biomarker variation is attributable solely to RA-mediated damage.

**Clinical indicators**

A number of clinical indicators have been shown to be predictive of RA progression. These include the presence of joint damage and signs of disease activity (e.g. larger numbers of swollen and tender joints) [5]. Joint inflammation leads to radiographic progression and the degree of radiographic damage directly

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**Table 1. Types of biological markers for evaluating rheumatoid arthritis [25]**

<table>
<thead>
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<th>Table 1: Types of biological markers for evaluating rheumatoid arthritis [25]</th>
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<tr>
<td><strong>Genetic markers</strong></td>
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<tr>
<td>HLA-D4; HLA DRB-1</td>
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<tr>
<td>Non-HLA markers 2q34 (TNP1) and 2q35 (K812, VILI, DES)</td>
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<tr>
<td><strong>Auto-antibodies</strong></td>
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<tr>
<td>Rheumatoid factor</td>
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<tr>
<td>Anti-nuclear antibodies (ANA)</td>
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<tr>
<td>Anti-citrulline or anti-CCP antibodies</td>
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<tr>
<td>Anti-A1/RA33</td>
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<tr>
<td><strong>Inflammatory markers</strong></td>
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<tr>
<td>Acute-phase reactants</td>
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<tr>
<td>– Erythrocyte sedimentation rate (ESR)</td>
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<tr>
<td>– C-reactive protein (CRP)</td>
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<tr>
<td>– SAA (serum amyloid-associated protein)</td>
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<tr>
<td>Cytokines/inhibitors (e.g. K-1, TNF-α, IL-6, IL-8)</td>
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<tr>
<td><strong>Cartilage markers</strong></td>
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<tr>
<td>Hyaluronic acid</td>
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<tr>
<td>Cartilage oligomeric protein</td>
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<tr>
<td>Aggrecan</td>
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<tr>
<td><strong>Bone markers</strong></td>
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<tr>
<td>Bone sialoprotein</td>
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<tr>
<td>Pyridinoline crosslinks</td>
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correlates with the level of physical function [43]. Furthermore, persistent joint swelling during therapy is associated with greater radiographic progression of joint damage [19], demonstrating the need to control inflammation.

The number of radiographic lesions has also been shown to strongly correlate with a longer duration of complaints (persistent pain and swelling). Furthermore, patients with a long duration of complaints prior to seeking intervention have more erosions at diagnosis and also show greater radiographic progression [36].

Rapid and sustained suppression of inflammation is critical to the prevention of disease progression. Clearly, some patients with RA progress more rapidly, irrespective of disease duration, and continued progression is driven by underlying inflammation [7, 24]. There is, however, no single characteristic to identify patients with rapidly progressing RA. What is needed are ways of showing how the clinical picture correlates with what is happening locally within the joint. In any one individual, there is a robust relationship between the volume of inflammation and the amount of joint damage; however, it is not possible to predict the course without looking at other factors. The best recorded predictors of rapidly progressing disease are swollen joints and acute-phase response. This is not surprising because swollen joints are the manifestation of the inflammation process, and the acute-phase response (CRP/ESR) acts as a surrogate marker of cytokine release and inflammation. It is now clear that high CRP is associated with increased risk of radiological progression [19]. In addition, joint swelling has been shown to predict bony damage and synovitis, and a correlation between synovitis and bone erosions has been established [38, 45].

In rapidly progressing RA, there is a need to evaluate not only structural damage, (i.e. joint destruction), but also the effects on patients’ functional ability by including functional tests such as the health assessment questionnaire (HAQ) or a combined predictor of progression such as the PISA (persistent inflammatory symmetrical arthritis) scoring system [1, 38]. It has been shown that high baseline HAQ scores correlate with future functional disability [46]. The PISA scoring system scores one point for a number of prognostic factors [e.g. female sex, RF positivity, shared epitope (HLA-DR1/DR4/DR10), CRP >20 mg/l, HAQ raw score >4] with a score of ≥3 indicating poor prognosis [1]. It predicts radiological damage and combines factors that are predictive of poor functional outcome. Although this test is used in clinical trials to identify patients with poor prognoses, it is not clear why PISA is not practical for routine use.

Several biological markers/clinical indicators, however, can be used in everyday clinical practice to help predict/establish which patients are rapidly progressing or are at most risk for rapid progression. These include elevated CRP level, evidence of erosion, number of swollen/tender joints, high DAS and functional ability (HAQ) (Table 2). Clearly, it is also important to monitor synovitis and the extent of underlying joint damage and bone erosion. Currently, X-rays are considered to be the standard method for doing this. Using X-rays, however, has a number of drawbacks: when patients first present, about 80% will have completely normal X-rays, and damage needs to occur for a long period of time before it becomes visible (1 yr). The gold standard

<table>
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<th>TABLE 2. Risk factors for rapidly progressing patients [19]</th>
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<tr>
<td>Clinical evidence</td>
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<tr>
<td>Early age of onset</td>
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<tr>
<td>Failed two DMARDs in 6 months</td>
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<tr>
<td>≥3 swollen joints</td>
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<tr>
<td>High DAS score (≥4.02)</td>
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| Failure to respond (CRP/ESR) acts as a surrogate marker of cytokine release and inflammation. It is now clear that high CRP is associated with increased risk of radiological progression [19]. Furthermore, it has been shown that the immediate use of intensive and aggressive combination therapies [e.g. methotrexate (MTX) plus infliximab] provides symptomatic and radiological benefits in rapidly progressing patients [19]. Employment of intensive management strategies may provide sustained, tight control of disease activity compared with routine outpatient care. In the TICORA study, the mean decrease in DAS was greater in the intensive group than in the routine group [−3.5 vs −1.9, (95% CI 1.1–1.2), P < 0.0001]. Additionally, patients who were treated intensively were more likely to have a good response [45/55 (82%) vs 24/55 (44%), OR 5.8 (95% CI 2.4–13.9), P < 0.0001] or be in remission [defined by DAS <1.6; 36/55 (65%) vs 9/55 (16%), 9.7 (3.9–23.9), respectively, P < 0.0010]. This intensive outpatient management strategy substantially improved disease activity, radiographic disease progression, physical function and quality of life. DAS-driven management may detect disease progression earlier, providing for potential earlier use of biologics [48].

Biologic therapy in rapidly progressing patients

All of the commercially available biologic agents have been evaluated in patients with RA of differing disease durations. Currently, there are three TNF-α inhibitors approved for use in RA: infliximab, etanercept and adalimumab, which act by different mechanisms to bind on and inhibit the activity of TNF-α. While there are no head-to-head comparisons of the agents to date, all have proven effective in relieving the symptoms of RA [49] and slowing or halting radiographic disease progression, with 50–70% of patients showing clinically significant improvement [50–52]. Importantly, all three anti-TNF-α agents when combined with MTX have been shown to be very effective in preventing radiological damage [53–55]. These studies of anti-TNF-α therapy plus MTX, compared with the effects with MTX alone, have shown that although MTX is relatively effective at relieving clinical symptoms, it has little or no effect on underlying radiological progression. Anti-TNF-α plus MTX combination therapy, however, completely prevented and in some cases actually slightly reversed the radiological progression of RA. These studies also confirmed that MTX plus biologic combination therapy is more effective than biologic monotherapy in inhibiting the progression of joint damage and improving the signs and symptoms of inflammation in RA patients.

Infliximab, an anti-TNF-α-specific therapy, has been shown to rapidly reduce/normalize CRP level and ESR. This demonstrates the ability of infliximab to suppress inflammation, and therefore
inhibit radiological progression in patients with RA (Fig. 3) [38], which is essential for long-term disease control. A significant association between a decrease in CRP level and clinical response to infliximab has been shown [56]. Furthermore, CRP can be used to predict and monitor response to infliximab therapy [57]. In addition, high CRP level or ESR or persistent disease activity has been shown to be associated with greater radiographic progression in patients receiving MTX monotherapy, while little radiographic progression was seen in patients receiving infliximab plus MTX combination therapy [19]. Patients with active RA who have high ESR or CRP level or persistent disease activity, therefore, are more likely to experience progression of joint damage when treated with MTX alone. Furthermore, the evidence suggests that patients with rapidly progressing RA may be candidates for initial treatment with infliximab plus MTX combination therapy [19].

While all anti-TNF-α therapies have been shown to be effective in average moderate-to-severe RA patients, few studies have been done in patients with rapidly progressing disease. In a subset of patients with rapidly progressing disease, infliximab has demonstrated significant improvement in symptoms and functional activity with inhibition of radiographic progression of joint damage when used with MTX regardless of disease duration [38, 52]. Quinn et al. [38] showed that remission induction with infliximab plus MTX provided a significant reduction in MRI evidence of synovitis and erosions in these patients (Fig. 3). Furthermore, the significant functional and quality of life benefits that were achieved with the combination were sustained for at least 2 yrs, despite withdrawal of infliximab therapy after 1 yr [38]. A subanalysis of the ATTRACT study in a cohort of patients with early disease (<3 years’ duration) has shown that in patients with rapid disease progression (defined as those patients with disease activity based on functional disability and radiographic damage) despite MTX therapy, early treatment with infliximab may provide improved long-term benefits by preventing radiographic progression more completely than if treatment was begun later in the course of the disease [58]. This suggests that there is a real gain in initiating biologic therapy in the early stages of RA in patients who have failed on MTX therapy, and it also demonstrates the benefits of more intensive therapy in patients with rapidly progressing disease.

The results of these studies may be explained, in part, by the pharmacokinetic and pharmacodynamic profiles of infliximab. The administration of infliximab, particularly through i.v. infusion, results in the achievement of maximal plasma concentrations immediately after infusion [59]. The consequent rapid and high exposure of tissues to infliximab produces a rapid and sustained suppression of inflammatory processes (i.e. therapeutic intensity), with significant clinical effects evident within 24 h of infusion [39, 60, 61]. A clinical observation trial has demonstrated that improvements in morning stiffness occur rapidly after an infusion of infliximab [47]. This has been confirmed to be a biological effect [62]. From biopsies, it was possible to show dramatic differences in the presence of activated lymphocytes in synovial tissue demonstrating a rapid suppression of inflammation within 48 h of receiving infliximab.

Perhaps the largest study to date regarding the use of etanercept in patients with RA was the ERA (early RA) study that compared clinical and radiographic outcomes in patients with RA after having received monotherapy with either etanercept or MTX for 2 yr. In this double-blind trial, 632 patients with early, active RA were randomized to receive either twice-weekly subcutaneous (SQ) etanercept (10 or 25 mg) or weekly oral MTX (mean dosage 19 mg/week) for at least 1 yr (512 of the 632 patients were followed for one more year in the open-label phase of the study) [63].

After 2 yrs of therapy with etanercept or MTX monotherapy, 72 and 59% of patients, respectively, met the American College of Rheumatology 20% improvement (ACR20) criteria (P < 0.005). With regard to Sharp scale, a greater number of patients had no increase in total score and erosion scores (P = 0.017 and P = 0.012, respectively). For etanercept 25 mg, mean changes were 1.3 units for total Sharp score and 0.66 units for erosion scores. These were significantly lower than those results achieved in the MTX group (3.2 and 1.86 units, respectively; P < 0.001). These data support the efficacy of etanercept in reducing disease activity, arresting structural damage and decreasing disability at 2 yrs in patients with early, aggressive RA [63].

With regard to adalimumab, the PREMIER study (a 2-yr, multicentre, randomized, double-blind clinical trial) compared the efficacy and safety of adalimumab plus MTX vs MTX monotherapy or adalimumab monotherapy in patients with early, aggressive RA who had not previously received MTX treatment [64]. The study evaluated 799 patients with active RA of <3 years’ duration who had never been treated with MTX. Treatments were administered under the following schedule: adalimumab 40 mg SQ every other week plus oral MTX, adalimumab 40 mg SQ every other week or weekly oral MTX. The study evaluated the results based on the attainment of a 50% improvement in ACR and mean change from baseline in the modified total Sharp score at 1 yr.

The results of this study showed that combination therapy was superior to both MTX and adalimumab monotherapy in measurements of all outcomes. After therapy for 1 yr, a significantly greater number of patients achieved ACR50 than patients on MTX or adalimumab monotherapy (62, 46 and 41%, respectively, P < 0.001). Regarding radiographic progression, greater number of patients on combination therapy showed significantly less progression (P ≤ 0.002) after both 1 and 2 yrs (1.3 and 1.9 Sharp units, respectively) than patients who received MTX (5.7 and 10.4 Sharp units) or adalimumab (3.0 and 5.5 Sharp units) monotherapy. Disease remission (based on the DAS28 of <2.6) and major response (defined as an ACR70 for six continuous months) were achieved by 49% of patients on combination therapy after 2 yrs of treatment [64].

Current clinical practice in RA

The goal of RA management should be to suppress inflammation and prevent structural damage and not simply to alleviate the clinical signs and symptoms. In many cases, this will require a more aggressive treatment strategy and close monitoring of structural damage. All patients not responding satisfactorily to conventional disease-modifying anti-rheumatic drugs (DMARDs), particularly those who are progressing rapidly despite this therapy, should be considered for more aggressive treatment, e.g. with a biologic plus MTX.

Recently, a large survey was conducted in Europe and Canada to establish how rheumatologists approach and treat patients with rapidly progressing RA in everyday practice [65]. Almost all of those surveyed (97%) identified rapidly progressing patients...
Treatment of rapidly progressing rheumatoid arthritis

Conclusions

In RA, inflammation drives the progression of structural damage. It is clear that some patients with RA progress more rapidly than others. The evidence suggests that patients with rapidly progressing disease may benefit from early aggressive treatment with a biologic agent. Consequently, the identification of rapidly progressing patients and effective management is particularly important in preventing irreversible joint damage. A number of biological markers/clinical measures can be used in clinical practice to help identify this group of patients, including elevated CRP level, evidence of erosion, number of swollen/tender joints and high disease activity. This will allow initiation of appropriate, intensive therapy and help reduce the progression of joint damage in these at-risk patients after high disease activity X-ray and, where available, MRI or ultrasound.

Infliximab has been evaluated in both short- and long-term disease in rapidly progressing patients and has been shown to rapidly reduce/normalize CRP level, demonstrating suppression of inflammation and inhibition of radiological progression. Infliximab plus MTX combination therapy significantly increases clinical response rates and decreases radiological progression of joint damage in patients with rapidly progressing RA compared with MTX monotherapy. Rapidly progressing patients may benefit from initial treatment with infliximab plus MTX combination therapy.

Rheumatology key messages

- Identification of patients with rapidly progressing disease is important to prevent irreversible joint damage.
- Certain treatment strategies are more appropriate than others for patients with rapidly progressing disease.

References


