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REVIEW

Evidence-based review of biologic markers as indicators of disease progression and remission in rheumatoid arthritis

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Abstract Rheumatoid arthritis (RA) is a chronic, immune-mediated inflammatory disease characterised by inflammation resulting in structural joint damage and functional disability. Tumour necrosis factor-alpha (TNFα) is a pivotal mediator and driver of inflammation in RA. Inflammation is closely related to the production of C-reactive protein (CRP), and a close correlation exists between serum CRP and TNFα levels. CRP levels are therefore a convenient, objective biomarker of disease activity. CRP correlates closely with changes in inflammation/disease activity, radiological damage and progression and functional disability. Identification of TNFα as a driver of RA progression has led to the introduction of TNFα-blocking agents and, subsequently, improvement of disease management. TNFα-blocking agents provide rapid, profound and sustained suppression of disease activity in correspondence with a marked reduction in CRP levels. A reduction in CRP level correlates closely with the positive clinical response to TNFα-blocking therapy. Thus, CRP levels can be used to predict, assess and monitor response to treatment with TNFα-blocking agents, and may be helpful in determining the optimal TNFα-blocker dosage. Given the close correlation between inflammation and disease progression and the relation between inflammation and CRP, the latter, if used effectively in clinical practice, may be means to identify patients likely to progress rapidly and who require intensive anti-TNFα therapy. The purpose of this review is to identify how CRP levels may be useful for monitoring the effect of therapy on halting disease progression and why monitoring CRP levels at baseline and after treatment should become a routine part of clinical practice.

Keywords Rheumatoid arthritis · C-reactive protein · Tumour necrosis factor α · Inflammation

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Introduction

Rheumatoid arthritis (RA) is considered an immune-mediated inflammatory disease (IMID), one of an expanding group of diseases that share common inflammatory pathways characterised by cytokine dysregulation [1]. The list of diseases fitting the IMID profile currently includes psoriasis, Crohn's disease (CD), ankylosing spondylitis (AS), type 1 diabetes mellitus, ulcerative colitis (UC), multiple sclerosis (MS) and uveitis [1]. In RA, cytokine dysregulation manifests as overproduction of proinflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, IL-15, IL-17, IL-18, IL-23 and tumour necrosis factor-alpha (TNFα) [2]. TNFα is both an autocrine stimulator and a potent paracrine inducer of these inflammatory cytokines [2] and, although these cytokines are involved in the pathogenesis of inflammatory conditions, TNFα predominantly drives the production of the inflammatory cytokines IL-1 and IL-6

[3, 4]. TNFα is produced by a variety of cells including monocytes, macrophages, dendritic cells, T cells and B cells [2, 5].

Rheumatoid arthritis is a chronic, progressive, systemic inflammatory disease characterised by persistent inflammation resulting in joint damage and functional disability. Disease progression occurs at any stage but has been suggested to have the fastest rate early on in the disease [6]. Certainly, the majority of damage experienced in RA occurs within the first 5 years of disease onset [7]. Within 3 months of symptom onset, approximately 13-25% of RA patients show radiological joint erosion [8, 9], and within 2 years, approximately 75% of patients have erosive joint damage [6].

Within the first 2–3 years of disease onset, 20–30% of patients are in a state of permanent work disability [10]. Several investigators have identified disease activity as the most important determinant of functional disability [11–14]. Inflammation of joints causes disability in early disease in the absence of detectable joint damage and continues to contribute to disability throughout the course of the disease [14]. The contribution of joint destruction to disability increases over time [11] and becomes significant after 5 or more years [11, 15]. Joint destruction accounts for approximately 25% of the disability in patients with established RA [14].

Prevention of disability is a major long-term goal of treatment in RA patients. Achievement of this goal requires rapid, profound and sustained suppression of inflammation (disease activity) and the arrested progression of radiological damage. It has been demonstrated that some patients progress faster than others [11], and those patients may require a more intense approach to therapy. The rapid rate of disease progression argues for early effective pharmacologic anti-inflammatory intervention and close monitoring of its effectiveness over time. Prognostic markers for RA severity, especially in patients with rapidly progressing disease, are playing an increasingly greater role in the diagnosis and management of RA because therapies that provide rapid and effective suppression of inflammation can halt structural damage [16–19].

Inflammatory pathogenic processes in RA

Uncontrolled inflammatory processes drive the progression of RA and subsequent joint damage and disability (Fig. 1) [20, 21]. Inflammation induces systemic acute phase responses with subsequent changes in hepatic production and plasma concentration of acute-phase proteins [5]. The prominent feature of the rheumatoid synovium is the overabundance of the proinflammatory cytokines TNFα, IL-1 and IL-6 that stimulate the hepatic production of large amounts of the acute-phase protein, C-reactive protein (CRP) [5, 22], thereby making CRP a convenient and appropriate surrogate marker of inflammation disease activity in RA (Fig. 2) [23]. Therefore, CRP is closely associated with response to therapy [24]. These cytokines drive the inflammatory and joint eroding processes forward by activating other cytokines and chemokines [21] and stimulate the release of tissue-destroying matrix metalloproteinases from synovial fibroblasts, osteoclasts and chondrocytes [2]. TNFα induces the inflammatory cytokines, IL-1, IL-6, IL-8 and granulocyte-monocyte colony-stimulating factor and stimulates the expression of adhesion molecules, such as intercellular adhesion molecule 1, from fibroblasts [2]. Both TNFα and IL-1 cause bone resorption [21]. On a clinical level, analysis of clinical and radiological data from the Combinatietherapie Bij Reumatoide Artritis (COBRA) trial revealed that in patients with early

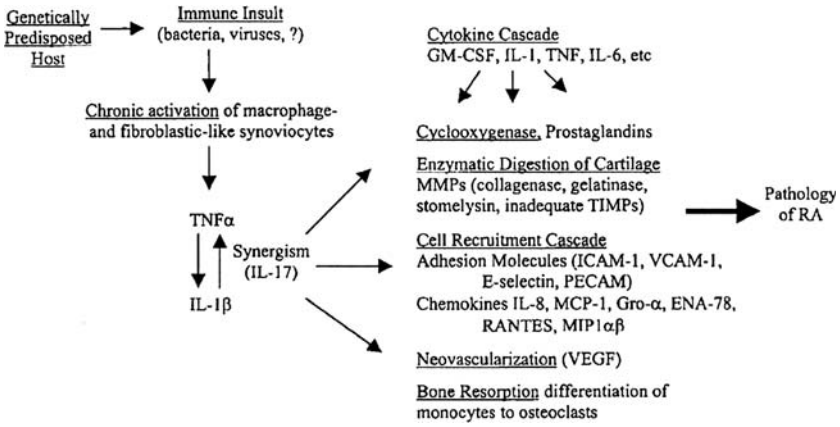

Fig. 1 The pathologic processes of rheumatoid arthritis. The rheumatoid synovium is comprised primarily of fibroblast and monocyte/macrophage cells, which produce proinflammatory cytokines of which TNFα and IL-1β are thought to be the central cytokines driving synovial inflammation, joint destruction and the development of systemic complications in RA [21]. Adapted with permission from Lippincott Williams & Wilkens

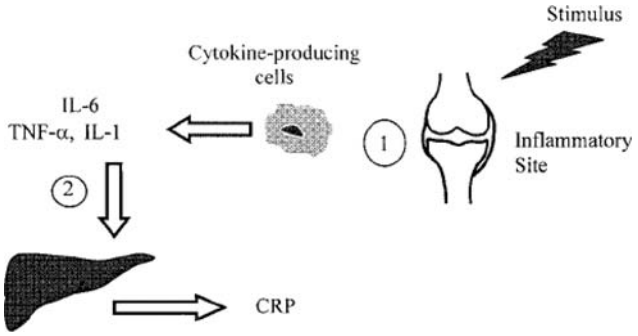

Fig. 2 Stimulation of hepatic production of acute phase proteins by proinflammatory cytokines participating in inflammatory processes in rheumatoid arthritis [22]. Adapted with permission from John Wiley & Sons, Inc

RA, symptoms of local inflammation (joint swelling or joint tenderness) in an individual joint, both at baseline and on follow-up, are independently and strongly predictive of progression of joint damage in that joint [20].

C-reactive protein

Role in inflammation

C-reactive protein may be more than just a marker of inflammation in RA. As a component of the innate immune system, CRP's main function is that of a pattern recognition receptor [5]. However, in vitro and in vivo studies [25] and recent clinical findings [26] implicate CRP in the promotion of inflammation in RA via activation of the complement system. Molenaar et al. (2001) found that median plasma levels of CRP-complement complexes (CRP-C3d and CRP-C4d, where C3d and C4d represent degradation products of the activated complement components) were elevated in ≥98% of RA patients and were significantly higher in patients with active RA than in those with inactive RA ($P < 0.001$ for between group differences in CRP-C3d and CRP-C4d levels). In patients with active RA, significant correlations were seen between plasma concentrations of CRP-C3d and CRP-C4d and disease activity (DAS28) ($r = 0.61$ and 0.55, respectively; $P < 0.001$ for both) that were more pronounced than the correlations seen in patients with inactive RA ($r = 0.28$ and 0.25, respectively; $P < 0.01$ for both). Increasing levels of complement-CRP complexes observed during IL-2 therapy suggest that CRP may be a link between complement activation and cytokines and that CRP-mediated complement activation may be one of the effector mechanisms triggered by cytokines [26].

The proposed mechanism for CRP-mediated complement activation involves interaction with secretory phospholipase A2 (sPLA2), whose production is stimulated by cytokines released at sites of tissue injury, with levels rising soon after inflammatory stimuli [27]. During apoptosis of injured (inflamed) cells, phospholipids of inner and outer leaflets may exchange ('flip-flop' phenomenon). 'Flip-flopped' (but not normal) membranes are susceptible to hydrolysis by sPLA2, which generates lysophosphatidylcholine in the outer leaflet and subsequently creates binding sites for CRP, triggering the activation of complement via the classical pathway.

Clinical evidence of the relationship between CRP complement activation and the progression of inflammation in RA was recently elucidated by Familian et al. [28]. In 35 patients with active RA, biologic therapy with infliximab 3 mg/kg at weeks 0, 2, 6, 14 and 22 was initiated. At 22 weeks, clinical response and plasma levels of complement activation products (C3 and C4), CRP and CRP-complement complexes were evaluated. Levels of C3 and C4 activation and plasma levels of CRP and CRP-complement complexes were significantly reduced at 2 weeks after the first dose and continued throughout the observation period. Since the decreases were greater in patients who demonstrated a clinical response to therapy, the authors concluded that complement activation may be included as an effector mechanism of TNF in RA [28].

Recently published data, however, indicate that the activity of CRP is more complex than this simple explanation and that over-expression of CRP may actually have an anti-inflammatory effect in experimental models of arthritis in transgenic mice capable of expressing high levels of rabbit CRP (serum concentration >50 mcg/ml) in response to dietary manipulation. The results showed that in these animals where CRP expression had been suppressed, inflammatory arthritis began to develop by day 4 and was fully developed by 7 days. Further evidence of this alternate effect was observed with the induction of CRP expression (serum concentrations >50 mcg/ml), resulting in the reduction at day 7 of an inflammatory response with little to no evidence of joint inflammation [29].

Role of CRP as inflammatory indicator

> In clinical practice, CRP has a role as a biological indicator which could be used as a tool for monitoring the course of RA and response to therapy, especially in rapidly progressing patients. [30]

Elevated CRP level is conclusive evidence of inflammation [30]. CRP concentration is closely related to the production of IL-1 and TNFα, and thus reflects levels of these cytokines [22, 31] and correlates with the magnitude and severity of inflammation [5, 30] and grade of disease activity [32]. The plasma CRP concentration increases sharply (by up to 1,000-fold) within hours of the inflammatory response and drops quickly as inflammation subsides [5, 30].

Inflammatory biomarkers and disease activity

Several types of biological markers are available for assessing disease activity and treatment response in RA (Table 1) [31]. Of these, CRP and erythrocyte sedimentation rate (ESR) are the most widely used [5] and are included in both the American [American College of Rheumatology (ACR)] [33] and European (European League Against Rheumatism [EULAR]) [34] guidelines for the diagnosis and assessment of RA. Although a high rheumatoid factor (RF) level correlates with systemic symptoms and severity of disease, CRP is more reliable than RF for monitoring disease activity or response to treatment [30]. Furthermore, 20–30% of RA patients have a negative RF test result throughout the course of their disease [10].

While ESR is considered to be a better predictor at very early stages of disease activity (it is more sensitive because of immunoglobulin changes), when elevated, CRP is superior to ESR as a measure of inflammation/disease activity because raised immunoglobulin levels and reduction in haemoglobin levels both act to increase ESR (Table 2) [5, 32, 35–41]. Unlike ESR, CRP is a direct measure of disease activity and is not influenced by patient- or blood-related factors. Because ESR is an imprecise measure of disease activity, values can be misleading [5]. Furthermore, more than 40% of patients with active RA have a normal ESR value [42].

Table 1 Types of biological markers useful for the evaluation of rheumatoid arthritis [31] Adapted with permission from John Wiley & Sons, Inc

Genetic markers
HLA-D4; HLA DRB-1
Non-HLA markers 2q34 (TNP1) and 2q35 (K812, VILI, DES)
Disease-associated autoantibodies
Rheumatoid factor
Antinuclear antibodies (ANA)
Anti-filaggrin (anti-keratin, anti-perinuclear factor)
Anti-citrulline epitope containing peptides
Anti-A1/RA33
Markers of inflammatory process
Acute phase reactants
Erythrocyte sedimentation rate (ESR)
C-reactive protein (CRP)
SAA (serum amyloid-associated protein)
Cytokines/inhibitors (e.g., IL-1, TNFα, IL-6, IL-8, IL-1Ra)
Joint and cartilage breakdown products
Hyaluronic acid
Cartilage oligomeric protein
Aggrecan
Bone turnover
Bone sialoprotein
Pyridinoline crosslinks

Table 2 Superiority features of C-reactive protein (CRP) over erythrocyte sedimentation rate (ESR) as a measure of inflammation/disease activity [32, 35, 39, 40, 41]

CRP correlates better than ESR with disease activity. Only occasionally is ESR a more sensitive predictor in early disease
CRP levels respond quickly to changes in inflammatory/disease activity; ESR levels change slowly
CRP levels are unaffected by age; ESR values increase with age
CRP levels are unaffected by gender; ESR levels are higher in women than in men
ESR is an indirect, but slowly responding and therefore imprecise measure of the acute-phase reaction; CRP is an acute phase protein and results from cytokine-driven inflammation
ESR is affected by abnormalities in size, shape and number of erythrocytes and other serum proteins (e.g., immunoglobulins); CRP is unaffected
A broader range of abnormal levels exists for CRP than for ESR
CRP level, but not ESR, correlates with histological changes in synovium
CRP serial measurements correlate with radiological progression more closely than ESR serial measurements

C-reactive protein level correlates more closely than ESR with subjective (morning stiffness, pain and fatigue after walking) and semi-objective (grip strength, articular index) clinical parameters of RA disease activity [32, 35, 43] and disability [35]. A recent study that evaluated correlations between disease activity based on the DAS28 score and serum levels of various acute phase reactants (including ESR) found serum CRP levels to be most closely correlated with disease activity and singled out CRP as the most useful biomarker for evaluating disease activity in RA. A strong positive correlation was observed between the DAS28 score and serum CRP level (Fig. 3) [44]. CRP can be substituted for ESR in calculation of the DAS28, with little difference in overall results [45] and no change in values defining disease activity (highly active, DAS28 CRP > 5.1; moderately active, DAS28 CRP 3.2–5.1; minimally active, DAS28 CRP < 3.2) [46].

> High-sensitivity CRP (hs-CRP) assays can be used to identify mild disease activity that is associated with inflammation but that is not detectable by routine CRP testing. [43] hs-CRP is also superior to ESR in predicting disease activity and disease severity. [43] The use of hs-CRP is valuable for determining the level of intensity of treatment in patients with mild RA.

C-reactive protein is also a better indicator of radiological progression than ESR [40, 47]. In a 3-year prospective

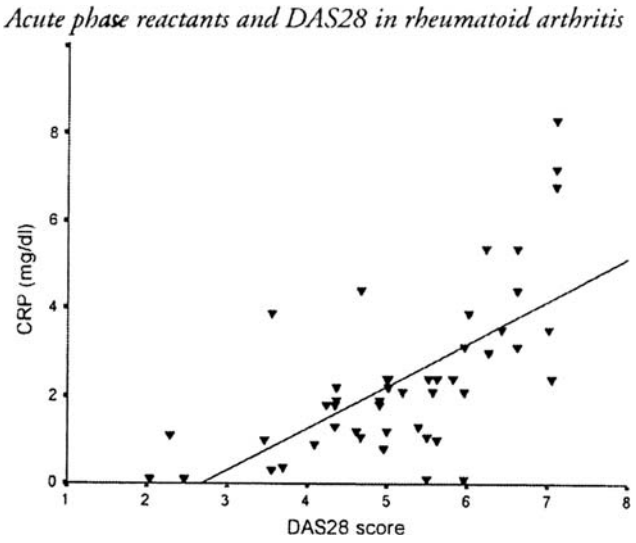

Fig. 3 Correlation between serum CRP level and DAS_{28} disease activity score in 47 RA patients. Spearman rank correlation coefficient was 0.65 ($P < 0.001$) [44]. Adapted with permission from The Association of Clinical Scientists

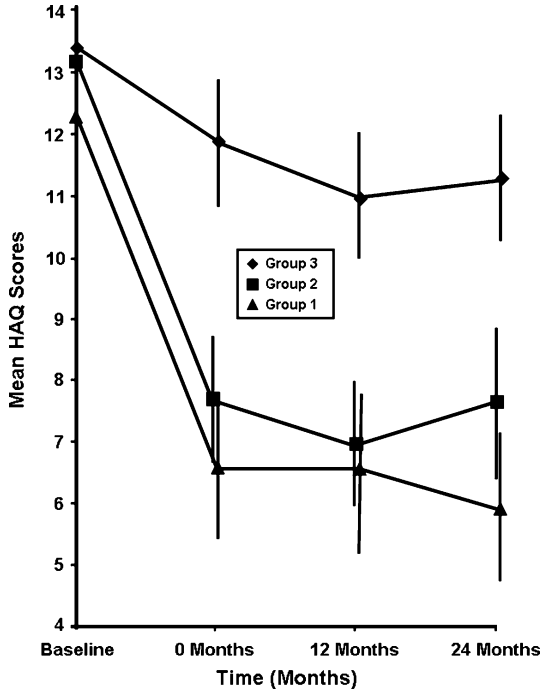

Fig. 4 Relationship between CRP response and functional outcome based on HAQ scores (*error bars* = lower to upper quartiles) [36]. Adapted with permission from The Journal of Rheumatology Publishing Company, Ltd

study of patients with early RA, van Leeuwen et al. (1994) found that although there was a statistically significant correlation between radiological progression and time-integrated values of either CRP and ESR, the correlation with CRP was stronger (Spearman correlation coefficient, 0.656 vs 0.536 for ESR). CRP levels are significantly associated with severity and progression of radiological parameters during all stages of RA, whereas ESR is significantly associated with severity of radiological parameters only in late RA [48].

Serum CRP level also has prognostic value in terms of progressive joint damage (discussed in the following section) [38] and functional status and outcome [36, 37]. With respect to function, in patients with early RA (symptom duration <3 years), Jansen et al. (2000) found elevated serum CRP levels at presentation to be an independent predictor of functional ability assessed by the Health Assessment Questionnaire (HAQ) with an odds ratio of 1.38 [95% confidence interval (CI) 1.13, 1.67] [37]. The functional status was predicted with an accuracy of 74% according to baseline CRP level. The correlation of CRP levels and functional outcome (HAQ score) was also examined in a 2-year prospective study of 109 patients with newly diagnosed, untreated RA (symptom duration <1 year) and median CRP level at baseline of 38 mg/l [36]. After 6 months of systemic steroid and/or disease-modifying treatment, patients were divided into three groups according to CRP response: Group 1 (CRP level normalised), Group 2 (CRP level reduced by 50% but not normalised) and Group 3 (<50% reduction in CRP level). A correlation was observed between CRP response and HAQ score that was maintained at 12 and 24 months (Fig. 4) [36]. Re-elevation of CRP level was associated with deterioration of HAQ score. At 12 and 24 months, HAQ score was more strongly associated with CRP response ($P < 0.001$) than with baseline grip strength, Steinbrocker function grade, ESR, Ritchie articular index or pain (visual analogue score). These findings demonstrate the association of reduced serum CRP level with improvement in functionality and suggest its usefulness in the assessment and monitoring of treatment efficacy and as a guide to treatment intensity [36].

A new group of bone biomarkers has also recently been identified as a method for determining disease activity and inflammation in RA. These relatively new biochemical assays focus on type-I and type-II collagen-based bone resorption, collagen synthesis and degradation and synovitis. Increased bone resorption associated with bone erosion is mediated by changes in receptor activator of nuclear factor kappa B-ligand and osteoprotegerin (RANKL and OPG) balance which is associated with long-term radiographic progression. These new biomarkers represent highly sensitive and specific biologic markers of systemic quantitative and dynamic changes in bone turnover rates. And while their use in assessing RA activity, severity and response to therapy appear to be promising, large clinical trials are necessary to determine their definitive utility [49, 50].

In addition to these biomarkers, recent interest has focused on both the acute phase response and autoantibody formation that develop years before the first symptoms of

RA [51]. In early arthritis, long-term damage relates to anti-CCP, RF and high long-term clinical disease activity characterised in part by CRP [52]. Interestingly, the differential effect of infliximab on IgM RF and anti-CCP antibodies and on changes in acute phase reactants suggests that RF and anti-CCP antibodies are independent autoantibody systems in RA [53].

CRP and radiological progression

Serum CRP levels correlate significantly with progression of radiological damage [19, 38, 41, 47, 54, 55, 56]. In a study of 130 patients with early RA (median disease duration, 3 months), logistic regression analysis of baseline variables revealed that a high CRP level (≥20 mg/l) was an independent predictor of radiographic severe progressive joint damage at 1 year (odds ratio, 3.59; 95% CI 1.53, 8.39) [38]. Åman et al. (2000) recently reported that the combination of elevated CRP level and positive RF increases predictive power for rapid progression of joint damage [54]. In their study, the odds ratio for progressive joint disease (change in Larsen score >20 over 3 years) in patients presenting with serum CRP ≥10 mg/l in combination with RF positivity was 5.7 compared with an odds ratio of 2.6 in patients presenting with CRP ≥10 mg/l alone. The Larsen score is a method of measuring radiographic joint damage by evaluating erosions and joint space narrowing in the small joints of the hands and wrists and scoring both for severity [57]. The presence of serum CRP ≥10 mg/l combined with RF positivity gave a sensitivity of 67% and specificity of 72%, with a positive predictive value of 59%. In comparison, CRP ≥10 mg/l alone gave a similar sensitivity of 71% but lower specificity of 51%, with a lower positive predictive value of 47%.

> Findings suggest that patients presenting with a high risk profile (CRP ≥10 mg/L plus RF positivity) in early RA are likely to have a rapidly progressive disease and are therefore candidates for aggressive drug therapy to improve clinical outcome.

In a 3-year follow-up, van Leeuwen et al. (1993) demonstrated a highly significant correlation between time-integrated CRP values and radiological progression of disease (Spearman's correlation coefficient = 0.582; $P < 0.001$) in 110 patients with newly diagnosed RA (disease duration <1 year) [47]. Substantial progression of radiological joint damage was consistently associated with persistently high CRP values. To account for inter-individual variation in absolute CRP value corresponding to particular levels of disease activity and joint damage and CRP levels that increase markedly yet still remain within the normal reference range, these investigators developed a mathematical model to describe the individual relationship between CRP level and radiological progression early in the disease (approximately the first 6 years), thus improving the prognostic value of serial CRP measurements. This model is based on CRP measurements and radiographic scores over 6 months and defines the individual relationship between time-integrated CRP value and progression of radiological damage. It is not suitable to use this model for patients with no radiological damage after 6 or 12 months. This model accurately predicts radiological damage at 6 years from CRP measurement and outcome from 6 months after presentation. It has been incorporated into a readily available software program in which it is combined with patient-specific prognostic factors, and radiological prognosis is updated with each new CRP measurement. This model is a useful tool that assists in decision making regarding treatment and the identification of target levels for CRP for prevention of further joint damage [41, 55].

Plant et al. (2000) prospectively examined the relationship between time-integrated CRP levels and radiological progression in previously normal joints ('new joint involvement') and already damaged joints ('damaged joint progression') in 359 patients with active RA treated with disease-modifying antirheumatic drugs (DMARDs; hydroxychloroquine, penicillamine or gold) [41]. After a 5-year follow-up period, the mean Larsen score increased from 15.9 to 36.2. Time-averaged CRP levels correlated significantly with the mean change in Larsen score over the 5-year period (Spearman correlation coefficient = 0.50; $P < 0.001$), and a stronger correlation was seen in patients with disease duration ≤2 years at study entry (correlation coefficient = 0.59). Stratification of radiographic progression by time-integrated CRP level showed a more marked relationship between new joint involvement and time-averaged CRP than between damaged joint progression and time-integrated CRP (Fig. 5) [41]. By 5 years, in patients with normal time-integrated CRP level (<6 mg/l), 7.3% of normal joints became involved/damaged (defined as having Larsen grade of ≥2) and 26.1% of damaged joints became further damaged. In patients with high integrated CRP level (≥25 mg/l), the rate of 'new joint involvement' was 39.1% and the rate of 'damaged joint progression' was 41.6%. This represents a 5.4-fold increase in 'new joint involvement' compared with a 1.6-fold increase in 'damaged joint progression' from normal to high CRP level. These findings imply that suppression of CRP value to <6 mg/l (by drug therapy) may minimise new joint involvement and support the introduction of disease-modifying therapy in the early stages of RA before the onset of erosive damage.

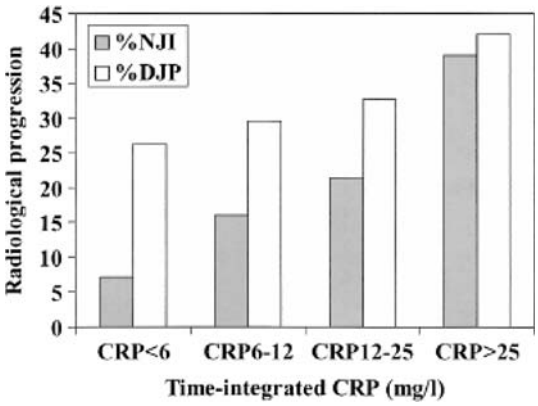

Fig. 5 Percentage new joint involvement (NJI) and percentage damaged joint progression (DJP) in relation to time-integrated CRP values during a 5-year observational period. Percentage NJI is the proportion of joints that were normal at baseline which became damaged by 5 years. Percentage DJP is the proportion of joints damaged at baseline that became further damaged by 5 years [41]. Adapted with permission from John Wiley & Sons, Inc

Suppression of inflammation in RA, clinical benefits and CRP response

It is well established that DMARDs suppress CRP and ESR, resulting in the minimisation of new joint involvement, and that the available data supports the use of DMARDs in the early stages of RA before the onset of erosive damage [41]. However, patients with established or early RA may be responding incompletely to the effects of DMARDs, particularly the ability of these agents to completely suppress CRP and ESR. Therefore, the elucidation of the immunopathogenesis of RA has led to the development of scientifically based biologic treatment options for RA and other IMIDs. Biologic DMARDs that inactivate the key proinflammatory cytokine, TNFα, are the forerunners of this new treatment approach. Infliximab is one of these compounds and the one with arguably the most rapid, profound and sustained effect on TNFα. Recent data indicate that TNFα blockade with agents such as etanercept, infliximab and adalimumab reduce CRP-mediated complement activation in patients with RA, which may contribute to the anti-inflammatory efficacy of TNFα-blocking agents [28].

Etanercept is a dimeric fusion protein consisting of the extracellular portion of the p75 TNF receptor linked to the Fc portion of human immunoglobulin G1. It is licensed for the treatment of adult RA, AS, psoriatic arthritis (PsA) and plaque psoriasis as well as juvenile RA. Etanercept is administered by subcutaneous (SC) injection once or twice weekly [58].

Infliximab is a chimeric human-murine monoclonal antibody that binds TNFα. It is licensed for the treatment of RA (in combination with methotrexate), CD, AS, PsA and plaque psoriasis and has recently been granted a license for use in UC. Infliximab is administered via intravenous infusion every 6–8 weeks after an initial loading regimen with infusions at 0, 2 and 6 weeks [59].

Adalimumab is a recombinant human monoclonal antibody specific to TNFα. It is licensed for use in RA and is administered via SC injection every 1–2 weeks [60].

TNFα-blocking agents are recommended for the treatment of active RA in patients with inadequate response to another DMARD, most commonly methotrexate [61]. A TNFα-blocking agent may be added to or, where appropriate, replace pre-existing treatment.

Clinical benefit of pharmacologic TNFα blockade

Treatment of early or advanced RA with a TNFα-blocking agent provides rapid and significant improvement in symptoms and signs of disease activity (joint inflammation, serum CRP level), slows radiographic progression of joint damage and improves physical functioning (Table 3) [16, 18, 19, 62–65]. A notable clinical response (ACR) criteria for 20% improvement in measures of disease activity is seen after 1 or 2 weeks of treatment with a TNFα-blocking agent (etanercept, infliximab or adalimumab) [62–65].

In a 24-week, double-blind clinical trial by Weinblatt et al. [62], 89 patients with persistent active rheumatoid arthritis despite 6 months of treatment with methotrexate were randomised to receive either etanercept (25 mg) or placebo SC twice weekly while continuing to receive methotrexate. The addition of etanercept to methotrexate therapy in these patients resulted in a rapid and sustained response to therapy which was significantly greater than for those patients receiving placebo ($P < 0.001$, 71% vs 27%, respectively). With regard to ACR50 scores, 39% of patients receiving etanercept and methotrexate attained an ACR50 vs 3% for placebo and methotrexate.

In the Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy (ATTRACT) study, over half of the patients responding to infliximab attained the ACR 20% improvement in clinical parameters as early as 2 weeks following an infusion of infliximab [64]. A subanalysis of data from nonresponders in the ATTRACT study showed that, relative to methotrexate alone, the concomitant use of infliximab provided significant radiographic benefit independent of a clinical response in patients with advanced RA [18, 66]. Data from the Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) study demonstrated that, compared with methotrexate, treatment with infliximab plus methotrexate significantly improved the likelihood that patients with early RA would maintain employability as a result of improved control of disease activity [67].

Table 3 Selected randomised, double-blind, placebo-controlled trials evaluating the efficacy of intravenous infliximab, subcutaneous etanercept and subcutaneous adalimumab in patients with active rheumatoid arthritis (RA)

Reference (study duration)	Study population (*n*, disease description)	Treatment regimen	Statistically significant outcomes for TNFα inhibitor regimens (vs placebo unless otherwise indicated)	
			Clinical	Radiological
Infliximab (INF)				
Maini et al. [64] (ATTRACT) (30 weeks)	428, advanced RA (mean duration, 7–9 years) refractory to MTX	INF 3 mg/kg, INF 10 mg/kg or PBO every 4 or 8 weeks *plus* MTX 10–35 mg/week	↓ Swollen joint count*** ↓ Tender joint count** ↓ Disability index[a]*** (except 3 mg/kg q 8 weeks) ↓ Pain[b]* ↑ Clinical response rate[c] (INF, ≥50%; PBO, 20%)*** ↓ CRP level***	
Lipsky et al. [18] (ATTRACT) (54 weeks)	(as above)	(as above)	↓ Swollen joint count*** ↓ Tender joint count*** ↓ Disability index[a]*** (except 3 mg/kg q 8 weeks) ↓ Pain[b]* ↑ Clinical response rate[c] (INF, 42–59%; PBO, 17%)*** ↓ CRP level***	
St Clair et al. [16] (ASPIRE) (54 weeks)	1049, early RA (duration ≤3 years), no prior MTX or anti-TNFα treatment	INF 3 mg/kg, INF 6 mg/kg, or PBO every 8 weeks *plus* MTX 20 mg/week	↑ Clinical response rate[c] (INF, 62, 66%; PBO, 54%)* ↓ DAS28 score*** ↓ Disability index[a]*	↓ Radiological progression[d]*** ↓ Joint erosion***
Etanercept (ETN)				
Weinblatt et al. [62] (24 weeks)	89, longstanding RA (mean duration, 13 years) refractory to MTX	ETN 25 mg or PBO twice weekly *plus* MTX 15–25 mg/week	↓ Swollen joint count*** ↓ Tender joint count*** ↓ Pain[b]*** ↓ Disability index[a]*** ↑ Clinical response rate[c] (ETN, 66%; PBO, 33%)*** ↓ CRP level***	
Moreland et al. [63] (24 weeks)	234, longstanding RA (mean duration, 12 years) refractory to DMARDs (90% received MTX)	ETN 10 mg, ETN 25 mg or PBO twice weekly (no concomitant DMARDs)	↓ Swollen joint count* ↓ Tender joint count* ↓ Pain[b]*** ↓ Disability index[a]* ↑ Clinical response rate[c] (ETN 51, 59%; PBO, 11%)*** ↓ CRP level***	

Table 3 continued

Reference (study duration)	Study population (*n*, disease description)	Treatment regimen	Statistically significant outcomes for TNFα inhibitor regimens (vs placebo unless otherwise indicated)	
			Clinical	Radiological
Bathon et al. [19] (48 weeks)	632, early RA (mean duration, <1 year), no prior MTX	ETN 10 mg twice weekly + oral PBO weekly; ETN 25 mg twice weekly + oral PBO weekly; PBO (SC injection) twice weekly + MTX 20 mg weekly	↑ Clinical response rate[c]* (ETN 25 mg vs MTX, $P < 0.05$ at 4 months)	↓ Radiological progression[d]*** (ETN 25 mg vs MTX) ↓ Joint erosion** (ETN 25 mg vs MTX)
Adalimubab (ADA)				
Weinblatt et al. [65] (ARMADA) (24 weeks)	271, longstanding RA (mean duration, 12 years) refractory to MTX	ADA 20, 40 or 80 mg or PBO every other week *plus* MTX (mean dose ≈17 mg/week)	↓ Swollen joint count** ↓ Tender joint count*** ↓ Pain[b]*** ↓ Disability index[a]** ↑ Clinical response rate[c] (ADA, 48–67%; PBO 14.5%)*** ↓ CRP level***	

ARMADA Anti-Tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimubab (D3E7) in Rheumatoid Arthritis, *ASPIRE* Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset, *ATTRACT* Anti-TNF Trial in Rheumatoid Arthritis With Concomitant Therapy, *DMARD* disease modifying antirheumatic drug, *MTX* methotrexate, *PBO* placebo, *SC* subcutaneous

*$P < 0.05$, **$P < 0.01$, ***$P \leq 0.001$

[a] Health Assessment Questionnaire score

[b] Assessed on visual analogue scale

[c] Clinical response defined according to the American College of Rheumatology (ACR) definition of a 20% decrease in number of tender joints, number of swollen joints, plus 20% improvement in three of the following: patient's global assessment of disease, patient's assessment of pain, HAQ estimate of disability and physician's global assessment of disease status (all were assessed with use of visual analogue scale (range 0–10)

[d] Defined as increase from baseline in the van der Heijde modification of the total Sharp score that was larger than the smallest detectable difference (9.03)

Using a similar study design, the ARMADA (Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab in Rheumatoid Arthritis) trial evaluated the use of adalimumab in patients with active RA despite treatment with methotrexate [65]. However, in this study, the attainment of an ACR20 was used as the primary efficacy endpoint at 24 weeks. For 24 weeks, 271 patients were randomised to receive adalimumab (20, 40 or 80 mg SC) plus methotrexate or placebo plus methotrexate every 2 weeks. For adalimumab 20, 40 and 80 mg, ACR20 response rates (48, 67 and 66%, respectively) were significantly greater than those achieved for placebo at 24 weeks (15%, $P < 0.001$). For measurements of ACR50 with adalimumab, the response rates were 32% for the 20-mg dose, 55% for the 40-mg dose and 43% for the 80-mg dose. These values were significantly greater than those observed for placebo (8.1%) ($P = 0.003$, $P < 0.001$ and $P < 0.001$, respectively). Adalimumab 40 and 80 mg were associated with an ACR70 response of 27 and 19%, respectively [65].

CRP response to TNFα-blocking therapy

The close relationship between cytokine-driven inflammation and CRP response makes CRP a good surrogate biomarker for the impact of pharmacological TNFα blockade in the management of RA. Treatment with TNFα-blocking agents significantly reduces CRP levels in patients with RA [18, 62, 64, 65, 68, 69], and numerous trials of anti-TNFα agents demonstrated that the significant reduction in CRP level occurred in parallel with significant improvement in clinical parameters and disability index as well as quality of life (Fig. 6) [18, 62, 64, 65, 68, 69]. While there are no head-to-head comparisons of the agents to date, all have proven effective in relieving the symptoms of RA [70] and slowing or halting radiographic disease progression, with 50–70% of patients showing clinically significant improvement with infliximab [71, 72].

In a placebo-controlled study of patients with early RA and poor prognosis, the introduction of infliximab treatment to ongoing methotrexate therapy resulted in normalisation of mean CRP level within 2 weeks after the addition of infliximab 3 mg/kg to preexisting methotrexate therapy, with suppression of CRP level being sustained over the treatment period [68]. Suppression of CRP response corresponded to suppression of inflammatory joint disease (joint counts, synovitis and bone oedema at 14 weeks) and prevention of joint damage (evidenced by reduction of joint erosions). In support of these findings, Familian et al. (2005) demonstrated a significant association between the decrease in CRP level and good clinical response to infliximab ($P < 0.01$) [28].

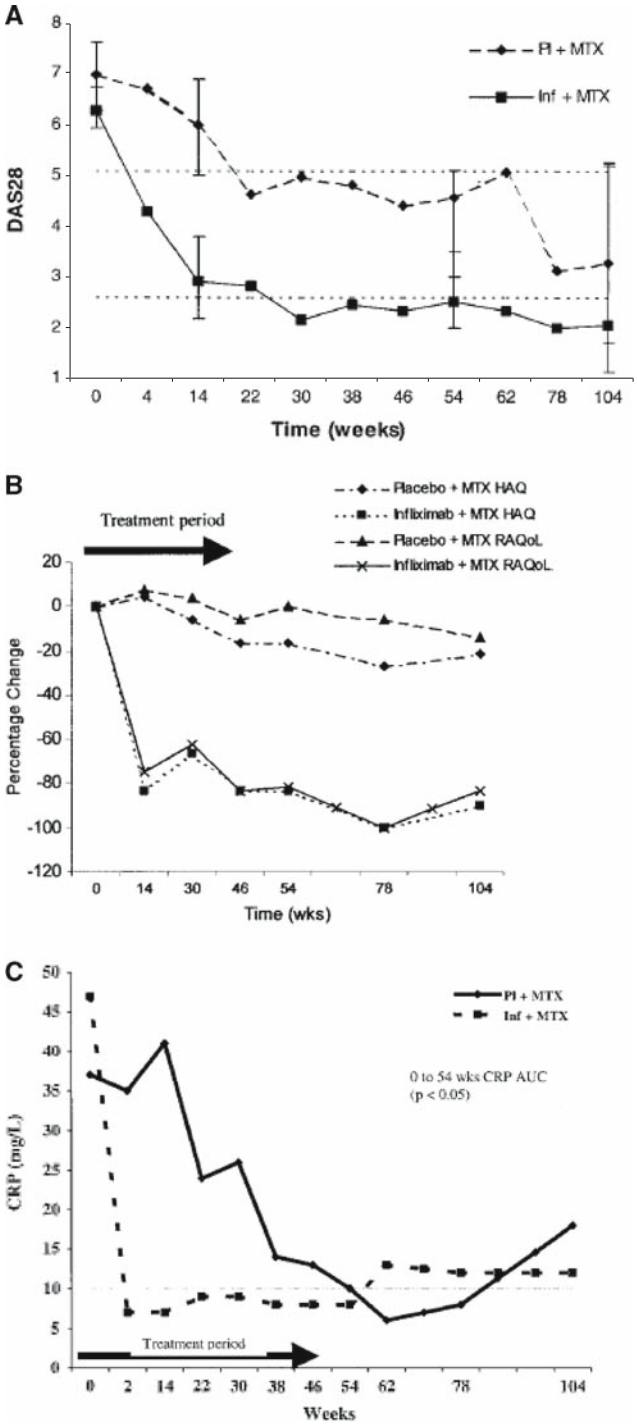

Fig. 6 Changes over time in mean C-reactive protein (CRP) levels, Disease Activity Score in 28 joints (DAS28) and Health Assessment Questionnaire (HAQ) and Rheumatoid Arthritis Quality of Life (RA-QoL) Questionnaire Score in patients treated with infliximab plus methotrexate and those treated with methotrexate alone. *AUC* area under the curve (CRP). Values for changes in DAS28 are the median and interquartile range. $P < 0.05$ for differences in changes between infliximab plus methotrexate vs methotrexate alone, for all study parameters [68]. Adapted with permission from John Wiley & Sons, Inc

Another study found that among different measures of disease activity, including swollen joint count, ACR clinical response and CRP, decreased serum CRP level was the strongest correlate of the absence of radiographic progression in patients receiving anti-TNFα (etanercept) therapy ($r = 0.45$, $P < 0.001$) [19].

CRP level for assessment of treatment

C-reactive protein level can be used to predict and monitor response to TNFα-blocking agents [22]. In the study of etanercept and methotrexate by Weinblatt et al. [62], where 39% of patients attained an ACR50 (vs 3% for placebo and methotrexate), 44% of patients with abnormal CRP levels at baseline had normal values at their last visit at 24 weeks. Median values decreased from a level of 22 mg/l for measures of CRP at baseline to 5 mg/l at week 24 ($P < 0.001$ for change vs placebo).

Buch et al. (2005) examined the value of CRP level as a predictor of response to TNFα-blocker therapy (infliximab) in patients with resistant RA. Their analysis revealed that 86% of patients who do not show at least a 20% reduction in CRP level at week 2 after the first infliximab infusion do not achieve a clinical response [according to the ACR 20% (ACR20) criteria] at week 12, whereas 57% of patients who show a ≥20% reduction in CRP level at week 2 achieve a clinical response at week 12. Among patients who showed a sustained reduction in CRP level during the first 12 weeks of infliximab treatment but failed to achieve an ACR20 clinical response, 59% showed a late clinical response (at 24 weeks) with continued infliximab therapy. These data suggest that reduction in CRP level following infliximab therapy is predictive of a clinical response within 12–24 weeks in over 50% of patients [22].

Pharmacokinetic data also suggest that baseline CRP levels may assist in TNFα-inhibitor dosage selection. Wolbink et al. (2005) found that infliximab responders had significantly higher median serum trough drug levels than nonresponders [defined as a decrease in DAS28 score after 14 weeks of ≤0.6 or a decrease of >0.6 and ≤1.2 with an attained DAS of >5.1 (3.6 vs 0.5 mg/l; $P < 0.01$)] and that clinical response significantly correlated with serum trough infliximab level [73]. They also found a significant negative correlation between serum trough infliximab levels and pretreatment CRP levels (Spearman rank correlation coefficient = <minus>0.43, $P < 0.001$ at 14 weeks) [73]. These data suggest that patients with high pretreatment CRP levels may require higher dosages of infliximab or shorter dosing intervals.

A subanalysis of data from the ASPIRE trial of infliximab showed that patients with baseline serum CRP values in the higher tertiles and/or high baseline joint damage derived greater radiographic benefit from combination infliximab–methotrexate compared with methotrexate alone [56]. This finding suggests that patients with early RA who have a high CRP level at presentation and/or greater radiographic evidence of joint damage may be candidates for early addition of infliximab therapy to methotrexate therapy [56]. Support for the benefits of early and profound suppression of inflammation comes from a prospective study of 139 patients with early RA (duration <1 year) in which Stenger et al. (1998) used CRP level to guide treatment intensity. In this study, a significant reduction in the rate of radiographic progression was achieved by titration of drug treatment intensity to a target reduction (≥50%) from baseline in CRP level [17].

In the study of adalimumab 20, 40 and 80 mg, where ACR20 response rates were 48, 67 and 66%, respectively, after 24 weeks, CRP response was also evaluated. The greatest change in CRP values from baseline was observed for the 40-mg dose of adalimumab plus methotrexate. The baseline value in this subset of patients ($n = 67$) was 21 ± 1.8 mg/l. A reduction of 16 ± 1.6 mg/l or 71% was observed, which was a significantly greater decrease than that observed for placebo (3.2%, $P < 0.001$). These reductions in CRP are reflective of the changes in disease scores which were greater for adalimumab 40 mg throughout the study (ACR20, ACR50 and ACR70) than those changes obtained with adalimumab 20 or 80 mg.

Summary and conclusions

Rheumatoid arthritis is a chronic IMID whose onset and progression is associated by over-expression of TNFα. Elevated levels of TNFα result in elevated levels of CRP, with close correlation between TNFα and CRP levels. CRP can be used as a single objective measure of disease activity because it is highly responsive to changes in cytokine (TNFα)-mediated inflammation/disease activity and it closely correlates with disease activity, radiological damage and progression and functional disability. High serum CRP level at presentation identifies patients with high levels of disease activity and at high risk for rapid radiological progression of joint damage and functional disability. These patients may benefit from a more intense approach to controlling inflammation to prevent disease progression. TNFα-blocking therapy significantly reduces disease activity, improves clinical response and physical function and reduces radiological progression. CRP level can be used to predict, assess and monitor response to treatment with TNFα agents and to titrate dosage. Identification and monitoring of these rapidly progressing patients using CRP, together with clinical signs and symptoms and early and aggressive treatment with anti-TNFα therapy to rapidly and profoundly control the inflammation, may improve the

treatment response and clinical outcomes. CRP should become a standard tool in clinical practice to objectively measure disease activity, progression and response to treatment.

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