Predictive Markers in Rapidly Progressing Rheumatoid Arthritis

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ABSTRACT. The emphasis in rheumatoid arthritis (RA) management today is on early diagnosis and intervention, but the choice of intervention has become increasingly complex. The number of disease modifying antirheumatic drugs available for treatment of RA has increased significantly. The efficacy, toxicity, and cost of those agents vary widely. And the progression of joint damage in RA is highly unpredictable and variable, ranging from self-limited disease to rapid progressive destruction. Prognostic markers that could identify patients with aggressive, rapidly progressing disease and predict the response to therapy would provide a rational basis for early, aggressive treatment. They would also protect patients with less aggressive disease from possible overtreatment and toxicities, and could have a significant influence on allocation of healthcare resources. The search for predictive markers of arthritis outcome has been and undoubtedly will continue to be the subject of many studies. This article will review both established and emerging predictive markers in RA. (J Rheumatol 2007;34 Suppl 80: 8-15)

Key Indexing Terms:
PREDICTIVE MARKERS RAPIDLY PROGRESSING RHEUMATOID ARTHRITIS
DISEASE MANAGEMENT DIAGNOSIS INTERVENTION

INTRODUCTION

The emphasis in rheumatoid arthritis (RA) management today is on early diagnosis and intervention, but the choice of intervention has become increasingly complex. The number of disease modifying antirheumatic drugs (DMARD) available for the treatment of RA has increased considerably in recent years and now includes biologic agents such as infliximab, etanercept, and adalimumab. The efficacy, toxicity, and cost of the available agents vary widely, and the course of RA and patients' response to therapy are extremely heterogeneous.

The availability of predictive markers that could identify patients with aggressive, rapidly progressive disease and poor prognosis would provide a rational basis for early, aggressive treatment. Equally important, early identification of patients with more "benign" disease, who may not require such aggressive therapy, would protect those patients from excessive treatment and possible toxicities, and could have a significant influence on allocation of healthcare resources. In addition to predicting prognosis per se, predictive markers may, in the future, be used to predict treatment effect — that is, to determine which patients will respond adequately to specific therapeutic strategies.

The search for predictive markers of arthritis outcome has been and undoubtedly will continue to be the subject of many studies. This article will review established and emerging predictive markers in RA.

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Rapidly Progressing RA

The progression of joint damage in RA is highly variable and unpredictable. In some cases radiographic progression is very slow; in other cases extensive destruction can occur within a few years after disease onset; and some patients show no evidence of erosion even after considerable disease duration[1,2].

Recent data from the Vienna Early Arthritis Cohort show a highly variable rate of radiological progression in patients with very early arthritis (≤ 3 months after onset of symptoms). Erosive disease developed in 63.6% of patients over 3 years, with the majority (74.3%) appearing in the first year and 97.2% by the end of the second year. Over 10% of patients had joint erosions at baseline (median 8 weeks from onset of symptoms). A few patients, despite DMARD therapy, developed rapidly progressive destruction, reaching approximately 40% of maximum damage scores by 3 years[3,4].

In clinical trials, investigators commonly express the rate of progression as units per time interval (e.g., Sharp-units per year)[1,5-7]. Study population progression rates may then be divided by halves or thirds to identify "slow" and "rapid" progressors. In patients with disease duration < 1 year, who were followed annually up to 4 years, this approach yielded a rapid radiographic progression rate of

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> 7.3 Sharp/van der Heijde units/year (the highest tertile), and a slow rate of < 2.3 units/year (the lowest tertile)[1]. In a population of patients with recent onset RA (symptoms < 2 years), median Sharp scores progressed from 0 to 10 over 2 years. The cohort was divided in half, yielding one group of "mild progressors" with joint damage scores ≤ 10 (or 5/year) and one group of "severe progressors" (joint damage score > 10, or > 5/year)[6]. Undoubtedly, current effective therapies contribute to slowing down radiographic progression, so that such high progression rates will no longer be seen so frequently. Although favorable and praiseworthy, these developments impede the search for predictors of progression, since the natural course of the disease can no longer be tested.

While many clinicians feel they intuitively "know" what rapidly progressing RA is, further work is required to define and quantify this concept in such a way that practical guidelines can be established to help appropriately identify *individual* patients with rapidly progressive disease.

Predictive Markers

Traditional predictors in RA, such as the presence of rheumatoid factor (RF), the level of disease activity, radiographic damage at baseline, and the presence of the "shared epitope" (SE) all enable some degree of prediction at the group level[8-12]. They do not, however, sufficiently enable prediction of radiographic progression in individual patients.

The traditional predictive markers also do not enable the prediction of treatment effect. Countless clinical trials have demonstrated an association, at the group level, between suppression of disease activity and reduction of radiographic progression. Measures of disease activity [e.g., erythrocyte sedimentation rate (ESR), Disease Activity Score] are thus considered appropriate tools to monitor and guide therapy[13]. However, monitoring disease activity does not provide adequate information to guide therapy choices.

There is a clear need for tools that will predict prognosis in individual patients at presentation, to assist clinicians in making initial treatment choices. There is an equally clear need for tools that will allow early differentiation between treatment responders and nonresponders, with respect to the development of future radiographic progression. To date there has been little investigation of the latter.

Autoantibodies: RF and Anti-CCP

RF is widely used for both diagnosis and prognosis in RA[14]. As a diagnostic test it is less than optimal, with low sensitivity and moderate specificity[15]. It is, however, useful in prognosis, as numerous studies have shown that it correlates with functional and radiographic outcomes in both RA and early inflammatory polyarthritis[16]. In a 2-year study that evaluated the predictive value of clinical and laboratory markers in 111 consecutive patients with early RA (disease duration < 1 year), positivity for RF was the strongest predictor of progressive disease (odds ratio 3.14, p = 0.015). The RF titer provided additional predictive information on patients with the highest risk of erosive damage[17].

Among several new autoantibodies described in recent years in patients with RA, anti-cyclic citrullinated peptide antibodies (anti-CCP) have generated particular interest. The sensitivity of the second-generation assay (anti-CCP2) is comparable to that of RF (68%), with higher specificity for distinguishing RA from other rheumatic diseases (95%)[18]. In addition, 35%–50% of RF-negative patients are anti-CCP antibody-positive, and anti-CCP antibodies have demonstrated prognostic utility with regard to radiographic outcomes[16].

A number of studies suggest anti-CCP positivity may be associated with substantially faster progression of joint destruction in early RA[19-21]. One prospective followup inception cohort included 200 patients with very early (< 3 months) inflammatory joint disease; RA was diagnosed in 102 patients[19]. Mean Larsen scores at baseline were similar in all groups (Figure 1). However, Larsen score progression was significantly greater in high-titer RF than in low-titer or negative RF patients ($p_{sm} < 0.0001$; Figure 1A), and in anti-CCP-positive versus anti-CCP-negative patients (data not shown). Importantly, within the subgroup of patients with low-titer or negative RF, anti-CCP-positive patients showed significantly more rapid radiographic progression ($p_{sm} = 0.038$; Figure 1B); and in the subgroup of anti-CCP-negative patients, those with high-titer RF showed significantly higher Larsen scores ($p_{sm} = 0.0014$; Figure 1C). Thus, the slope of progression of joint destruction was much steeper in patients presenting with high-titer RF or anti-CCP, or both, at baseline than in those negative for these autoantibodies.

Acute-Phase Response

Numerous studies have suggested that high ESR and high C-reactive protein (CRP) levels at onset or in the first 6 months of early RA independently predict longterm radiographic progression[2,22]. There are reports, however, that suggest the opposite — that ESR and CRP do not discriminate well between RA and non-RA and do not predict erosive disease. The fact that these measures may change with treatment may also limit their utility as prognostic factors for disease[23].

Early Radiographic Evidence of Erosions

The presence of erosive disease at baseline is an important predictor of radiographic progression. However, the prognostic value of plain radiographs may become less relevant as the paradigm of RA management shifts

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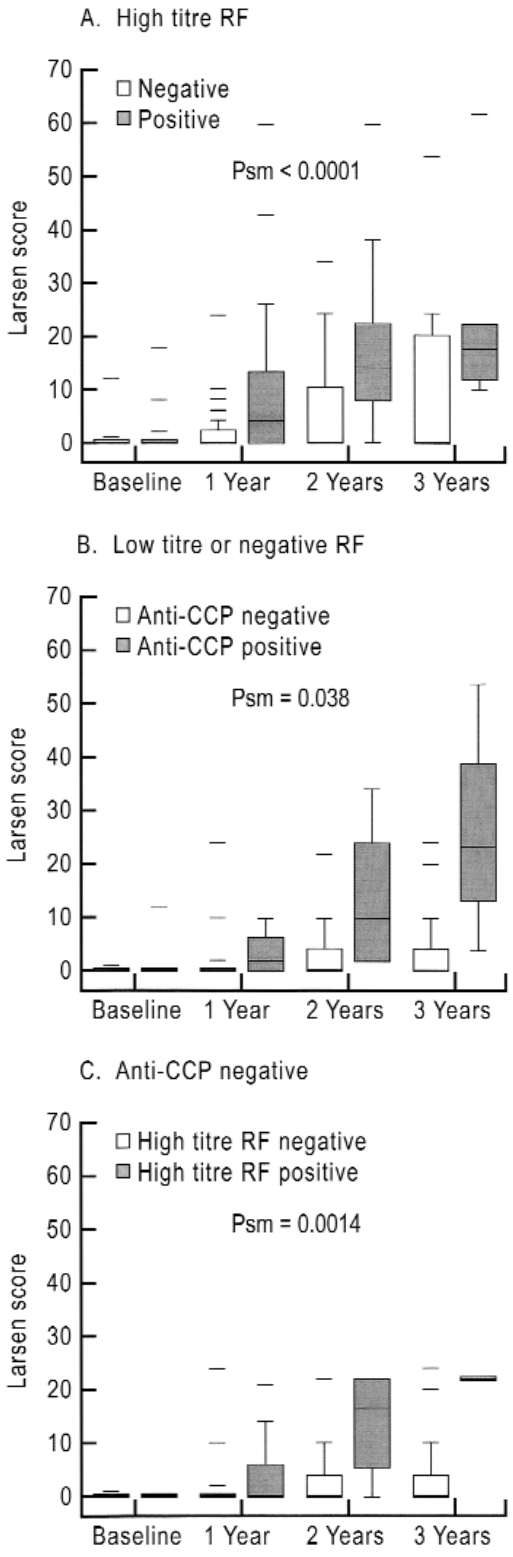

Figure 1. High-titer RF and anti-CCP are associated with rapid radiographic progression of RA[18]. Box plots show the difference in Larsen scores (grade 1 abandoned) and show median values and 25th/75th centiles. p_{sm} values indicate differences in regression coefficients between groups. From Nell VP, et al. Ann Rheum Dis 2005;64:1731-6, with permission.

toward earlier diagnosis and treatment. Destruction of bone and cartilage is a relatively late process in RA and erosions as a marker in early disease may be a non sequitur[5,24,25].

Magnetic resonance imaging (MRI) is being increasingly used as an outcome measure in clinical trials in RA[26]. Longitudinal studies have demonstrated a direct relationship between inflammatory disease (MRI-detected synovitis) and subsequent damage (MRI-detected erosions)[27,28]. Erosions on MRI have also been shown to correspond to and precede detectable radiographic erosions by a median of 2 years[29].

Recently, extremity MRI (E-MRI) has been used to assess joint damage among patients with early RA. E-MRI is less expensive than whole-body MRI and more comfortable for patients. Twenty-four previously untreated patients with joint symptoms for < 1 year were evaluated at diagnosis and after 6 and 12 months of methotrexate (MTX) treatment using radiographs of both hands and wrists and E-MRI of the dominant wrist and metacarpophalangeal (MCP) joints. In bones with MRI erosions at baseline, the relative risk of radiographic erosions at 1 year was 12.1, compared with bones without baseline MRI erosions. In patients with baseline MRI bone erosion or edema, the relative risk of radiographic erosions at 1 year was 4.0, compared with patients without these signs at baseline[30]. The investigators concluded that E-MRI is promising for assessment and prognostication of early RA. Further study will be required to determine whether it has utility in predicting rates of progression in very early RA. An unresolved issue is that MRI erosions can disappear before radiographic erosions develop, which raises questions of specificity.

Genetic Typing

Genetic factors are especially appealing prognostic markers because they are present at (indeed, before) disease onset and are unchanged by treatment. Several genes have been investigated in RA but only HLA-DRB1* genes have repeatedly been found to be associated with RA. This association seems to hold particularly true for HLA-DRB1 alleles that share a similar amino acid sequence known as the shared epitope (SE)[23]. Carriership of SE alleles both increases the risk of RA and is associated with more severe RA[31,32].

HLA alleles have also been reported to be associated with the presence of anti-CCP antibodies. A study investigating this association found that in patients with early RA, more severe disease progression is seen in those with both anti-CCP antibodies and SE alleles[33]. An increased rate of joint destruction was observed in SE-positive, anti-CCP-positive patients (mean Sharp score 7.6 units/year) compared with that in SE-negative, anti-CCP-positive patients (2.4 units/year) ($p = 0.04$), SE-positive, anti-

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CCP-negative patients (1.6 units/year) ($p < 0.001$), and SE-negative, anti-CCP-negative patients (1.6 units/year) ($p < 0.001$).

More recently another group of investigators determined concentrations of anti-CCP antibodies in sera from 126 patients with recent-onset RA (median disease duration prior to study enrollment 6 months) who had been followed prospectively for 6 years[34]. Radiographs of hands and feet at baseline and at 1, 2, 4, and 6 years were used to evaluate the progression of joint destruction. Simultaneous presence of both anti-CCP antibodies and an SE-positive DRB1*04 allele in a patient was associated with higher Larsen scores in comparison with patients positive for only one of the 2 markers (Figure 2), suggesting a possible additive effect of the 2 markers. In contrast, patients negative for both markers were found to have significantly lower Larsen scores throughout the observation period.

Other studies have reported that SE alleles are associated only with anti-CCP-positive RA and not with anti-CCP-negative disease, suggesting that SE alleles are associated, not with RA as such, but rather with a distinct phenotype of the disease[35]; and that SE alleles are not an independent risk factor for the development of RA after correction for anti-CCP antibody status, but are rather primarily a risk factor for anti-CCP antibodies and may indeed act as classic immune response genes[36]. Further study will be required to investigate this relationship and clarify what role it may play in determining the rate of progression of RA.

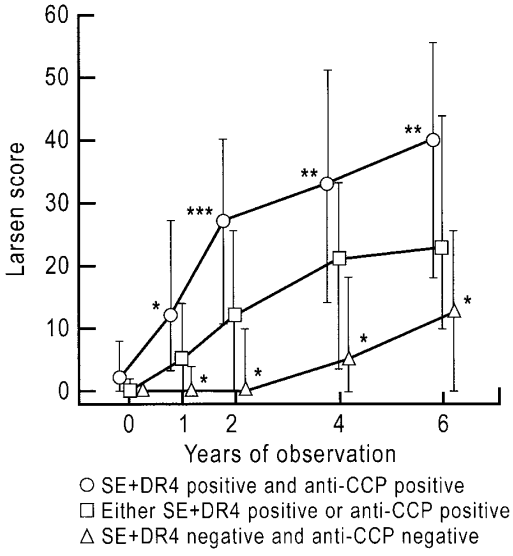

Figure 2. Radiographic progression of joint destruction as a function of SE and anti-CCP[34]. Larsen scores are shown as medians and standard error of the mean. Asterisks indicate level of significance of bivariate comparison with the middle group (patients positive for only one of the 2 markers): *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. From Kaltenhauser S, et al. Rheumatology Oxford 2007;46:100-4, with permission.

Biochemical Markers of Joint Destruction

In RA, radiographs provide a direct measure of bone erosion and an indirect measure of cartilage loss[37,38]. However, radiographs have poor sensitivity and by the time a radiologic diagnosis is made, joint damage is often significant. Molecular markers, on the other hand, that reflect the turnover and activity of the synovium, cartilage, and bone tissues may allow earlier identification of patients at high risk of rapid progression[39].

Results of early studies on the association between biochemical markers of joint destruction and the rate of progression of disease were inconsistent[40]. The inconsistencies were likely due to limitations in study design and execution, including the use of small numbers of patients, patients with advanced disease, and nonstandardized methods for measuring radiographic progression. Larger, more recent studies suggest that biochemical markers of joint destruction may be of considerable utility in determining the prognosis of patients with RA.

Synovial Markers and Cartilage Collagen Breakdown

Urinary glucosyl-galactosyl-pyridinoline (Glc-Gal-PYD) is a marker of destruction of the synovium; urinary C-terminal crosslinking telopeptide of type I and type II collagen (CTX-I and CTX-II) are markers of bone and cartilage destruction, respectively; and serum matrix metalloproteinase 3 (MMP-3) is a proteinase expressed by synovial tissue and chondrocytes[39,41].

A study of 116 patients with early RA (mean disease duration 12 months) who participated in a large randomized trial comparing etanercept with MTX[42] showed that high baseline levels of Glc-Gal-PYD, CTX-II, and MMP-3 are associated with increased risk of progression of joint destruction over 1 year in early RA[41].

A prospective study of 110 patients with early RA (median disease duration 4 months) who were participating in the COBRA clinical trial and followup study[43,44] investigated the relationship between CTX-I and CTX-II over a (median) 4-year period[39]. High baseline levels of urinary CTX-I and CTX-II were shown to independently predict an increased risk of radiologic progression and to be significantly correlated with a more rapid progression of destruction. These associations were most marked in patients with no radiographic evidence of joint destruction at baseline. In addition, patients whose baseline levels of urinary CTX-I or CTX-II were in the highest tertile of the population had a rate of progression that was 2–2.5 times higher than the rate in patients whose baseline levels of these markers were in the lowest tertiles. The relative risk of demonstrating a significant progression was 5.8 and 13.7, respectively. The investigators concluded that these findings suggest that CTX-I and CTX-II could be useful for detecting RA patients who are at high risk of joint damage progression very early in the course of the

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disease, before abnormalities can be detected radiographically.

Matrix Metalloproteinases

MMP are enzymes involved in the degradation of articular cartilage in RA. Increased levels of MMP are found in tissue and in the synovial fluid and systemic circulation of patients with RA[45]. Early studies (conducted in relatively small numbers of patients with established disease; often tested in a cross-sectional manner) failed to show a correlation between MMP serum levels and progression of joint damage[46,47]. However, more recently, larger and longitudinal studies in patients with early RA have suggested there may be a role for these markers in early disease[45,48,49].

In 85 patients with early RA (mean disease duration 7 months) followed for 18 months, time-integrated serum levels of MMP-3 (stromelysin-1) were highly correlated with the acute-phase response, but not with the number of new joint erosions. In contrast, time-integrated serum MMP-1 (collagenase-1) levels were associated with new bone erosion but not with systemic inflammation. These findings emphasize the dissociation between inflammation and the progression of joint damage in early RA[48].

In a study of 98 patients with early RA (< 12 months' duration) followed for 12 months[49], patients with a high rate of radiographic progression were found to have significantly greater baseline serum levels of both MMP-1 and MMP-3 compared with patients with a low rate of radiographic progression (MMP-1, mean value 56.0 vs 39.0 ng/ml, $p < 0.001$; MMP-3, 60.0 vs 39.4 ng/ml, $p < 0.001$). Analysis of the group of patients with normal CRP at presentation ($n = 21$) showed correlation of baseline MMP-3 and MMP-1 levels with the presence of erosive disease ($r = 0.52$ and 0.65, respectively, $p < 0.05$). Logistic regression analysis in patients who were non-erosive at presentation ($n = 81$) showed that the strongest correlation with radiographic progression score was the baseline MMP-3 level ($r = 0.30$, $p = 0.01$).

One hundred nine patients with early RA (median duration of symptoms 162 days) were followed for 2 years[45]. During that time the joint damage score progressed from 0 to 10 (median Sharp score; $p < 0.001$). Regression analysis showed that serum pro-MMP-3 levels at disease onset were independently associated with the progression of joint damage ($\beta = 0.7$, 95% CI 0.3 to 1.1, $p = 0.001$). Based on the rate of joint destruction, patients were divided into 2 subgroups: patients with mild joint damage progression (joint damage score ≤ 10 during the 2-year followup) and patients with severe joint damage progression (joint damage score > 10). Comparison of serum pro-MMP-3 levels between the 2 subgroups showed significantly higher pro-MMP-3 levels in patients with severe progressive disease at baseline and at 1 and 2 years. The authors concluded that pro-MMP-3 levels predict the loss of articular cartilage and total joint damage progression.

RANKL and Osteoprotegerin

Osteoclasts play a central role in the mechanism of joint destruction in RA[7]. RANKL and its receptor RANK, both of which belong to the tumor necrosis factor receptor superfamily, are key factors in the stimulation of osteoclast formation and activation[50]. The soluble receptor-like molecule osteoprotegerin (OPG) is a natural inhibitor of RANKL, and the balance between RANKL and OPG regulates bone resorption[51].

A study of patients who had participated in the COBRA trial was undertaken to test the hypothesis that osteoclast activation, reflected by the serum OPG:RANKL ratio at baseline, is negatively associated with progression of bone damage, independent of inflammation[24]. OPG and RANKL levels, and first-year time-averaged ESR (tESR; a measure of inflammation) were measured in 92 patients with early (mean duration 4 months), highly active disease.

The first-year tESR and the OPG:RANKL ratio, as measured at baseline, independently predicted 5-year radiographic progression of joint damage (both $p \leq 0.001$). Radiographic progression was highest (median 26 Sharp units/year) in patients with a high first-year tESR and a low OPG:RANKL ratio and lowest (median 1 Sharp unit/year) in patients with a low first-year tESR and a high OPG:RANKL ratio[24].

This study is the first to demonstrate that inflammation and osteoclast activation add to each other's effect on longterm radiographic progression in early RA. The results also confirm the importance of osteoclasts in the mechanism of joint destruction in RA, and provide an explanation for the previously clinically suspected partial dissociation between inflammation and joint destruction. The study also suggests that the OPG:RANKL ratio is apparently so important that one baseline value is predictive for 5-year progression[24].

Cartilage Oligomeric Matrix Protein

Cartilage oligomeric matrix protein (COMP) was originally isolated as a cartilage matrix component, and has subsequently also been found in other tissues (e.g., synovium, tendon, and meniscus). Numerous studies in humans and experimental arthritis, however, clearly indicate that changes in COMP serum concentrations are related to processes in cartilage. It has been suggested that serum COMP may be a marker of changes in cartilage turnover and that increased serum levels may occur early in the course of RA[52,53].

In a small early study, 2 groups of 9 patients each with recent-onset RA were selected from a larger cohort of

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150. One group had rapidly erosive disease; the other group (matched for age, sex, and disease duration) had slowly-erosive disease. Elevated serum COMP levels measured early after disease onset were the most important indicator of unfavorable prognosis in this study[54].

A larger, more recent study (n = 183) investigated the prognostic utility of 7 laboratory markers in early RA[52]. The markers analyzed were ESR, HLA-DRB alleles, CRP, COMP, RF, anti-CCP, and anti-interleukin 1α (IL-1α). After 5 years, ESR, IgA RF, COMP, and anti-CCP were significantly associated with more severe joint damage. Anti-IL-1α was associated with less severe joint damage. Baseline CRP and anti-CCP predicted radiographic outcome after 10 years. A stronger prediction was obtained by combining the prognostic factors.

Other studies have reported conflicting findings, showing that COMP is not predictive of joint damage[55,56]. A possible explanation for these varied results is the use of different COMP assays in the different trials.

Calprotectin

Calprotectin is a major leukocyte protein that has been shown to correlate well with laboratory and clinical assessments in several inflammatory rheumatic diseases[57,58]. High levels of calprotectin have been found in the synovial fluid of patients with RA[59].

In a recent study, 145 RA patients were analyzed cross-sectionally with laboratory measurements (calprotectin, CRP, and ESR), clinical measurements [28-joint counts of tender, swollen joints, physician global rating on visual analog scale, DAS28, and RA Articular Damage score (RAAD)], and radiographic measurements (plain hand radiographs; modified Sharp method), on the same day. Calprotectin showed a highly significant correlation with joint damage measures: modified Sharp score $r = 0.43$ ($p < 0.001$) and RAAD $r = 0.40$ ($p < 0.001$). The association with modified Sharp score and RAAD was maintained after adjustment for CRP, ESR, RF, DAS28, sex, and age in a multiple regression analysis ($p = 0.018$ and $p = 0.04$, respectively), while neither CRP nor ESR showed any independent associations. Highly significant correlations ($p < 0.001$) were also found between calprotectin and both laboratory and clinical markers of inflammation[60].

Longitudinal studies will be required to investigate whether calprotectin may predict the progression of joint damage in RA.

Prediction of Treatment Efficacy

To date, there has been little investigation of treatment efficacy. It is conceivable that markers that directly reflect structural damage of cartilage and bone will facilitate the prediction of treatment response and effect, and the future progression of radiographic damage[40].

We measured urinary CTX-I and CTX-II levels at baseline and 3, 6, 9, and 12 months after initiation of treatment in patients with early active disease (median duration 4 months) who participated in the COBRA trial. COBRA compared aggressive step-down combination therapy [the COBRA regimen, including temporary high-dose prednisolone, temporary low-dose MTX, and sulfasalazine (SSZ)] with mild monotherapy (SSZ)[61].

Both COBRA therapy and SSZ monotherapy produced a significant decrease in urinary CTX-I and CTX-II levels at 3 months, and this decrease was amplified at 6 months. COBRA therapy suppressed CTX-II, but not CTX-I, significantly better than did SSZ. The magnitude of the decrease in urinary CTX-II levels at 3 months significantly predicted longterm (5-year) radiographic progression (Figure 3). Patients whose CTX-II levels were normalized at 3 months had a significantly higher chance of radiographic stability (no progression over 5 years) than did patients whose CTX-II levels were increased both at baseline and at 3 months (odds ratio 4.5, 95% CI 1.5, 13). The results of this study suggest that urinary CTX-II levels may be used as early markers of treatment efficacy in patients with RA. A clinical trial exploring this hypothesis is currently under way.

Conclusion

As the number of effective therapy options in RA has grown, so has the need for reliable prognostic markers to identify patients with aggressive, rapidly-progressive disease and to predict the response to therapy. This should prove a dynamic and fruitful field of research for years to come.

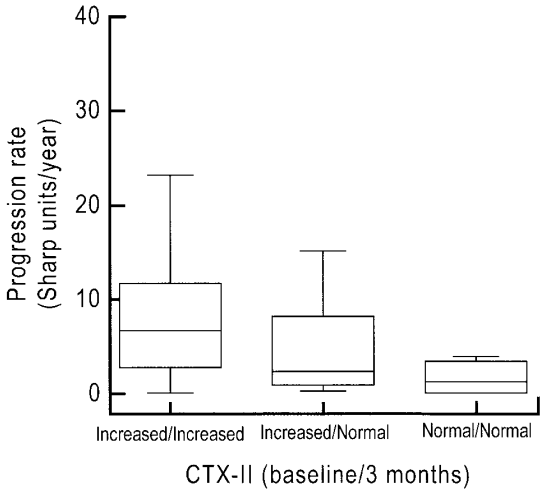

Figure 3. Radiographic progression according to the CTX-II profile of patients in the COBRA trial[61]. CTX-II was measured at baseline and 3 months after the start of therapy. Urinary CTX-II level of 150 ng/mmole of creatinine was considered an increased value. Each box represents 25th/50th (median) to 75th percentiles. Lines outside the box represent 10th and 90th percentiles. From Landewe R, et al. Arthritis Rheum 2004;50:1390-9, with permission.

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