Clinical aspects of rheumatoid arthritis: highlights from the 2010 ACR conference

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The American College of Rheumatology meeting is one of the premier medical education events for rheumatologists and features advances in the field of rheumatology that are presented by the world's leading experts and investigators. The 2010 conference included over 2000 abstracts along with a number of state of the art lectures and topical symposia. This review will highlight key abstracts presented at the meeting that dealt with the clinical aspects of rheumatoid arthritis. This article, the first of two parts, will review selected abstracts on diagnostic criteria, predictors of disease severity, lab tests and imaging. A follow-up article will focus on abstracts on remission and treatment of rheumatoid arthritis.

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2010 Rheumatoid arthritis classification criteria

A joint working group from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed a new classification criteria for rheumatoid arthritis (RA) in 2010 [1]. These criteria were developed to enable the rheumatologist to make an early diagnosis of RA and thereby facilitate treatment earlier in the disease course. The ACR/EULAR 2010 criteria are comprised of the following variables – joint involvement, serology, acute-phase reactants and duration of symptoms. Based on these new criteria a score of 6 or more, in a patient with clinically active synovitis in at least one joint that cannot be explained by a disease other than RA, is indicative of definite RA. Several abstracts reported on the application of the new criteria in different study populations. Kolfenback *et al.* applied the new criteria to identify patients with definite RA in subjects at high risk for RA based on genetic factors [2]. From a cohort of 1790 first-degree relatives of probands with RA, the new criteria were applied to 153 subjects who had synovitis in one or more joints. Definite RA was found in 21 subjects, suggesting that the new criteria can indeed identify RA early in high-risk populations. Bykerk *et al.* tried to determine the proportion of patients with recent-onset early inflammatory arthritis of less than a year that will be identified as having RA based on the new criteria [3]. From a North American cohort of 1146 patients, 74% of the subjects eligible for analysis were diagnosed with definite RA based on the new ACR/EULAR criteria. Additionally, 79% of the patients previously classified as undifferentiated inflammatory arthritis that were now classified as RA had a disease activity score 28 (DAS28) of more than 3.2. This study supports the role of the new criteria in making an early diagnosis of RA in patients hitherto diagnosed with undifferentiated inflammatory arthritis. In a study from the Netherlands, van der Linden *et al.* evaluated the 1987 and 2010 criteria in 2258 patients with early arthritis [4]. At initial presentation 1090 patients fulfilled the 2010 criteria and 726 the 1987 criteria. Interestingly, 68% of patients who did not fulfill criteria at baseline but did so at 1 year based on the 1987 criteria, fulfilled the 2010 criteria at baseline. Chitale *et al.* also applied the new criteria to a cohort of 208 patients with early arthritis (duration less than 12 months) and 91 with very early arthritis (duration of ≤3 months) diagnosed with RA based on the opinion of a rheumatologist [5]. In this study, a diagnosis of early RA and very early RA was made in 82% and 81% of patients respectively, based on the 2010 criteria, compared with 58% and 53% for early RA and very early RA respectively, based on the 1987 criteria. Taken together the above studies suggest that the use of the ACR/EULAR 2010 criteria provide the ability to detect RA early in its disease course. An earlier diagnosis of RA should facilitate rapid initiation of therapy with DMARDs, which in turn can help improve long-term outcomes.

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Fransen *et al.* reported on the validity of the 2010 criteria to predict persistent arthritis and joint erosions after 2 years, in 566 patients with early undifferentiated arthritis [6]. At year 2, persistent arthritis was noted in 45% and erosions in 48% of patients classified with RA based on the 2010 criteria. Patients with a score of 6 or more at baseline on the new criteria had a 0.74 probability of developing persistent arthritis and 0.68 probability of developing erosions at 2 years. This study shows that, in addition to detection of RA at an earlier stage, the 2010 RA criteria are useful for prediction of persistent arthritis and joint erosions in patients with early undifferentiated arthritis. In another report involving the new criteria, a fair concordance between the 1987 and 2010 criteria was noted in a French cohort of early arthritis patients [7].

Predictors of disease severity in RA

Severe arthritis with multiple joint involvement, rheumatoid factor (RF) positivity, high C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), the presence of rheumatoid nodule, the slow onset of disease, comorbidities, onset in old age and female gender have traditionally been considered to be predictors of more severe disease activity [8]. The 2010 conference had several abstracts that reported on recently identified prognostic factors for disease severity. Van den Broek *et al.* compared the clinical and radiological outcomes between patients who were positive and negative for the anticitrullinated protein antibody (ACPA) [9]. The patients were selected from the BeSt study in which 508 patients were randomized to four different treatment regimens to achieve a target DAS of 2.4 or less [10]. At baseline, ACPA-positive patients (n = 297) had more radiographic damage than ACPA-negative patients (n = 183) with median Sharp–van der Heijde scores (SHS) of 4 and 1.5, respectively. More ACPA-positive patients also had significant radiographic progression than ACPA-negative patients. The odds ratio of SHS progression of >5 was 3.27 at 1 year while odds ratio of SHS progression being >25 at 5 years was 5.95 in ACPA-positive patients. The chance of patients remaining in drug-free remission was also lower in the ACPA-positive patients although there was no difference in the chance of achieving remission between the two groups.

The same authors attempted to identify predictors of persistent low disease activity in the infliximab group within the BeSt study cohort [11]. In the BeSt study 229 patients received infliximab therapy and of these infliximab was discontinued in 103 patients, on achieving remission. In 47 patients infliximab had to be reintroduced due to disease flare. Multivariate analysis revealed that smoking, positive shared epitope status and treatment with infliximab for 18 months or more were independent predictors for reintroduction of infliximab therapy.

Kuriya *et al.* reported on baseline and early treatment predictors of DAS28 remission at 1 year [12]. A total of 893 subjects were recruited from the Canadian arthritis cohort and data were available from 363 subjects at ≥1-year follow-up, of which 147 achieved DAS28 remission. Univariate analysis revealed that younger age, male sex, lower Health Assessment Questionnaire (HAQ) scores, lower ESR and lower DAS at baseline were predictors for achieving remission at 1 year. Interestingly, use of DMARDs within the first 3 months did not appear to be a predictor for remission at 1 year. Sharpley *et al.* studied patients from an early arthritis clinic to identify predictors for very early RA, defined as symptom duration of less than 12 weeks [13]. Multivariate analysis done on 225 patients with early RA or probable early RA revealed smoking, ACPA-negative status and ESR as independent predictors of very early RA presentation. These studies highlight that in addition to the traditional risk factors for RA, ACPA status, smoking and shared epitope status are important risk factors for early RA.

Laboratory tests

The anticyclic citrullinated peptides (anti-CCP) test has higher specificity and comparable sensitivity to the RF test for the diagnosis of RA. A discussion on the role of anti-CCP is beyond the scope of this article but has been reviewed elsewhere [14]. Grados *et al.* described the clinical characteristics of a cohort of patients with positive anti-CCP antibodies [15]. In this retrospective study there were 418 positive tests, defined as a titer of 20 U/ml or more, out of 1222 determinations. Further analysis was carried out in 320 of the positive cases, of which 234 (73%) had a rheumatic disease. Seropositive, erosive RA was seen in 64.5% of patients who had titers higher than 100 U/ml. Other rheumatic diseases such as vasculitis and connective tissue diseases were associated with positive tests at lower titers (between 20 and 100 U/ml). Among the 86 patients that did not have rheumatic disease there were six cases with positive tests at titers above 100 U/ml. This study supports the notion that anti-CCP antibody tests at high titers have high specificity for RA while at lower titers they can be seen in other rheumatic diseases.

The anti-CCP2 test is widely used to detect the anti-CCP antibodies. However the anti-CCP2 test may fail to detect the entire population of patients with anticitrulline reactivity. Bromberg *et al.* performed multiplex autoantibody profiling using the Bio-Plex system to evaluate the presence of 16 ACPAs in sera from 360 untreated early RA patients from the Treatment of Early Aggressive RA (TEAR) trial and 80 non-RA controls [16]. A total of 270 were positive and 90 were negative for the anti-CCP antibodies. Among those with negative anti-CCP antibodies, two, three or four ACPAs were detected in 33, 18 and 1%, respectively, suggesting that testing for other ACPAs in addition to the anti-CCP2 assay may increase sensitivity for the diagnosis of RA.

The diagnostic value of antibodies to mutated citrullinated vimentin (anti-MCV) has been explored by several investigators in recent years [17,18]. Zablocki *et al.* performed anti-MCV, anti-CCP2 and RF (IgM) in 460 subjects from the Leiden Early Arthritis Clinic cohort [19]. Patients from this cohort presented with undifferentiated arthritis and 153 were diagnosed with RA within 1 year. In this study anti-MCV had the highest sensitivity (63%) and negative predictive value but with a reduced positive predictive value of 60%. Authors therefore conclude that the anti-MCV test could be used in patients with undifferentiated arthritis to identify those who are more likely to develop RA.

The benefits of tight control of disease activity in RA have led to an increase in use of various disease activity measures, which frequently incorporate clinical features and lab tests. Bakker *et al.* presented data on the development of a multibiomarker blood test to assess disease activity in RA [20]. Initially, 25 protein biomarkers were selected from a total of 137 candidates based on their relationship to disease activity. These markers were analyzed in sera from a cohort of North American RA patients. A set of 12 biomarkers with the best ability to evaluate for RA disease activity were chosen. This 12-biomarker, disease activity (DA) test, was then assessed in the CAMERA cohort where, in line with clinical response, the DAS also decreased significantly at 6 months compared with baseline score [21]. Vectra DA scores range from 1 to 100, and has thresholds for low (1 to ≤29), moderate (>29 and ≤44) and high (>44) disease activity. Curtis *et al.* presented an abstract on the validation of the Vectra DA [22]. DA test scores were measured in 230 RA patients with various levels of disease activity and compared with DAS28 scores of these patients. The correlation between the DA test score and DAS28-CRP was 0.56 with a significant association between change in DA test score and change in DAS28-CRP ($p<0.01$) on longitudinal analysis. These studies suggest that the DA test may provide an objective measure of treatment response and therefore provide additional means of optimizing clinic care.

Imaging

Plain radiographs

Joint damage is a frequent and often early finding in patients with RA and is a major contributor to disability. Plain radiographs are routinely used to assess the extent of joint damage. The Sharp score (TSS) and its modifications (mTSS) have been used to measure joint damage in several of the recent clinical trials of biologic agents in RA. TSS comprises evaluation of bone erosions and joint space narrowing (JSN) [23,24]. The contribution of these individual components of the mTSS to long term physical function however is unknown. Van der Heijde *et al.* investigated the longitudinal relationship between physical function as assessed by the HAQ and JSN or joint erosion [25]. They evaluated data at 8 years from completers of the DE019 adalimumab study [26]. They noted that a 20 unit increase in JSN and erosion were associated with 0.1 and 0.06 increases in the HAQ scores, respectively, suggesting that JSN has a greater impact on physical function than joint erosion. Smolen *et al.* demonstrated similar findings when they compared the effects of erosion and JSN on HAQ at the time of remission, which was defined as a score of ≤3.3 on the simplified disease activity index [27]. Data from several randomized controlled trials (ASPIRE, ATTRACT, DE019, ERA, PREMIER, TEMPO and leflunomide trial) were analyzed and revealed that irreversible physical disability as measured by the HAQ is primarily mediated by cartilage and not bone damage. The same authors, through their analysis of the same database, showed that clinical features (joint swelling) rather than serologic markers (CRP) of inflammation were the determinants of radiographic progression in RA [28].

Vermeer *et al.* reported on the relationship between disease activity and radiographic progression after 1 year, in patients with very early RA (symptoms for 1 year or less) [29]. Patients from the Dutch RA monitoring (DREAM) remission induction cohort were treated with DMARDs with the aim of achieving remission defined as a DAS28 less than 2.6. Adjustments were made to medications (methotrexate,

addition of sulfasalazine followed by methotrexate and anti-TNF agent) based on DAS28 measurements at 4–8 weekly intervals. Radiographs were assessed at baseline, 6 and 12 months. An increase in the SHS of 5 or more was considered clinically relevant progression. A hundred of the 143 patients had no radiographic progression. More patients in the remission group were without radiographic progression (73%) compared with the group with active disease (59%).

Ultrasound

Musculoskeletal ultrasound (US) provides a valuable tool in the assessment of bone erosions and has been shown to be more sensitive than conventional radiography in the detection of bone erosions [30,31]. The results of the ESPOIR cohort US study investigated the predictive role of US for future radiographic erosion [32]. US of targeted small joints of hands and feet were done on 813 patients with early arthritis, to detect erosion and synovitis. X-rays of hands, wrists and feet were performed and scored based on the SHS. Baseline US findings were compared with joint erosions on x-ray at 1 year. Univariate analysis showed that synovitis on power Doppler (PD) and US erosions at baseline were associated with the presence of erosions on radiographs at 1 year, supporting the current view that US is a reliable technique to predict future erosions in early arthritis patients.

Ultrasound studies of patients in remission have revealed evidence for persistent disease activity in the form of synovitis on grayscale (GS) and synovial hyperemia on PD [33,34]. Kitchen *et al.* evaluated 29 RA and 12 psoriatic arthritis patients on anti-TNF therapy who were thought to be in clinical remission, based on assessment by the treating rheumatologist [35]. Patients were formally assessed with a DAS28-CRP score and US examinations performed on the 28 joints assessed for DAS28 as well as the ankles and metatarsophalangeal joints and scored for synovitis on GS and PD on a 0–3 scale. The mean disease duration of the cohort was 9.9 years and the average duration of biologic therapy was 31.5 months. Of these patients 51% were in remission based on the DAS28-CRP criteria but 90% had persistent inflammation on GS and PD. Even among those in DAS28 remission, 81% were noted to have US evidence for inflammation. Senabre *et al.* performed a 12-joint US assessment, using GS and PD techniques, in 33 consecutive RA patients in clinical remission based on the DAS28 criteria [36]. PD signal was recorded in 52% of patients suggesting persistent inflammation.

MRI

MRI has been demonstrated to be more sensitive for the detection of synovitis and bone erosions in RA than conventional radiography [37,38]. There were several abstracts on the use of MRI in the diagnosis and management of RA. Østergaard *et al.* tried to identify bones in RA patients wrists and metacarpophalangeal joints most frequently involved with erosions and progression of erosions [39]. An MRI data set of RA patients was evaluated according to the RA MRI scoring (RAMRIS) system [40]. The ulnar, scaphoid, lunate, triquetrum and capitate were the bones most frequently involved with erosions and also showed most change over time, based on this analysis of 223 RA patients.

MRI is increasingly being used as an outcome measure in clinical trials of RA subjects. The RAMRIS system comprises assessment of bone erosions, bone edema and synovitis [40]. As discussed above, recent studies suggest that cartilage damage is an important part of structural damage in RA and therefore it is speculated that the assessment of JSN would add to the value of the current RAMRIS system. The OMERACT MRI group conducted an exercise to develop definitions and then proposed a scoring system for JSN [41]. MRI scores were compared with radiographic JSN scores (SHS) for the same hands. A good inter- and intra-reader agreement (0.92 and 0.90, respectively) and a good correlation with radiographic scores (0.77) was noted for the scoring system and may therefore add to the value of MRI.

Two abstracts reported on the correlation between MRI inflammatory scores and disease activity measures. In one study, MRI (1.5 T) with contrast, of the dominant hand were performed in 118 early RA patients from the TEAR study at the end of the 2-year treatment period [42]. MRI scores as assessed using the RAMRIS method were correlated to DAS28 and clinical disease activity index scores done at 2 years. The total composite MRI scores correlated better with disease activity, as assessed by DAS28 and clinical disease activity index, than with individual components (erosion, synovitis and osteitis) of the MRI scores. In the other study a subset of patient from the GO-BEFORE and GO-FORWARD trials had MRIs of dominant wrist at weeks 12, 24, 52 and 104 [43–45]. MRI scores as assessed using the RAMRIS were compared with disease activity measured using the DAS28 (CRP) and structural damage using the SHS. Significant

correlations were noted between baseline synovitis, bone edema and bone erosion scores and baseline SHS scores. A moderate correlation was noted between changes in RAMRIS scores and changes in DAS28-CRP and only a weak correlation between changes in RAMRIS scores and changes in radiographic measures.

Gandjbakhch *et al.* determined the MRI characteristics of RA patients in clinical remission or low disease activity (LDA) states [46]. Databases from six different cohorts were evaluated for patients in clinical remission or LDA states (latter defined as DAS28-CRP of less than 3.2) and in which MRIs were available. Among 300 patients in remission or LDA, MRIs were available for 287 subjects and were evaluated using the RAMRIS. MRI inflammatory activity was observed in the majority with synovitis and bone edema noted in 95 and 35% of MRIs of wrists or metacarpophalangeals, respectively. The presence of subclinical inflammation has been shown to explain structural progression seen in some patients in remission.

Taken together these studies demonstrate the pivotal role of imaging studies as outcome measures for joint damage. If confirmed in large prospective studies that cartilage damage manifest as JSN is a more important contributor to physical disability, future treatments may need to aim at preventing cartilage destruction. The role of US and MRI in early detection of joint damage was further highlighted by several investigators. Most interesting were studies that showed evidence for persistent disease activity on US and MRI, in patients thought to be in remission based on currently accepted clinical measures.

Conclusion

The 2010 annual scientific meeting of the ACR was again the largest gathering of rheumatologists for the year. A comprehensive range of topics were covered but this article focused on scientific presentations on the clinical aspects of RA. Several abstracts validated the use of the new ACR/EULAR RA criteria in the early detection of RA. Advances in laboratory testing to identify RA early and measure disease activity more accurately were reported on by several scientists. Investigators also continue to use newer imaging modalities to identify early signs of joint damage and to redefine disease remission in RA. In summary, further advances have been made to facilitate an early diagnosis of RA, an important concept of the past decade, along with the dawn of a new era that aims to redefine disease remission in RA.

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