Highlights of Recently Presented Studies

Evaluation of Patients With RA: The Role of Structural Assessments and Patient-Reported Outcomes

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Capitalizing on Advances in Rheumatoid Arthritis: Optimizing Patient Assessment

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This activity is designed for rheumatologists. Internists and other health care professionals who provide care and support to patients with rheumatoid arthritis (RA) may also participate.

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Despite the availability of clinical trial results documenting the efficacy of biologic agents and the availability of treatment guidelines, clinicians struggle with interpreting clinical evidence. This has resulted in an inconsistent application of clinical trial results and practice guidelines in a way that can be translated into beneficial care for patients. While the publication of guidelines and important study findings have, in some instances, resulted in changes in prescribing practices, other studies suggest that guidelines are not routinely followed. It has been suggested that factors such as the credibility of content, the credibility of source, and dissemination strategies are important factors for the implementation of prescribing recommendations. Thus, important new information needs to be presented in an effective manner and targeted toward this activity. The existence of these interests or relationships is not viewed as implying bias or decreasing the value of the presentation. All educational materials are reviewed for fair balance, scientific objectivity, and levels of evidence. Disclosures are as follows:


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The use of tocilizumab will be discussed in relation to treating rheumatoid arthritis. The use of infliximab for early or new onset of rheumatoid arthritis is also discussed; infliximab is currently approved for use in combination with methotrexate for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. The use of etanercept is discussed in use in patients with active early rheumatoid arthritis; etanercept is currently approved alone or in combination with methotrexate for reducing signs and symptoms, keeping joint damage from getting worse, and improving physical function in patients with moderate to severe rheumatoid arthritis.

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Rheumatoid arthritis (RA) is a systemic inflammatory disease that is associated with substantial clinical symptoms and functional impairment. RA-related pain and disability has a major impact on quality of life, preventing patients from performing normal daily activities, including social and work-related functions. The treatment of RA has advanced recently with a better understanding of the underlying disease pathology and the introduction of biologic therapies. Biological agents licensed for some time include antitumor necrosis factor (TNF) agents (infliximab, etanercept, adalimumab), an interleukin (IL)-1 receptor antagonist (anakinra), an anti-CD20 antibody (rituximab), and a CTLA-4 fusion protein (abatacept). New agents include the anti-TNF agents golimumab (approved in the US and Canada and recommended for approval in Europe) and certolizumab (approved in the United States and recommended for approval in Europe). Most recently, tocilizumab (an anti-IL-6 receptor agent) was approved in Europe and is currently under review with the US Food and Drug Administration. These agents are summarized in Table 1.

There are a number of outcome measures for assessing disease activity in RA, but because no single parameter adequately assesses the disease, it is essential that a composite index be employed. The optimal method for reporting disease activity varies depending on the outcome of interest. American College of Rheumatology (ACR) response criteria require a relative improvement from a baseline value, irrespective of baseline or endpoint activity. However, information on the response from baseline may not provide sufficiently detailed information. In contrast, other disease activity measures, such as the Disease Activity Score (DAS or DAS28), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI), are continuous instruments that allow evaluation and comparison of the actual disease activity and the absolute improvement. Moreover, these scales allow for the definition of particular disease activity states (ie, high, moderate, low, or remission).

### Structural Assessments

Currently used disease activity and response measures include joint counts and laboratory measures (eg, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]). ACR improvement criteria also comprise a measure of physical function. Over the last decade, the importance of assessing radiographic joint damage has been increasingly recognized and more commonly used as an outcomes parameter in clinical trials. This is because joint destruction is a hallmark of the disease, and radiographic changes are its surrogate. Damage often occurs early in the disease process of RA and can occur even in the presence of a clinical response to treatment if remission (or at least low disease activity) is not achieved.

#### Table 1. Biologic Therapies for the Treatment of RA

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic</th>
<th>Molecule</th>
<th>Mechanism of Action</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actemra/RoActemra*</td>
<td>Tocilizumab*</td>
<td>Humanized anti-IL-6R monoclonal antibody</td>
<td>Anti-IL-6</td>
<td>8 mg/kg IV q 4 wks</td>
</tr>
<tr>
<td>CIMZIA®†</td>
<td>Certolizumab</td>
<td>Humanized anti-TNF Fab’ fragment of monoclonal antibody</td>
<td>TNF-inhibitor</td>
<td>400 mg SQ at wks 2, 4, then 200-400 mg q 4 wks</td>
</tr>
<tr>
<td>ENBREL®</td>
<td>Etanercept</td>
<td>TNF-R2-IgG construct</td>
<td>TNF-inhibitor</td>
<td>50 mg SQ q wk</td>
</tr>
<tr>
<td>HUMIRA®</td>
<td>Adalimumab</td>
<td>Human anti-TNF monoclonal antibody</td>
<td>TNF-inhibitor</td>
<td>40 mg SQ q 2 wks</td>
</tr>
<tr>
<td>KINERET®</td>
<td>Anakinra</td>
<td>Recombinant human IL-1 receptor antagonist</td>
<td>Anti-IL-1</td>
<td>100 mg SQ q day</td>
</tr>
<tr>
<td>ORENCIA®</td>
<td>Abatacept</td>
<td>CTLA-4-IgG receptor construct</td>
<td>Anti-CD-28 (CD80/86)</td>
<td>500-1000 mg IV at 0, 2, 4 wks, then q 4 wks</td>
</tr>
<tr>
<td>REMICADE®</td>
<td>Infliximab</td>
<td>Chimeric anti-TNF monoclonal antibody</td>
<td>TNF-inhibitor</td>
<td>5-10 mg/kg IV infusion at 0, 2, 6 wks, then q 8 wks</td>
</tr>
<tr>
<td>MABHERA®</td>
<td>Rituximab</td>
<td>Chimeric anti-CD20 monoclonal antibody</td>
<td>Anti-B-cell</td>
<td>Two 500-1000 mg doses IV separated by 2 wks, usually repeated every 6-12 months</td>
</tr>
<tr>
<td>SIMPONI®‡</td>
<td>Golimumab</td>
<td>Human anti-TNF monoclonal antibody</td>
<td>TNF-inhibitor</td>
<td>50 mg SQ q mo</td>
</tr>
</tbody>
</table>

* Tocilizumab (ACTEMRA(R)) is currently approved in Japan, the European Union (as RoACTEMRA(R)), Switzerland, India, Moldova, Peru, Kuwait, Brazil, and Liechtenstein
† Certolizumab (CIMZIA(R)) is currently approved in the United States and was recommended for approval in the European Union in June 2009
‡ Golimumab (SIMPONI(R)) is currently approved in the United States and Canada and was recommended for approval in the European Union in June 2009
Progression of structural damage has historically been assessed by radiologic imaging. Radiography provides an objective measure of the extent of anatomical joint damage and is often a primary endpoint assessing the effects of treatment in clinical trials. For example, in the TICORA study (Tight Control Of Rheumatoid Arthritis), tight control of disease activity with nonbiologic disease-modifying antirheumatic drugs (DMARDs) was associated with frequent clinical remission and a reduced progression of structural damage.\(^{10}\) Biologic therapy is also associated with improvements in structural outcomes. This has been shown in several trials of TNF-inhibitors as well as in trials of rituximab and abatacept.\(^{11}\) Also, in randomized phase III trials conducted in adult RA patients in Japan and internationally, treatment with tocilizumab was associated with a significantly greater reduction in structural joint damage than conventional DMARDs or placebo (Figure).\(^{12,15}\)

With over 30 years of clinical experience, the Sharp and Larsen methods are commonly used for scoring radiographic abnormalities in RA.\(^{14}\) The Sharp method is a composite index that scores erosions and joint space narrowing separately and then adds these to give a total radiographic score. The Larsen method provides a single, global score for each joint that represents erosions, juxta-articular osteoporosis, and soft-tissue swelling.\(^{14}\) Modifications to these methods (eg, van der Heijde, Genant) have altered the selection, number, or way of scoring specific joints that are assessed.\(^{18}\)

Evaluation of progression of radiographic changes remains the best method of assessing changes in structural damage, allowing clinical researchers to follow changes over time and establish the effects of treatment on joint destruction.\(^{18}\) However, in clinical practice, performing radiographic scores is not feasible on a routine basis. Therefore, it is important to recognize risk factors for radiographic progression.

A recent analysis of data from the ASPIRE trial (Active-controlled Study of Patients Receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset)\(^{17}\) has helped to identify prognostic factors for radiographic damage in early RA over a short period of time, improving the physician’s ability to predict patients at highest risk for radiographic progression. This study expanded previous analyses on longitudinal risk factors\(^{18,19}\) by showing that even a single measure assessed before the start of treatment is of predictive relevance. Prognostic factors for radiographic progression included baseline Sharp score, baseline swollen joint counts, and CRP level, as well as composite measures of disease activity. Further, the presence of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) is associated with more severe joint damage.\(^{20-22}\) All these data were confirmed in the SONORA trial (Study Of New Onset Rheumatoid Arthritis) in which IgM rheumatoid factor, ACPA positivity, DAS28 score, CDAI, and SDAI were identified as predictors for radiographic progression.\(^{23}\)

Moreover, these risk factors can be incorporated into a matrix that allows one to determine the risk of progression.\(^{24}\)

Radiographs have been shown to reliably detect short-term changes in joint damage due to RA. Bruynesteyn and colleagues found that plain radiographs are able to identify changes in joint damage within 5 months, suggesting that radiographic progression can be a primary outcome even in short-term randomized clinical trials.\(^{25}\) Notably, such short-term effects are correlated with changes in physical function. Data from the SONORA study, presented at EULAR 2009, indicated that progression of radiographic damage over 4 months is significantly associated with worse physical function in patients with early RA.\(^{26}\) After controlling for baseline Health Assessment Questionnaire (HAQ) score, age, gender, treatment, disease duration, and DAS, Sharp Score and change from baseline in Sharp Score were significantly associated with higher HAQ scores.\(^{27}\) This confirmed previous findings on the irreversible nature of damage-associated changes in physical function.\(^{27}\)

Joint damage is related to disease activity and usually lags behind, as indicated by the association of change in radiographic score with cumulative disease activity. Using data from the Best Life In RA (BELIRA) trial and several other clinical studies, the numerical relationship between joint damage and HAQ was shown at EULAR 2009 to amount to 0.01 HAQ points per 1 Total Sharp Score point. This information allows for the correlation of radiographic score findings with functional changes.\(^{28}\) However, continued radiographic damage has been suggested to occur even in patients with stably low or no clinical disease activity.\(^{29,30}\) For example, Jayakumar and colleagues reported at EULAR 2009 that among patients recruited into the Early RA Study (ERAS), progressive radiographic damage was evident even though the mean DAS remained unchanged and relatively low (ie, 2.4–2.6). However, even low disease activity or smoldering disease will be associated with some progression of joint damage; only remission, and particularly its rapid achievement, will halt joint destruction.\(^{3}\) Another study observed that 19% of patients in clinical remission had continued
joint damage. However, there appears to be a latency in the effect of disease activity on radiographic progression, which should be considered when judging progression of damage in remission and evaluating the results of clinical trials.

The reproducibility of a primary outcome measure is an important prerequisite for its use and validity. Most studies have found considerable agreement between readers for the assessment of radiographs. Generally speaking, when scoring radiographs, the experience of the reader may be more important for reliability than the method of scoring used. Variability in how radiographic outcomes are reported in clinical trials (ie, descriptions of radiographic acquisition, assessment, and reproducibility) has also been addressed. This underscores the importance of following guidelines when reporting radiographic data in clinical trials.

The availability of new therapies has also generated interest in the possibility of repair of structural damage in patients with RA. For example, treatment with a combination of etanercept plus methotrexate (MTX) in the TEMPO trial (Trial of Etanercept and Methotrexate with radiographic Patient Outcomes) was associated with a small decline in mean Total Sharp Score (-0.54; 95% confidence interval [CI] -1.00 to -0.07) compared with small increases for those receiving methotrexate (2.80; 95% CI 1.08 to 4.51) or etanercept (0.52; 95% CI -0.10 to 1.15). However, this was true only for the first year and thus appears to be a play of chance, since subsequently there was no further decline in scores, and the 95% confidence interval of radiographic changes overlapped with 0. Thus, on the group level, halt of progression is possible, while repair is not. On the individual patient level, there are indications of repair; but currently reversal of damage, ie, repair beyond a bit of filling in erosions and especially repair of joint space narrowing, is not possible. Nevertheless, a recent OMERACT workshop (Outcome Measures in Rheumatoid Arthritis Clinical Trials) concluded that radiography can be used to assess repair, although there was no agreement on the best means of measurement. Thus, structural repair, at least on an individual patient level, may become an outcome parameter in future clinical trials.

Emerging data suggest that biomarkers may be useful as indicators of structural damage, although the strength of evidence is variable. Several studies have shown that CRP levels are a marker of inflammation and correlate with levels of structural damage. A few randomized therapeutic trials have also shown that, among patients treated with MTX, CRP is associated with radiological progression. Data presented at EULAR 2009 revealed that CRP and Helix-II (a marker of cartilage turnover) were associated with a decreased risk of structural progression after 52 weeks of therapy with tocilizumab 4 or 8 mg/kg in the LITHE study (tocilizumab safety and THE prevention of structural joint damage trial). Serum metalloproteinase-3 has also been shown to be an independent predictor of structural damage. Together, these data suggest that bone and cartilage markers could provide useful information on structural damage, particularly when combined with imaging techniques.

New Imaging Modalities

Power Doppler ultrasonography (PDUS) and magnetic resonance imaging (MRI) are promising technologies for assessing joint inflammation and structural damage in patients with rheumatoid arthritis. Although these modalities still require extensive validation and proof of relationship with long-term clinical outcomes, they may provide clinicians a useful quantitative assessment tool because they may be able to detect subclinical inflammation and demonstrate bone erosion undetected by conventional radiography. Unlike radiography, MRI has a unique ability to quantify inflammation and image-soft tissue structures revealing synovitis, tenosynovitis, and joint effusions, as well as an ability to quantify the extent of joint damage (ie, bone erosion, cartilage loss, tendon rupture). Some evidence suggests that MRI allows early detection of bony erosions with a 7- to 9-fold greater sensitivity compared with plain radiography for detecting erosions in early disease. However, the superiority of MRI over radiography remains to be determined in clinical trials. For example, in trials evaluating denosumab in patients with RA, radiography was equally as sensitive as MRI for assessing erosive damage. Moreover, with respect to outcomes in RA, the fate of erosions visualized by MRI but not radiography, is currently unknown and has to await respective long-term studies.

Although MRI is increasingly being used as an outcome measure in clinical trials, it is generally included as a secondary or exploratory endpoint in addition to radiography. The OMERACT MR Imaging Group has developed the RA-MRI scoring system (RAMRIS), which provides a reliable instrument for scoring inflammation and damage in patients with RA. However, a disadvantage of MRI is that it cannot reliably visualize cartilage changes. Joint damage is reflected by both bone erosion and cartilage changes, and RAMRIS only measures bone erosion. Moreover, the RAMRIS spares the proximal interphalangeal joints (PPPs), which often have evidence of joint destruction, and thus MRI may not be able to detect destructive disease if limited to the PPPs.

Sonography is also gaining increased interest for the assessment and management of RA. An advantage of sonography is the ability to image synovitis, bone erosion, and cartilage damage in the early phase of disease as well as vascularity; particularly when combined with PDUS. PDUS is a promising tool for the monitoring of synovial vascularity changes induced by therapeutic agents including intra-articular steroids and biologics. Nevertheless, PDUS has several limitations. These include the physical properties of ultrasound that prevent its use in some conditions (ie, does not penetrate bone or metallic prostheses), the high-quality equipment required, the fact that results are operator dependent, and the lack of standardized scanning protocols. In a study presented at EULAR 2009, Scire and colleagues demonstrated that among patients with early disease and in remission after tight-control therapy with conventional DMARDs, synovial hypertrophy on PDUS was a significant predictor of clinical relapse (hazard ratio 3.89, 95% CI 1.70-8.89). Like with MRI assessment, the long-term consequences...
of sonographic changes will have to be ascertained, particularly given the operator dependence.

**Patient-Reported Outcomes**

There is an increased recognition of the importance of including patient-related assessments of physical function and health-related quality of life in the overall evaluation of RA. Patient-reported outcomes are useful for capturing changes in the status of illness because they depict the effects of the many interacting factors (ie, biologic, economic, emotional, cultural, social) on the patient’s well-being. Current assessments such as ACR response criteria, DAS, SDAI, and CDAI include some patient-reported measures such as pain, functional disability, and/or patient global assessment. Such traditional assessments do account for important disease-related symptoms such as fatigue and disturbed sleep. While instruments exist to assess these items, their importance for inclusion in composite scores of disease activity is not established. Indeed, these symptoms are partly captured by quality of life (QOL) measures such as SF-36, and indirectly also by the patient’s global assessment.

Patient-reported assessments of physical function are often congruent with measures of inflammation and accurately reflect improvements in signs and symptoms of RA. Patient-reported outcomes may also be less susceptible to placebo effects than physician-reported measures, although this depends on the instrument employed and, if looking at physical disability, on the underlying cause of disability. In the presence of much damage, a patient with physical disability will be less responsive to active treatment due to the irreversible nature of such disability than a patient with little damage and much disease activity. The variables least responsive to placebo effects are laboratory measures, such as CRP or anemia.

Importantly, however, patients often do not sufficiently appreciate the importance of joint swelling, which correlates with long-term joint destruction and thus future, not actual, disability. In addition, the perception of improvement by patients can vary depending on the baseline disease activity. In order to be clinically useful, patient-reported outcomes should be designed to capture meaningful and personally relevant changes. Patient education is a critical factor for the optimization of patient-reported outcomes. Data from EULAR 2009 indicate that patient education can only slightly and not invariably improve the ability of patients to accurately self-assess tender and swollen joints.

A number of generic and disease-specific instruments have proven validity and sensitivity for the assessment of changes in patient-reported QOL in clinical trials. Generic instruments are those that can be used across a variety of disease states, medical interventions, and patient populations, while disease-specific instruments may be more appropriate for specific populations or settings. Table 2 summarizes QOL instruments that are commonly used in RA. However, because of time constraints, such instruments are rarely used in routine clinical practice. It is important to recognize that with increasing joint damage (or disease duration), these measures become less responsive to therapy, since physical function cannot be improved beyond the level that is governed by disease activity. This can be seen by the lesser therapeutic responsiveness of these outcomes with increasing disease duration or damage. All this underscores the need for clinicians to have a way of measuring the impact of the disease and treatments on patients’ everyday lives. To this end, EULAR is sponsoring the development of a patient-derived assessment (ie, RA Impact of Disease [RAID] score) in an effort to more fully capture relevant information on a wide range of outcomes that are important to patients. The RAID score includes seven domains that have been prioritized by patients and given weights: pain (21%), functional disability (16%), fatigue (15%), emotional well-being (12%), sleep (12%), coping (12%), and physical well-being (12%). RAID is currently undergoing validation in a large European study.

**Conclusion**

Due to the availability of new therapeutic agents and strategies, there has been a major paradigm shift in the management of patients with RA. They have allowed remission and low disease activity to become broadly attainable goals. Outcome assessments

<table>
<thead>
<tr>
<th><strong>Table 2.</strong> Quality of Life Instruments in RA&lt;sup&gt;45&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td><strong>Generic Instruments</strong></td>
</tr>
<tr>
<td>Health Assessment Questionnaire-Disability Index (HAQ-DI)</td>
</tr>
<tr>
<td>Short Form-36 (SF-36)</td>
</tr>
<tr>
<td>EuroQOL (EQ-5D)</td>
</tr>
<tr>
<td><strong>RA-Specific Measures</strong></td>
</tr>
<tr>
<td>Arthritis Impact Measurement Scales-2 (AIMS-2)</td>
</tr>
<tr>
<td>RA Quality of Life (RAQoL)</td>
</tr>
</tbody>
</table>

Source: Filippucci et al<sup>45</sup>
have also advanced and continue to evolve; new assessment tools have been investigated to evaluate their utility for measuring disease activity. Further, the importance of assessing structural changes and patient-reported outcomes is increasingly being recognized. Long-term studies are needed to determine optimal assessment paradigms that can predict long-term outcomes.

Discussion

What are the assessment tools that are most easily performed for monitoring response to therapy in the community setting?

Dr Smolen: I would recommend clinicians use one of the simplified assessment scales such as the SDAI and CDAI because they are easy to use and as effective as the more complicated scales for assessing disease activity. Of these, the CDAI is the simplest to use because it does not require laboratory monitoring.

How can rheumatologists incorporate patient-reported outcomes into their assessment of therapy?

Dr Smolen: Patient-reported outcomes can be valuable because they capture the effect of disease on a patient’s well-being. To be most clinically relevant, patient-reported instruments need to include parameters that are personally relevant to the specific circumstances of individual patients.

Which patient-reported instruments are most appropriate for use in the community setting?

Dr Smolen: In general, a disease-specific instrument is more appropriate for patient assessments. It is hoped that the EULAR-RAID instrument will be validated in clinical trials. This instrument assesses 7 domains (pain, functional disability, fatigue, sleep disturbances, coping, and overall physical and psychological well-being) that have been prioritized by patients with RA. However, patient-reported instruments should only be seen as tools employed in addition to the composite measures of disease activity associated with joint damage and disability, which have been validated in numerous studies.

What are the limitations of quality of life or functional assessments in RA?

Dr Smolen: The biggest limitation is that most assessments are time-consuming and need to be performed regularly to be useful for assessing therapy. In addition, patient perception of improvement in well-being depends on the level of disease activity at baseline.

What is the value of assessing structural deterioration in clinical trials of RA?

Dr Smolen: Assessment of structural damage is important because joint destruction is the hallmark characteristic of RA. Structural damage and disease activity are highly correlated. It has been suggested that progression of joint damage can occur during remission; this is likely due to the carry-over effects of damage, namely, the time lag until damage can be visualized radiologically; to bad clinical judgment; or to the use of inappropriate definitions of remission. In the long term, there is no continuation of joint damage in true clinical remission. Nevertheless, in routine clinical practice, performing radiographs is not feasible; therefore, one should make use of existing models that predict rapid progression of joint damage.

Which imaging techniques are the most well established for assessment of structural damage?

Dr Smolen: Radiography remains the gold standard for the assessment of structural damage and is a validated surrogate marker for joint destruction. Radiography is a well-validated outcome parameter in clinical trials and is useful for assessing response to therapy.

Will newer modalities (eg, MRI, PDUS) replace radiography for assessing structural damage?

Dr Smolen: These measures may be useful in the future in addition to radiography, because they are able to visualize aspects of the disease other than joint damage that are not apparent on radiography (eg, subclinical inflammation). However, rigorous clinical trials are required to clearly establish the validity of new modalities before they should be used in routine clinical practice.

What is the role of soluble biomarkers for assessing structural damage?

Dr Smolen: Preliminary data suggest that several biomarkers (eg, CRP, Helix-II, metalloproteinases) are correlated with structural damage, although much work remains to be done before these biomarkers can be incorporated into routine clinical practice. Once validated, they may allow risk assessment and may even replace imaging modalities such as MRI and sonography.

Is repair of structural damage an achievable goal with current treatment regimens?

Dr Smolen: The dramatic effectiveness of biologic therapies has made it possible to think about structural repair; however, this pertains only to a small proportion of patients. In general, healing of bone and especially cartilage changes is not yet possible with the current therapies. Importantly, though, halt of progression of damage is not only a valuable but a desired goal that is now indeed achievable.
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The introduction of biologic therapies has revolutionized the treatment of rheumatoid arthritis (RA). These agents produce clinically meaningful improvements in health-related quality of life (HR-QOL) including physical function, fatigue, and emotional and mental health. The development of new effective therapies for the treatment of RA is partly related to the significant progress in the design of clinical trials and the establishment of clear regulatory pathways. These improvements have led to recent updates in RA treatment guidelines by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). Both organizations now recommend disease-modifying antirheumatic drugs (DMARDs), including biologic agents, for the goal of remission or low disease activity.

Despite the availability of clinical trial results documenting the efficacy of biologic agents and the existence of treatment guidelines, clinicians struggle with interpreting evidence from randomized controlled trials (RCTs). Guidelines are difficult to use in everyday practice because they are based on clinical trials that have variable study designs and clinical endpoints; they are conducted in populations that may not reflect patients seen in clinical practice. Thus, clinicians often have difficulty applying the results of clinical trials in a way that can be translated into improved care and better outcomes for patients. This hurdle is related to a number of factors including the different types of clinical trials performed (ie, regulatory vs “real-world” trials) and the fact that no two RCTs are the same. Even with similar designs, trials enroll patient populations with variable demographic and disease characteristics and employ a variety of treatment approaches. Comparisons are especially difficult given the lack of head-to-head trials, particularly between the newer agents, and the fact that therapeutic responses are not consistent across clinical trials. Thus, it is important to interpret results of individual trials in the context of the demographic and baseline disease characteristics of each population rather than simply compare response rates across heterogeneous trials.

### Design of Clinical Trials

An improved understanding of the design and purpose of different types of clinical trials can help clinicians interpret their results in a manner that is relevant to the needs of day-to-day practice. The evolution of clinical trial design in RA is summarized in Table 1. Regulatory RCTs and “real-world” trials are designed to answer different questions and may measure clinically meaningful endpoints differently. Although RCTs are considered the gold standard, they are designed to establish the safety and efficacy of therapeutic agents, not their optimal use in practice. In an effort to identify a population of patients potentially responsive to a new therapy, RCTs have strict inclusion/exclusion criteria with strict treatment protocols, lacking the flexibility to adjust doses to individual patient needs. It would not be ethical to discontinue therapy in successfully-treated patients for purposes of inclusion in a clinical trial nor would such patients be good candidates for establishing the benefit of new therapies. Thus, most patients seen in clinical practice would not be eligible for inclusion in RCTs.

One of the biggest difficulties in translating results of clinical trials into everyday clinical practice is that RCTs do not mimic real-world experience. In contrast to RCTs, “real-world” trials provide the flexibility to adjust treatments to individual patient needs. Such treatment-to-target trials cannot be designed for regulatory approval, but allow for therapeutic decisions that more closely resemble everyday practice. While many of the early treatment-to-target trials had significant methodological challenges, including lack of blinding, lack of intent-to-treat analyses, and inclusion of relatively small sample sizes, recent designs of such trials have progressed. Initial treat-to-target studies used ACR and/or EULAR/Disease Activity Scale (DAS) responses as clinical endpoints, whereas more recent trials, such as the Combination of Methotrexate and Etanercept in active early rheumatoid arthritis Trial (COMET), aim to achieve low disease activity or “remission” as well.

### Table 1. Types of Trials Used in the Evaluation of Antirheumatic Agents

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Background DMARD trials</td>
<td>Placebo is superimposed upon background therapy (eg, MTX)</td>
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<tr>
<td>Step-up trials</td>
<td>Includes patients who are partial responders following incomplete or loss of therapeutic effect of DMARDs</td>
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<tr>
<td>Proof of concept trials</td>
<td>Require ≥3 months of treatment to ensure that efficacy is durable</td>
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<tr>
<td>Treatment-to-target trials</td>
<td>“Real-world” design allows ability to evaluate regimens with the flexibility to change therapy</td>
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Source: Strand and Sokolove

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as clinically meaningful endpoints in imaging and physical function. Another example of a new blinded RCT using a treat-to-target approach is the Treatment of Early Aggressive Rheumatoid arthritis (TEAR) trial. Objectives of this trial are to assess whether it is better to intensively treat all early RA patients with multiple DMARDs or reserve such treatment only for those who do not appropriately respond to methotrexate (MTX) monotherapy, as well as, to assess if treatment with MTX plus etanercept is superior to a triple combination of MTX, sulfasalazine, and hydroxychloroquine. The SWEFOT trial had a similar design to TEAR except that treatment was not blinded. It demonstrated that a significant number of subjects respond well to initial MTX monotherapy and do not require biologic DMARDs in their first years of disease.

**Clinical Measures of Disease Activity**

ACR and EULAR/DAS response criteria are the most commonly used assessments in clinical trials. There are differences between these criteria with respect to the types of outcomes included and the way they are calculated. ACR response criteria have three physician-reported and three patient-reported measures and one laboratory assessment (Table 2). ACR responses are defined as ≥20%, 50%, or 70% improvement in tender-joint and swollen-joint counts, and in ≥3 of the other five criteria, evaluating improvements from baseline rather than disease activity. Nonetheless, these are all continuous measures that demonstrate change. ACR criteria are useful for assessing efficacy in RCTs but impractical for use in daily clinical practice. ACR criteria for ‘remission’ are defined by six components: morning stiffness absent or ≤15 minutes duration, no fatigue, no joint pain by history, no joint tenderness, no joint or tendon sheath swelling, and no elevation of erythrocyte sedimentation rate (ESR) for at least 2 consecutive months. Despite being proposed almost 40 years ago, they remain criteria that are difficult to achieve.

EULAR response criteria use DAS28 responses by 28-joint tender and swollen joint counts, ESR or C-reactive protein (CRP), and patient global assessment. In contrast to ACR criteria, DAS28 provides a continuous measure of disease activity and is designed to limit the variability in physician assessments. Both ESR and CRP DAS28 response criteria are well-validated and correlate closely. Based on DAS scores, patients are classified as in remission (≤2.6) or to have low (≤3.2), moderate (3.2 to ≤5.1), or high disease activity (≥5.1), allowing for comparison of the proportion of patients who achieve clinically relevant disease states. However, the scale can undervalue patient global assessments because the scores can be more strongly influenced by changes in acute phase reactants (APRs), ESR and CRP, and swollen-joint counts. Although DAS is a useful instrument for use in clinical trials, requiring the use of a calculator may limit its use in clinical practice because its scores are not intuitively obvious.

An optimal method for assessing efficacy in clinical trials depends on the outcome of interest. For example, an analysis of data from the Abatacept in Inadequate responders to Methotrexate (AIM) trial found that ACR20 and a moderate disease activity state (ie, DAS28 <5.1) had the highest ability to discriminate between treatments, while a low disease activity state by DAS28 was most reflective of a lack of radiographic progression. Patient satisfaction was best reflected by stringent assessments (ie, ACR70, DAS28-defined remission) with the most important factors being a more rapid onset (ie, within 3 months) and sustainability of response.

**Simplified Disease Activity Indices**

While ACR response criteria and DAS scores are effective for assessing efficacy of therapy and identifying when treatments should be initiated or changed, they pose difficulty for practicing rheumatologists to use in routine clinical practice. Logistical and time

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**Table 2. ACR and EULAR Response Criteria**

<table>
<thead>
<tr>
<th>ACR Criteria</th>
<th>DAS28 Criteria</th>
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<tbody>
<tr>
<td><strong>Physician assessments</strong></td>
<td><strong>Physician assessments</strong></td>
</tr>
<tr>
<td>• Tender-joint count</td>
<td>• Tender-joint count of 28 joints (square-root transformed)</td>
</tr>
<tr>
<td>• Swollen-joint count</td>
<td>• Swollen-joint count of 28 joints (square-root transformed)</td>
</tr>
<tr>
<td>• Assessment of disease activity (VAS 0-100)</td>
<td><strong>Patient assessments</strong></td>
</tr>
<tr>
<td>• Assessment of pain</td>
<td>• Global assessment of disease activity (VAS 0-100)</td>
</tr>
<tr>
<td>• Global assessment of disease activity</td>
<td><strong>Laboratory evaluation</strong></td>
</tr>
<tr>
<td>• Assessment of physical function (HAQ, MHAQ, MDHAQ)</td>
<td>• Acute-phase reactant (ESR or CRP, log transformed)</td>
</tr>
</tbody>
</table>

| Laboratory evaluation | One acute-phase reactant (ESR, CRP) |

| VAS=visual analog scale |
constraints associated with ACR and DAS assessments underscore the need for simplified indices. Simplified patient-related outcomes can be clinically applicable in practice because they can easily be completed by patients and/or clinicians. Examples include the Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI), and the Routine Assessment of Patient Index Data 3 (RAPID-3) (Table 3). The SDAI includes four physician and one patient-reported parameters, scored by summing values of tender and swollen joint counts, patient and evaluator global assessments, and CRP (in mg/dL). CDAI further simplifies the process by eliminating CRP measurements, thereby increasing the ease of use and timeliness of assessment. These instruments are highly correlated with ACR and DAS28, but unlike DAS, also include physician-reported global assessment of disease activity. As numeric sums of the individual components, data from EULAR 2009 showed that the APR has little impact on the classification of remission when the CDAI is compared with the SDAI among patients receiving tocilizumab.13 This is an important observation because tocilizumab has a profound and direct effect on CRP, which is mediated by interleukin-6.

**Patient-Reported Outcomes**

The importance of patient-reported outcomes is being increasingly recognized primarily because patient-reported outcomes are best for capturing changes in the status of illness.16-18 For example, a primary analysis of two randomized trials evaluating leflunomide in patients with active RA found that patient-reported outcomes were less susceptible to placebo effects than physician-reported measures, and that self-report questionnaires, ESR, and CRP better differentiated between active and placebo treatment.17 Similarly, a pooled analysis of three RCTs involving anakinra found that the patient-reported components of the ACR measurements were more sensitive to treatment effects than physician-reported components.19 Patient-reported assessments of physical function are objective, congruent with measures of inflammation, and accurately reflect improvements in signs and symptoms of RA.20

Instruments that assess physical function and HR-QOL can also provide useful outcomes information. Indeed, these outcomes are now required for labeling claims, partly in response to requirements by the US Food and Drug Administration to establish durability of effect on physical function and HR-QOL over 24 months of treatment.1 Generic HR-QOL instruments such as the Medical Outcomes Study 36-Item Short Form (SF-36) and EQ-5D are commonly used.2,19 RA-specific instruments include those assessing physical function such as HAQ and Arthritis Impact Measurement Scales-2 (AIMS-2) as well as RA Quality of Life (RAQoL).19

Despite the value of patient-reported outcomes for identifying the impact of disease that are relevant to individual patients, such assessments may not be easy to use in clinical practice.20 Practical, reliable, simple, and convenient instruments are needed for measuring disease activity, physical function, and treatment efficacy.7 The Health Assessment Questionnaire Disability Index (HAQ-DI), the modified HAQ (MHAQ), and the multidimensional HAQ (MDHAQ) have become well-established methods for assessing physical function in RA.21-22 HAQ-DI, MHAQ, and MDHAQ exhibit robust sensitivity to change in individual patients and are predictive for long-term outcomes.7 Importantly, these instruments can quickly be completed by patients in under 5 minutes, are easy to score, and have become widely used for measuring physical function in patients with RA.19 For example, in the OPTION trial, treatment with tocilizumab 4 and 8 mg/kg was associated with significant improvements in HAQ-DI versus placebo in patients with moderate-to-severe RA and an inadequate response to MTX.23 Clear differences in favor of tocilizumab-treated patients were evident by week 4 of treatment (Figure). In the COMET trial, MTX-naïve patients with moderate to severe RA were randomized to receive MTX or MTX/etanercept with treatment titrated to low-disease activity; a clinically meaningful endpoint that includes the HAQ-DI.24 Combination therapy was associated with a significantly greater likelihood of achieving DAS28-defined remission (50% vs 28%) and “normative” HAQ scores ≤0.5 (55% vs 39%) compared with MTX monotherapy.25

**Table 3**

<table>
<thead>
<tr>
<th>Change From Baseline in HAQ-DI in Patients Receiving Tocilizumab or Placebo in the OPTION Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time (weeks)</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>8</td>
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<tr>
<td>12</td>
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<tr>
<td>16</td>
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<tr>
<td>20</td>
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<td>24</td>
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In response to the need for a relevant and rapid assessment, RAPID-3 has been developed as an instrument that includes three “patient-only” components of the ACR core data set including physical function, pain, and patient global assessment (Table 3). The goal is to facilitate quantitative assessment and monitoring of patient status in routine rheumatology practice.21 RAPID-3, which does not include formal joint counts or laboratory measurements, has been shown to be as informative as the ACR and DAS measurements in clinical trials.24-26 Notably, it can be scored in 10 seconds, compared to 90 seconds for a 28-joint count and 40 seconds for a standard HAQ.25 In a study presented at EULAR 2009 evaluating results of two infliximab clinical trials (ATTRACT and ASPIRE), RAPID-3 was similarly effective as the DAS28 and CDAI for distinguishing high/moderate activity versus low activity/remission,27 as has previously been shown with adalimumab and abatacept.25,28 Another
study presented at EULAR 2009 found that the RAPID-3 was effective for assessing changes in disease activity over time in biologic-naïve patients treated with abatacept plus MTX.29

**Joint ACR/EULAR Recommendations**

ACR and EULAR have collaborated to develop evidence-based recommendations on the evaluation of disease activity in RA and to allow a more uniform presentation of clinical trial results.30 These guidelines will also focus trial results to be more clinically relevant, by reporting each of the following:

- Disease activity response and disease activity states
- Appropriate descriptive statistics
- Baseline disease activity levels
  - Percentage of patients achieving a low disease activity state and remission (ie, outcomes other than ACR/EULAR response rates can be used [eg, DAS, DAS28, CDAI, SDAI])
- Time to onset of the primary outcome
- Sustainability of the primary outcome
- Fatigue levels
- Multidimensional function (eg, SF-36).

This type of harmonization has a number of beneficial effects for translation of clinical trials into everyday practice. Trial reporting will include a greater level of detail regarding clinically meaningful outcomes, providing an increased interpretability of results. Results of clinical trials will also be more amenable to the performance of meta-analyses and individualization of therapy, based on the more detailed information concerning patients and outcomes.30

**Conclusion**

Evaluation of patients with RA should include clinically meaningful outcomes in order to optimize the use of effective new therapies for individual patients and bridge the gap between clinical trials and patient care. To this end, RCTs should be designed to capture relevant and personally meaningful clinical benefits using assessments that can be incorporated into routine clinical practice. Several simple and validated assessments are now available that can be performed easily by patients and clinicians in the office setting. Ideally, monitoring of disease activity and therapeutic efficacy in routine practice should include assessments in three domains: 1) a patient-reported assessment of physical function, pain, and global disease activity; 2) a physician assessment of disease activity; and 3) imaging of hands and/or feet, including an evaluation of problematic joints, when change in treatment is considered. RCTs such as the COMET trial have begun a transition to this approach, looking at clinically meaningful outcomes in these three domains (ie, HAQ-DI as a patient-reported domain, DAS28 as a physician-reported domain, and Sharp score as an imaging domain). Such study designs go a long way towards increasing the clinical relevance of RCTs and helping rheumatologists manage therapy in ways that are personally important to individual patients.

**Discussion**

**How have clinical trials in RA evolved in recent years?**

**Dr Strand:** I’ve seen an increased inclusion of outcome measures that better reflect the impact of active RA on patients, including fatigue and productivity both at work and in the home. For example, instruments such as the Work Productivity Survey in RA (WPS-RA) and the Work Instability Scale (WIS) that measure home and work productivity have been included in recent trials such as RAPID-1 and 2, COMET, and PROWD (PRevention Of Work Disability). I would really like to emphasize the importance of these measures.

**How can the results of clinical trials be incorporated into routine clinical practice?**

**Dr Strand:** Overall, it should empower physicians to know that recent RCT results have demonstrated that the therapies we use

<table>
<thead>
<tr>
<th>Table 3. SDAI, CDAI, and RAPID-3 Response Criteria</th>
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<tbody>
<tr>
<td><strong>SDAI</strong></td>
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<tr>
<td><strong>Criteria</strong></td>
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<tr>
<td>Tender-joint count of 28 joints</td>
</tr>
<tr>
<td>Swollen-joint count of 28 joints</td>
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<tr>
<td>Acute-phase reactant (C-reactive protein)</td>
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<tr>
<td>Patient global assessment of disease activity (VAS 0–100)</td>
</tr>
<tr>
<td><strong>Scoring</strong></td>
</tr>
<tr>
<td>Remission: ≤5</td>
</tr>
<tr>
<td>Low disease activity: ≤20</td>
</tr>
<tr>
<td>Moderate disease activity: 20–40</td>
</tr>
<tr>
<td>High disease activity: &gt;40</td>
</tr>
<tr>
<td>Major improvement: decrease of ≥22</td>
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</table>
reduce the number of days lost at work outside and within the home, improve productivity (‘presenteeism’), enable participation in social, leisure, and family activities (RAPID-1 and 2), and reduce impending work loss (PROWD). With that foundational thinking, I think what is most important is the general understanding of clinically meaningful outcomes. Clinical trials have provided measures for these, including

- Improvements in patient-reported outcomes that meet or exceed minimal clinically important difference
- Achieving “normative” values in physical function (eg, HAQ DI ≤ 0.5)
- “Treatment to target” trials, which have clearly demonstrated that “tight control” should be the goal of therapy in all subjects.

What are the advantages or limitations of ACR and EULAR response criteria? Are these criteria practical/useful for practicing physicians?

Dr Strand: Well, insofar as they can be used in a busy clinical setting, I’ve often found that waiting for APRs (ie, ESR, CRP) may not be feasible. I would encourage doctors to collect patient-reported outcomes. Allowing patients to keep track of their own results would simplify many of the issues surrounding data collection in regular practice.

Which assessment tools are most appropriate for everyday clinical practice? How can patient-reported outcomes best be incorporated into clinical practice?

Dr Strand: I think patient-reported outcomes are the most critical. The use of disease activity scales (eg, DAS, DAI, SDAI) are appropriate choices for monitoring therapy because they all include a patient-reported outcome. However, the use of RAPID-3 should also be considered because three patient-reported outcomes are better than one. Imaging is important when changes in treatment are considered.

What are the benefits of treatment guidelines (ie, ACR, EULAR) for community practice?

Dr Strand: The guidelines available do help define the status of the disease state. Using the given classifications, I can aggressively treat with ‘low disease activity,’ for example, as my goal.

How can treatment guidelines be improved to be more relevant to community-based rheumatologists?

Dr Strand: By facilitating ways patients can keep track of their own progress. A helpful addition to the current guidelines would include a Web-based program for patients to use. An example would be www.arrive-online.org, which enables patients to obtain SF-36 scores and compare them to age- and gender-matched normative values in patients without arthritis.

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