Anti-TNF Therapies: Improving Patient Outcomes in the Treatment of Rheumatoid Arthritis

CLINICAL CONFERENCE HIGHLIGHTS

Introduction 3
The Role of TNF Inhibitors in Evolving RA Strategies 3
Evidence-Based Guideline Development 7
Practical Application of Clinical Guidance 8
Emphasis on Quality of Life and Patient-Reported Outcomes 10
CME Posttest and Evaluation 15

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TARGET AUDIENCE
This educational activity is designed for rheumatologists, primary care physicians, and other health care professionals involved in the care of patients with rheumatoid arthritis (RA).

ACCREDITATION
This educational activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Louisville School of Medicine Continuing Health Sciences Education (CHSE) and Global Academy for Medical Education, an Elsevier business. CHSE is accredited by the ACCME to provide continuing education for physicians.

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EDUCATIONAL NEEDS
Rheumatoid arthritis (RA) affects more than two million Americans and more than three million Europeans, causing substantial morbidity, debilitation, and loss of productivity. Despite decades of research, no cure exists for the disease. Recent advances in treatment have produced more effective therapies, such as inhibitors of tumor necrosis factor (TNF) and other biologic agents, which can suppress disease activity to low levels and offer the potential of remission for many patients.

Improved understanding of the RA disease process has led to recognition that the disease often progresses rapidly, causing radiographically visible joint damage and disability. Within the first year after diagnosis, such observations have created a sense of urgency surrounding the clinical management of RA, as opposed to the long-standing conceptualization of RA as a benign process.

With early diagnosis and aggressive treatment, patients with RA can live long and productive lives. However, many patients do not receive appropriate care for RA, and for reasons that are not well understood, some patients do not obtain adequate or available therapies. As a result, evaluation of new approaches to the use of existing agents is ongoing, as is the search for more effective treatment and, eventually, a cure.

The field of rheumatology continues to evolve. Clinicians are challenged to stay abreast of changes in the field to ensure that patients with RA receive the best care possible.

LEARNING OBJECTIVES
After completing this educational activity, clinicians should be able to:

- Discuss recent advances in the management of RA
- Understand the concepts of aggressive treatment and treatment to target
- Discuss key principles of recent recommendations for clinical management of RA
- Develop clinical strategies to achieve and maintain low levels of disease activity
- Recognize the adverse effects RA has on social and emotional aspects of a patient’s life and on quality of life
- Understand the role of newer therapies, such as TNF inhibitors, in the treatment of RA

DISCLOSURE
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Introduction

Most patients with rheumatoid arthritis (RA) receive one or more nonbiologic disease-modifying antirheumatic drugs (DMARDs), and the use of biologic DMARDs continues to increase.\(^1\)\(^,\)\(^2\) This growing use of DMARDs reflects an emphasis on more aggressive treatment of RA, a trend that emerged from scientists’ and clinicians’ recognition of RA as a condition that may progress rapidly and cause substantial joint damage and disability within a short time after diagnosis.

More aggressive treatment strategies for RA also reflect expansion of the spectrum of effective therapeutic options. In particular, the development of biologic DMARDs has given clinicians more opportunities to employ aggressive treatment strategies, including a multitude of combination therapies.

The emergence of inhibitors of tumor necrosis factor (TNF) created the scientific pathway to more specific and effective treatment of RA. More than a decade after the introduction of the class, the role of TNF inhibitors in the treatment of RA continues to expand.

Recent guideline development has reinforced the prominence of biologic therapy for RA. The American College of Rheumatology and the European League Against Rheumatism (EULAR) recommend early consideration of TNF inhibitors and other biologic therapies for patients who do not achieve satisfactory disease control with conventional therapy, including nonbiologic DMARDs.\(^3\)\(^,\)\(^4\)

The following educational activity highlights key presentations from the 2010 EULAR Congress, including new findings related to the role of TNF inhibitors in the treatment of RA. The authors, all of whom are specialists in RA, offer their insights into recent developments in this rapidly evolving field.


The Role of TNF Inhibitors in Evolving RA Strategies

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Clinical strategies for rheumatoid arthritis (RA) continue to evolve as understanding of the disease process increases. Once considered a benign condition that progresses slowly over time, RA has come to be viewed as a disease that can progress quickly, producing evidence of joint destruction within the first year after diagnosis. The disease’s detrimental effects on physical functioning also can arise and progress more rapidly than has been previously recognized.

The emergence of therapies that inhibit tumor necrosis factor (TNF) have had a major role in the recent evolution of clinical strategies for RA. Drugs in this class were the first to target a specific component of the inflammatory cascade that drives the RA disease process. Although TNF inhibitors have been available for more than a decade, clinicians and researchers continue to improve their knowledge about how to optimize use of the agents in the treatment of RA.

The scientific program of the 2010 Congress of the European League Against Rheumatism (EULAR) highlighted ongoing efforts to address some of the unresolved issues related to the use of TNF inhibitors in the treatment of RA. The discussion that follows summarizes some of the presentations that reflected ongoing efforts to refine the use of anti-TNF therapy to ensure that patients have every opportunity to obtain maximal benefit from treatment that offers the potential to slow disease progression and preserve physical functioning.

From Clinical Trials to Clinical Practice

New therapies must demonstrate their safety and efficacy in clinical trials before they are made available for general use in clinical practice. Most clinical trials provide a controlled environment for evaluating a therapy, wherein enrollment is limited to specific types of patients whose clinical care follows a prespecified, standardized protocol. In many respects, a clinical trial represents a setting that affords a new therapy the best circumstances possible to demonstrate safety and efficacy.

In contrast, physicians in clinical practice typically have heterogeneous patient populations, whose clinical and demographic characteristics vary widely. The multiplicity of differences between the controlled environment of a clinical trial and the heterogeneity of clinical practice often lead to questions about the applicability of clinical trial results to general practice.

At the 2010 EULAR conference, investigators from Denmark and Norway indirectly examined the generalizability issue in a study of radiographic progression of RA among patients treated within a clinical practice. More specifically, they assessed the impact of treatment with inhibitors of TNF on radiographically defined joint destruction.\(^1\)
The study involved 522 patients with RA who had a median age of 54 years and a median disease duration of 5 years. The study population had a female predominance (76%); 80% of subjects tested positive for rheumatoid factor, and 65% tested positive for anti-cyclic citrullinated peptide antibodies.

Conventional radiographs were obtained about 2 years prior to the start of anti-TNF therapy, at initiation of therapy, and after 2 years of anti-TNF therapy. The patients’ mean baseline 28-joint Disease Activity Scale (DAS28) score was 4.4. Prior to starting anti-TNF therapy, 90% of the patients had at least one disease-modifying antirheumatic drug (DMARD), including 45% treated with methotrexate.

At the start of anti-TNF therapy, the mean DAS28 score had declined to 3.1. About 60% of patients received infliximab, 25% adalimumab, and 15% etanercept. In 78% of cases, anti-TNF therapy was combined with methotrexate.

Two years after initiation of TNF inhibitor therapy, 60% of patients remained on their initial anti-TNF agent, 29% had switched to a different TNF agent, and 11% had stopped anti-TNF therapy. The mean DAS28 score had declined to 3.1.

By multiple radiographic parameters, patients had significantly less progression of joint destruction during treatment with TNF inhibitors than in the 2-year period of joint destruction during treatment with DMARDs, including 45% treated with methotrexate.

Delta A–B/year=annual progression rate time A to B; Delta B–C/year=annual progression rate time B to C; DMARD=disease-modifying antirheumatic drug; ES=erosion score; IQR=interquartile range; JSN=joint space narrowing; RA=rheumatoid arthritis; SD=standard deviation; TNFI=tumor necrosis factor inhibitor; TSS=total Sharp/van der Heijde score. Source: Ørnbjerg et al.1 Used with permission.

Table 1. Radiographic Progression During Treatment With DMARDs and Subsequent Treatment With TNFIs in Patients With RA in Clinical Practice

<table>
<thead>
<tr>
<th></th>
<th>A DMARDs</th>
<th>B TNFIs Start</th>
<th>C 2-Year Follow-Up</th>
<th>Delta A–B/Year</th>
<th>Delta B–C/Year</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSS, mean (SD)</td>
<td>21.0 (29.8)</td>
<td>25.7 (32.0)</td>
<td>27.0 (32.8)</td>
<td>2.1 (3.8)</td>
<td>0.67 (2.3)</td>
<td>&lt;0.0001a</td>
</tr>
<tr>
<td>TSS, median (IQR)</td>
<td>7 (1-31)</td>
<td>13 (2-40)</td>
<td>14 (3-42)</td>
<td>0.73 (0-2.9)</td>
<td>0 (0-0.89)</td>
<td>&lt;0.0001a</td>
</tr>
<tr>
<td>ES, mean (SD)</td>
<td>13.1 (19.9)</td>
<td>15.5 (21.3)</td>
<td>16.2 (21.7)</td>
<td>1.04 (2.0)</td>
<td>0.36 (1.4)</td>
<td>&lt;0.0001a</td>
</tr>
<tr>
<td>ES, median (IQR)</td>
<td>4 (0-18)</td>
<td>6 (1-23)</td>
<td>7 (1-24)</td>
<td>0.2 (0-1.4)</td>
<td>0 (0-0)</td>
<td>&lt;0.0001a</td>
</tr>
<tr>
<td>JSN, mean (SD)</td>
<td>7.8 (11.5)</td>
<td>10.2 (12.7)</td>
<td>10.8 (13.2)</td>
<td>0 (1.2)</td>
<td>0.31 (1.2)</td>
<td>&lt;0.0001a</td>
</tr>
<tr>
<td>JSN, median (IQR)</td>
<td>2 (0-12)</td>
<td>5 (0-16)</td>
<td>6 (0-17)</td>
<td>0 (1.4)</td>
<td>0 (0-0)</td>
<td>&lt;0.0001a</td>
</tr>
<tr>
<td>Progressing patients, %</td>
<td>59</td>
<td>31</td>
<td></td>
<td>0</td>
<td>0</td>
<td>&lt;0.0001a</td>
</tr>
</tbody>
</table>

Patients who completed the 24-week randomized phase of RAPID 2 could enter an open-label extension phase, during which they would receive certolizumab pegol 400 mg every other week plus methotrexate. Follow-up data from the trial now extend to 3 years.

Of 355 patients who completed the randomized phase of RAPID 2, 342 (96%) entered the open-label extension phase. The patient population had high baseline disease activity, reflected in a mean DAS28 score of 6.8 and a modified Total Sharp Score (mTSS) of 33.6. The data showed that 79% of patients who entered the long-term extension remained in treatment after 3 years. Only two patients discontinued because of loss of efficacy.

After 3 years of follow-up, the improvement that had been observed after 24 weeks of treatment was maintained or increased. From week 24 to week 148, the proportion of patients who achieved American College of Rheumatology (ACR)–rated responses increased, and the mean DAS28 score continued to decline. Improvements in the Health Assessment Questionnaire (HAQ) score and pain score were maintained, and mTSS values exhibited minimal change (Table 2).

Another assessment of long-term safety and efficacy of anti-TNF therapy showed favorable results with golimumab.3 The findings came from a randomized, double-blind trial involving patients whose RA remained active despite treatment with methotrexate.

Patients continued taking methotrexate and were randomized to receive placebo or one of two doses of golimumab (50 or 100 mg), or they were randomized to monotherapy with golimumab 100 mg. After 24 weeks of treatment, placebo-treated patients crossed over to the lower golimumab dose and were followed for an additional 52 weeks, at which time unblinding occurred and patients receiving the lower dose could have it increased to 100 mg at physician discretion.

Data reported at EULAR included follow-up to 104 weeks. Of 224 patients who had at least a 0.25 improvement in HAQ score after 24 weeks (the minimum for clinical significance), almost 90% maintained the improvement at 2 years. The proportion from each group that maintained the improvement ranged from 86.7% to 91.5%.

Overall, patients had low rates of serious adverse events (SAEs), but rates were
of TNF inhibitors. Investigators assessed provided some insights into the sequential use of the agents to treat a chronic condition that may require extended therapy.

**Issues in Sequential Use of TNF Inhibitors**

The expansion of the TNF inhibitor class of therapy not only has given physicians and their patients more options, but also has created a potential for therapeutic switching or sequential use of agents in the class. Until recently, few studies had examined outcomes associated with changing from one TNF inhibitor to another, although the practice has been employed informally in clinical practice for some time.

A multicenter European study provided some insights into the sequential use of TNF inhibitors. Investigators assessed the potential to achieve low disease activity with adalimumab in patients with RA and a history of therapy. In some cases, prior therapy included a different TNF inhibitor, whereas in other cases, patients had not previously received anti-TNF therapy.

The investigators used the DAS28 to assess treatment effectiveness, and they defined low disease activity as a DAS28 score of ≤3.2.

The analysis included 3,025 patients with no prior exposure to anti-TNF therapy and 408 who had been treated with a different TNF inhibitor. Baseline DAS28 scores averaged about 6.0 in both groups of patients, who were followed for 48 months.

Within 3 months of starting adalimumab therapy, 41.9% of patients with no prior exposure to anti-TNF therapy achieved low disease activity. The proportion with low disease activity increased throughout the follow-up period and stood at 55% after 48 months. The change from baseline DAS28 score averaged 2.7.

Among patients with prior anti-TNF therapy, 28% had achieved low disease activity by 3 months. The proportion increased more gradually than that in the group with no history of anti-TNF therapy but was consistent throughout follow-up, reaching 42.2% at 36 months and 40.4% at 48 months. The mean improvement from baseline in DAS28 score was 2.5.

In the patients with a history of anti-TNF therapy, the proportion achieving low disease activity at 48 months was similar among those who switched to adalimumab because of lack of response (40.8%) or loss of response (36.6%) to the initial TNF inhibitor.

The results are consistent with those of other studies, showing that a proportion of patients with RA do respond to anti-TNF therapy following prior exposure to a different TNF inhibitor. In general, response rates tend to be lower in anti-TNF–experienced patients, but a substantial proportion of patients with and without prior anti-TNF therapy derive clinical benefit, as shown in Table 3.

### Table 2. Efficacy of Certolizumab Pegol Plus Methotrexate Over 3 Years in Patients with RA

<table>
<thead>
<tr>
<th>Week 24</th>
<th>Week 100</th>
<th>Week 148</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRI</td>
<td>Observed (n=310)</td>
<td>NRI Observed (n=240)</td>
</tr>
<tr>
<td>ACR50 responders</td>
<td>46.6</td>
<td>51.3</td>
</tr>
<tr>
<td>ACR70 responders</td>
<td>19.1</td>
<td>21.0</td>
</tr>
<tr>
<td>DAS28, mean (SD)</td>
<td>4.0 (1.2)</td>
<td>3.8 (1.2)</td>
</tr>
<tr>
<td>DAS28 change from BL, mean (SD)</td>
<td>-2.8 (1.3)</td>
<td>-3.0 (1.3)</td>
</tr>
<tr>
<td>HAQ-DI, mean (SD)</td>
<td>0.96 (0.60)</td>
<td>0.93 (0.61)</td>
</tr>
<tr>
<td>HAQ-DI change from BL, mean (SD)</td>
<td>-0.64 (0.50)</td>
<td>-0.66 (0.56)</td>
</tr>
<tr>
<td>Pain VAS change from BL (0–100 mm), mean (SD)</td>
<td>-30.0 (22.4)</td>
<td>-30.9 (25.1)</td>
</tr>
<tr>
<td>mTSS change from BL, mean (95% CI)</td>
<td>0.61 (0.1–1.3)</td>
<td>0.58 (0.1–1.1)</td>
</tr>
</tbody>
</table>

*Last observation carried forward; †Linear extrapolation; ‡The actual number of subjects in the summaries varies slightly from N=342 because of nonimputable missing data for each parameter. †Week 12/8.

### Table 3. Percentages of Patients Achieving Low Disease Activity During 4 Years of Adalimumab Treatment (LOCF Analysis) in Subgroups of Patients Without and With a History of Anti-TNF Therapy

<table>
<thead>
<tr>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 24</th>
<th>Month 36</th>
<th>Month 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior anti-TNF therapy (n=3,025)</td>
<td>41.9</td>
<td>48.3</td>
<td>51.0</td>
<td>54.5</td>
<td>55.1</td>
</tr>
<tr>
<td>Prior anti-TNF therapy (n=408)</td>
<td>28.0</td>
<td>30.9</td>
<td>34.1</td>
<td>39.7</td>
<td>42.2</td>
</tr>
<tr>
<td>Lack of response (n=76)</td>
<td>17.8</td>
<td>22.4</td>
<td>27.6</td>
<td>36.8</td>
<td>40.8</td>
</tr>
<tr>
<td>Loss of response (n=142)</td>
<td>19.4</td>
<td>26.8</td>
<td>33.8</td>
<td>38.7</td>
<td>37.3</td>
</tr>
<tr>
<td>Intolerance (n=87)</td>
<td>39.8</td>
<td>36.8</td>
<td>40.2</td>
<td>40.2</td>
<td>48.3</td>
</tr>
</tbody>
</table>

*Anti-TNF=antibody against tumor necrosis factor; LOCF=last observation carried forward. Source: Smolen et al. Used with permission.*
For 50% inhibition of IL-1β (IC50), the values were 0.1 ng/mL for certolizumab pegol, 20 ng/mL for golimumab, and 50 ng/mL for infliximab. Certolizumab pegol caused no increase in apoptosis above levels observed with control.

The results showed that certolizumab pegol and etanercept resulted in greater neutralization of human TNF than did the other three TNF inhibitors and that certolizumab pegol was the most potent inhibitor of IL-1β secretion by monocytes. Certolizumab pegol also differed from the other members of the class with respect to induction of apoptosis.

The investigators acknowledged that the potential clinical relevance of the in vitro findings is unclear, but they provide direction for future investigation of differences among members of the anti-TNF class.

**Comparing Efficacy and Persistence**

Direct comparisons of different TNF inhibitors have been uncommon to date. Patient registries offer an indirect means for comparing results with different members of the class, albeit an imperfect means. Registries and longitudinal observation cohorts provide information about clinical practice to complement results from randomized clinical trials.

An analysis of a large Danish registry yielded data for examining the activity and persistence associated with etanercept, adalimumab, and infliximab. The analysis involved 2,326 patients with RA and a history of treatment failure with one or more conventional DMARDs. Almost half of the patients (1,134) began anti-TNF therapy with infliximab, 675 with adalimumab, and 517 with etanercept. Some patients received a TNF inhibitor by itself, and others were treated with a TNF inhibitor plus methotrexate.

The primary end point of the analysis was outcomes at 6 months. Investigators excluded 449 patients who stopped anti-TNF therapy before 6 months. Outcomes of interest included an ACR70 response, a EULAR-rated “good” response (a DAS score of <3.2 plus improvement of >1.2 in DAS28 score), DAS28 remission (<2.6), and Clinical Disease Activity Index remission (<2.8).

By each outcome parameter, adalimumab resulted in the highest response rates, followed by etanercept, then infliximab (Table 4).

For example, the proportion of patients achieving an ACR70 response was 19% with adalimumab, 17% with etanercept, and 11% with infliximab. Using infliximab as the reference, the odds ratios for achieving an ACR70 response were 2.05 for adalimumab and 1.78 for etanercept. The odds ratio for adalimumab versus etanercept was 1.15, which was not significant.

Patients were significantly more likely to continue using adalimumab and etanercept at 48 months. Persistence rates at that point were 52% with adalimumab, 56% with etanercept, and 41% with infliximab ($P<0.0001$).

The findings from the study of the Danish registry are consistent with those of other European registries. Data from a Dutch registry showed that patients achieved greater improvements in DAS28 scores with adalimumab and etanercept than with infliximab. A Swedish registry showed higher ACR20 response rates and better adherence with etanercept than with infliximab. Similar to the Danish registry, a French study showed that treatment persistence was longest with etanercept, intermediate with adalimumab, and shortest with infliximab.

**Predicting Clinical Benefit Before Switching Agents**

Physicians and patients alike would benefit from knowing whether switching from one TNF inhibitor to another will result in a clinically important response. Data from a Dutch cohort study suggested that patients who develop antibodies to infliximab or adalimumab during initial anti-TNF therapy may have a greater likelihood of responding to etanercept.

The study involved 293 consecutive patients with RA treated with etanercept, 89 (30%) of whom had been treated previously with infliximab or adalimumab. Antibody testing showed that 47 of the 89 patients had developed antibodies to their prior anti-TNF therapy and 42 had not.

The primary outcome of interest was response to etanercept after 6 months of therapy, as defined by the change from baseline DAS28 score, which averaged 5.0 to 5.5.

Patients with no prior exposure to anti-TNF therapy had a mean improvement of 2.1 in DAS28 score as compared to 1.6 in patients who switched to etanercept from another anti-TNF agent ($P=0.015$). However, DAS28 improvement averaged 2.0 in patients who had antibodies to infliximab or adalimumab. In contrast, patients without antibodies had a mean improvement of 1.2, which was significantly lower than the mean improvement in patients who had no prior anti-TNF therapy ($P=0.001$) and compared to patients who had antibodies to infliximab or adalimumab ($P=0.017$).

Although the results should be considered preliminary, they suggest that determining antibody status prior to changing from one anti-TNF agent to another might help identify patients who are more likely to benefit from the change.

**Recognizing the Benefits of Combination Therapy**

Methotrexate continues to be a mainstay of therapy for RA. However, a substantial proportion of patients with RA do not achieve satisfactory disease control with methotrexate alone. As a result, add-on therapy with a TNF inhibitor has become increasingly common and frequently improves disease control and reduces symptoms.

<table>
<thead>
<tr>
<th>Table 4. Response to Biologic Therapy After DMARD Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>ACR70</td>
</tr>
<tr>
<td>Odds ratioa</td>
</tr>
<tr>
<td>EULAR “good” responseb</td>
</tr>
<tr>
<td>DAS28 remission (&lt;2.6)</td>
</tr>
<tr>
<td>CDAI remission (&lt;2.8)</td>
</tr>
</tbody>
</table>

*a Using infliximab as the reference; DAS score of <3.2 plus improvement of >1.2 in DAS28 score.
*b DAS28=28-joint Disease Activity Scale; DMARD=drug; EULAR=European League Against Rheumatism.

Source: Adapted from Hetland.6
Evidence-Based Guideline Development

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Treatment of rheumatoid arthritis (RA) has changed dramatically over the past decade. Much of the change has centered on the use of disease-modifying antirheumatic drugs (DMARDs) including biologic DMARDs. Recognition of RA as a disease that progresses rapidly in many patients has led researchers and clinicians to rethink the basic approach to the use of DMARDs. The evolving treatment paradigm emphasizes aggressive therapeutic strategies designed to slow or prevent disease progression and its associated joint destruction, disability, and morbidity.

Aggressive treatment encompasses principles such as early use of conventional and biologic DMARDs, use of novel DMARD combinations, sequential use of biologic agents, and treatment designed to achieve and maintain a specific disease activity target. The availability of more treatment options, as well as more effective treatment, has made disease remission a reasonable therapeutic goal for a substantial proportion of patients with RA.

Even for patients who do not achieve remission, tight control of disease activity affords opportunities to stall progression, preserve function, and allow more patients with RA to live active, productive lives.

Within the context of more aggressive therapy and a growing number of treatment options for RA, the European League Against Rheumatism (EULAR) recently published new recommendations for the use of synthetic and biologic DMARDs. Based on a series of systematic reviews of the RA literature, the recommendations support the principles of aggressive treatment and tight control. They also reflect recognition of the costs of RA, including direct medical costs, indirect costs in the form of lost productivity, and the social and emotional costs to the patient.

The recommendations embrace many of the same principles of clinical management that were articulated in the American College of Rheumatology (ACR) guidelines for use of DMARDs in the treatment of RA. Both sets of recommendations affirm the use of DMARDs—synthetic and biologic—as the mainstay of therapy for RA. EULAR and ACR encourage a more aggressive approach to the treatment of RA: earlier referral to rheumatology specialists; earlier use of tumor necrosis factor (TNF) inhibitors and other biologic agents; earlier use of combination therapy; appropriate switching of drug treatment (even within the same class), and tight control of disease activity, including treatment to specific targets defined by objective measures of disease activity.

Inherent to the EULAR and ACR recommendations is the desire to give patients with RA the opportunity to live full and productive lives, despite a chronic, debilitating disease for which no cure currently exists.

Initial Therapy
The ACR and EULAR recommendations emphasize early use of DMARDs, noting that most patients with an RA diagnosis use nonbiologic DMARDs. Additionally, the ACR pointed out that a growing number of patients use biologic DMARDs earlier in the disease course. The EULAR guidelines panel stated that early use of DMARDs has been associated with achievement of low disease activity or remission in a substantial proportion of patients.

Both organizations cited methotrexate as appropriate initial therapy for patients with disease of all durations, with all levels of disease activity, and irrespective of the presence or absence of unfavorable prognostic features. The ACR also gave leflunomide that recommendation. EULAR characterized methotrexate as the “anchor drug” for treatment of RA because of its efficacy as monotherapy and its ability to enhance the efficacy of biologic DMARDs.

The goal of treatment for all patients with RA is disease remission or low disease activity, according to EULAR. The recommendation is based on evidence that patients who attain remission or low disease activity have better structural and functional outcomes.

Consistent with the goal of remission or low disease activity, EULAR encourages early consideration of combination therapy that includes a synthetic DMARD. The ACR limited its consideration of nonbiologic DMARDs to five agents (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, and minocycline). Nonetheless, more than 170 two- and three-drug combinations are possible with those five drugs.

Beyond Initial Therapy
The ACR and EULAR encourage close monitoring of patients’ disease activity. For patients who have little or no improvement with initial therapy, clinicians should give early consideration to switching DMARDs or combining nonbiologic DMARDs. The consideration should extend to the addition of a biologic agent for patients with high disease activity despite initial DMARD therapy, particularly if the DMARD is methotrexate.

The ACR and EULAR suggest that the combination of methotrexate and a TNF inhibitor is appropriate as initial therapy for patients with high disease activity and other features consistent with a poor prognosis.

Summary
An earlier EULAR document addressed management of early RA. The current document expands recommendations to include all patients with RA. Notably, the new set of recommendations begins with an approach advocated in the earlier document: initiation of DMARD therapy as soon as RA is diagnosed. Collectively, the two EULAR publications, as well as the ACR treatment recommendations, reflect the increased recognition of RA as a structural and functional menace that requires an early and aggressive therapeutic intervention to help patients preserve their health and quality of life.

References on page 14
Recent recommendations for treatment of rheumatoid arthritis (RA) reflect the improved understanding of the disease process and the ongoing evolution of therapeutic principles, both of which have undergone dramatic changes in the past decade. Presentations at the 2010 Annual Congress of the European League Against Rheumatism (EULAR) provided numerous examples of the application of new knowledge and therapeutic strategies in the clinical management of RA.

**A Randomized Trial of “Treating to Target”**

Treatment that achieves remission or low disease activity has been associated with improved short- and long-term outcomes in RA. Targeting treatment to a prespecified target value or range, which is the normal procedure in the treatment of hypertension or diabetes, could be appropriate for the treatment of RA as well. However, the association of a low disease-activity state with better prognosis has been demonstrated most clearly in early RA. Investigators in a randomized clinical trial sought to extend the principle of “treating to target” to patients with more advanced stages of RA.

Participating physicians randomized patients with established, active RA to receive routine care or treatment to one of two clinical targets: a 28-joint Disease Activity Scale (DAS28) score of <3.2 or swollen joint count (0 out of 28). The primary outcome was the change in DAS28 score from baseline to 12 months.

Of 309 patients enrolled, 209 (68%) completed the 12-month trial and were included in the analysis. The patients had a mean age of 55 years and a mean baseline DAS28 score of 5.9, and 80% were women. The patients’ treatment history included an average of 2.7 prior disease-modifying antirheumatic drugs (DMARDs).

At the end of the study, patients in all three groups had similar and statistically significant improvements in DAS28. End-of-study DAS28 values averaged 3.2 with routine care, 3.1 with treatment to DAS28 target, and 3.5 with treatment to swollen-joint-count target (P<0.001 vs baseline). The groups also did not differ with respect to change in the number of swollen and tender joints, or individual assessments of disease activity, including patient global assessment, physician global assessment, the Health Assessment Questionnaire, erythrocyte sedimentation rate, C-reactive protein (CRP) levels, and patient satisfaction. Overall, 55% of patients had a DAS28 score of <3.2 at 12 months, and the proportion was similar in all three groups.

Investigators noted a trend toward a higher proportion of patients achieving remission (DAS28 score of <2.6) in the DAS28 target group (42%) and the swollen-joint target group (47%) than in the routine care group (37%). However, the difference did not achieve statistical significance. Additionally, the drop-out rate was lower in the two targeted-therapy groups.

Thus, results of this preliminary clinical study showed no significant improvement in disease activity with “treatment to target” compared with routine care. However, this important study does not necessarily detract from the importance of aiming for low disease activity or remission in all patients. The negative result may well be due to the fact that even in the “routine care” control group, individual rheumatologists were applying the principle of “treating to target” informally. The rather high rates of remission for this patient population with established RA would support that view. Moreover, the numerically higher proportion of patients achieving remission with targeted therapy, as well as the lower drop-out rate in those groups, suggest that there is indeed a benefit from a “treating to target” strategy.

**Early Response May Predict Long-Term Outcomes in RA**

Achieving and maintaining remission or low disease activity has been associated with better long-term outcomes in patients with RA. Whether the time course to low disease activity influences later outcomes had not been examined.

Post-hoc analyses of clinical trials have shown that a majority of patients with active RA respond quickly to certolizumab pegol and that lack of response by week 12 predicts a high likelihood that a patient will not achieve low disease activity later on. To assess the relationship between time to low disease activity and later disease control, investigators combined data from a clinical trial that evaluated two doses of certolizumab pegol plus methotrexate for treatment of active RA.7 The randomized phase of the study included 783 patients, 670 of whom entered an open-label evaluation following completion of the primary trial.

Patients who achieved low disease activity (DAS28 score of <3.2) at 1 and 2 years were assessed according to the change in DAS28 from baseline at various time intervals, beginning at week 1 and continuing through week 12.

At baseline, 98% of patients had DAS28 values of >5.1, and the mean DAS28 value was 6.9. The data showed that 86% of the patients had a 1.2-point improvement in DAS28 by week 12. Patients who had DAS28 changes of <0.3 at week 4, <0.9 at week 6, <1.2 at week 10, or <1.8 at week 12 had less than a 5% likelihood of having low disease activity at both years 1 and 2. For any level of DAS28 improvement, failure to respond by week 12 was the strongest predictor of failure to achieve low disease activity at 1 and 2 years.

The investigators concluded that patients who are unlikely to achieve long-term low disease activity with certolizumab pegol can be identified by the combination of the DAS28 change from baseline and the time to DAS28 response after starting certolizumab pegol therapy.

**Long-Term Outcomes With Targeted Therapy**

Although the benefits of “treating to target” have been documented, the optimal strategy to achieve the target has yet to be determined. Investigators in a multicenter Dutch trial reported findings from a long-term evaluation of four different treatment strategies to achieve DAS28-defined low disease activity (the BeSt [Dutch acronym for Behandel-Strategieën, “treatment strategies”] trial).8

The study involved 508 patients with early RA, randomly allocated to four treatment groups: sequential monotherapy, step-up combination therapy, an initial combination with prednisone, or an initial combination with infliximab.
Each patient had three DAS28 assessments each month, and if the score exceeded 2.4, treatment was adjusted in an attempt to lower the score to the target. On the other hand, if the DAS28 value remained <2.4 for 6 or more months, the primary therapy’s dose could be tapered. If a patient remained in remission (DAS28 score of <1.6) for 6 months or longer, DMARD therapy could be stopped.

The study initially included 508 patients, and 99 patients withdrew during 6 years of follow-up. After 6 years, 83% of patients had a DAS28 score of <2.4, and 51% had a DAS28 score of <1.6, equally distributed among the four treatment groups. Patients assigned to the prednisone or infliximab group exhibited more rapid improvement in physical functioning, but from year 1 to the end of follow-up, physical functioning was similar in the four groups.

The prednisone and infliximab combination regimens were successfully tapered to monotherapy in 26% and 45% of patients, respectively. At 6 years, 17% of patients were in drug-free remission for a median duration of 32 months (14%–19% of each group). Among patients with sustained drug-free remission, radiographic progression (as defined by change in the Sharp/van der Heijde score) was 0.13 per person-year drug free. Toxicity was similar in the four groups (Table).

The results demonstrate the feasibility of a long-term DAS28-based “treatment to target” approach for patients with RA. Early functional improvement was mostly maintained over time, and radiographic progression remained stable. It may be disappointing that the early aggressive strategies (high-dose glucocorticoids in one group and anti-tumor necrosis factor [TNF] in another) did not lead to higher rates of remission on long-term follow-up, but it must be emphasized that the more intensive treatment options were available to all patients after 1 year within the design of this trial.

**Impact of Smoking on RA Outcomes**

The high cost of treating RA is a worldwide concern. Two presentations at the EULAR meeting showed that a nondrug intervention could improve the efficiency of RA therapies for a subgroup of patients. Both studies showed that smoking adversely affects a patient’s response to RA therapy.9,10

Smoking has been associated with higher disease activity in patients with RA and with evidence of a poorer response to therapy. A study from Sweden expanded these observations by showing that smoking dampens the response to methotrexate and to TNF inhibitors, two of the most widely used therapies for RA.9

The study involved almost 2,000 patients enrolled in an RA registry. Current smokers accounted for 27% of the study population, and another 30% were former smokers. The current and former smokers had a median of 17 pack-years’ smoking history.

The primary end point was a EULAR-rated “good” response 3 months after starting methotrexate as monotherapy or a TNF inhibitor as the first biologic therapy. A good response consisted of a DAS28 score of <3.2 plus a change of >1.2 in DAS28 score.

Among patients in the methotrexate group, 36% of never-smokers and 37% of former smokers achieved a good response at 3 months, compared to 27% of current smokers (P<0.05 vs never-smokers). Among patients who received a TNF inhibitor as the first biologic agent, 43% of never-smokers and 39% of former smokers met the criteria for a good response after 3 months, compared to 29% of current smokers (P=0.03 vs never-smokers).

Current smoking also was associated with a reduced likelihood of a good response to methotrexate or a TNF inhibitor at 6 months. Results were similar in an analysis of remission.

The second study, also from Sweden, examined the effect of smoking intensity (in pack-years) on the response to initial anti-TNF therapy. The analysis included 934 patients from an RA treatment registry. According to patient responses, 23% were current smokers, 40% previous smokers, and 37% never-smokers.

The primary outcome was a EULAR-rated good or moderate response after 3 months of treatment. (The EULAR response criteria classify patients as good responders, moderate responders, or non-responders.) Current smoking reduced the odds of a EULAR response by almost 50% (odds ratio, 0.53). However, smoking intensity did not influence the likelihood of a response.

In a secondary analysis, current smoking reduced the odds of a response as measured by the Simplified Disease Activity Index (SDAI) by more than 50% at 3 and 6 months, and former smoking predicted almost a 60% lower probability of an SDAI response at 12 months. Smoking intensity also had a negative impact on SDAI response, as a smoking history of 11 to 20 pack-years reduced the odds of a response at 12 months by 70%.

Together, these two studies make a persuasive case for including smoking cessation as a component of therapy for all patients with RA who are smokers.

**Summary**

European and North American clinical guidelines for treatment of RA share a number of characteristics. EULAR and the ACR recommend aggressive approaches to treatment, early consideration of DMARD and combination therapy, and early use of TNF inhibitors and other biologic therapies. Accumulating evidence suggests that clinical strategies that embrace concepts associated with aggressive therapy, such as tight control and treatment to a prespecified target, can slow progression of RA and improve long-term outcomes. Data reported at the EULAR congress also underscore the value of multifaceted, multidisciplinary RA care that includes attention to lifestyle factors, such as smoking cessation.

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Table. Tight Control of RA: 6-Year Outcomes Reported from BeSt Trial

<table>
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<tr>
<th></th>
<th>SQ</th>
<th>SU</th>
<th>P+C</th>
<th>I+C</th>
<th>P Value</th>
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<td>126</td>
<td>121</td>
<td>132</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>DAS28 score &lt;2.4, % of patients</td>
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<td>80</td>
<td>84</td>
<td>84</td>
<td>NS</td>
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<tr>
<td>DAS28 score &lt;1.6, % of patients</td>
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<td>50</td>
<td>51</td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>Still on initial Rx, % of patients</td>
<td>23</td>
<td>21</td>
<td>40</td>
<td>62</td>
<td>&lt;0.001a</td>
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<tr>
<td>Mean HAQ score</td>
<td>0.70</td>
<td>0.70</td>
<td>0.63</td>
<td>0.56</td>
<td>&lt;0.02a</td>
</tr>
</tbody>
</table>

*SQ=Sequential monotherapy; P+C=prednisone combination; RA=rheumatoid arthritis; Rx=prescription therapy; SU=step-up combination.*

Source: Adapted from Klarenbeek et al.9

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**References**

2. European and North American clinical guidelines for treatment of RA share a number of characteristics. EULAR and the ACR recommend aggressive approaches to treatment, early consideration of DMARD and combination therapy, and early use of TNF inhibitors and other biologic therapies. Accumulating evidence suggests that clinical strategies that embrace concepts associated with aggressive therapy, such as tight control and treatment to a prespecified target, can slow progression of RA and improve long-term outcomes. Data reported at the EULAR congress also underscore the value of multifaceted, multidisciplinary RA care that includes attention to lifestyle factors, such as smoking cessation.

3. References on page 14
Rheumatoid arthritis (RA) affects virtually every aspect of a patient’s life. The adverse impact manifests much earlier in the disease process than previously recognized. With improved understanding of the disease process, clinicians and researchers have come to recognize that joint destruction and disability occur within a year or even months of diagnosis.

Patients with RA have disability rates that are as much as 15 times greater than those seen in the general population. Within 5 years of RA diagnosis, as many as 40% of employed patients are disabled and unable to continue working. Half of patients have significant disability or deformity within 10 years, increasing to 80% or more 20 years after diagnosis.

Aggressive treatment of RA has been shown to help preserve functional ability and quality of life. Emerging evidence also suggests that effective treatment of RA can help reduce absenteeism from work and improve work-related and household productivity.

Increased recognition of the wide-ranging adverse effects of RA has helped raise awareness of the value of including patient-reported outcomes in clinical evaluation. Some evidence has suggested that patient-reported outcomes correlate with more traditional measures of RA disease status.

Presentations at the European League Against Rheumatism (EULAR) 2010 Congress reflected the growing appreciation of the importance of the patient’s perspective in clinical evaluation. The discussion that follows offers a summary of findings that have relevance for clinicians and patients alike.

**Women Less Likely to Achieve Remission**

The advent of more effective therapy for RA has made disease remission a reasonable goal for treatment, and one that is being achieved more often with aggressive treatment. Studies of RA remission had not previously shown whether men and women have a similar likelihood of achieving remission. To examine the issue, Furst et al analyzed the Consortium of Rheumatology Researchers of North America (CORRONA) database, a practice-based registry of patients with RA.

Investigators defined remission as a Clinical Disease Activity Index (CDAI) score of <2.8, as a 28-joint Disease Activity Scale (DAS28) score of <2.6, and by American College of Rheumatology criteria (no swollen or tender joints, normal erythrocyte sedimentation rate, and no morning stiffness, pain, or fatigue). The analysis included 6,668 patients who were not in remission at enrollment for whom complete 12-month follow-up data were available.

By all three definitions of remission, women were less likely to achieve remission than were men, and the differences achieved statistical significance for the CDAI score of <2.8 (15% vs 20.1%; \(P=0.001\)) and the DAS28 score of <2.6 (21% vs 30.2%; \(P=0.003\)) (Table 1).

For each definition of remission, the analysis revealed certain factors that influenced the likelihood of remission. The factors included disease duration, depression, work status, disease severity, and whether treatment included prednisone and/or a tumor necrosis factor (TNF) inhibitor.

The findings suggest a need for increased awareness of the sex-based difference in remission rates. Identification of additional factors associated with remission provides some direction for areas to address in clinical strategies that aim to achieve remission.

**Disease Activity and Disability**

Several studies have shown that disability in patients with RA is closely associated with disease activity. Moreover, the degree of disability at diagnosis predicts subsequent disability over time. Whether these associations differ between men and women with RA has not been determined.

To assess the evolution of disability, Swedish investigators analyzed prospectively gathered clinical data on 149 patients who had an RA disease duration of less than 1 year at diagnosis and who had had 8 years of follow-up.

Assessments included DAS28 scores, pain by visual analogue scale (VAS), grip strength, range of motion, walking speed, and the Health Assessment Questionnaire (HAQ).

Disease activity, as indicated by DAS28 scores, decreased from baseline levels throughout the 8 years of follow-up. Range of motion and walking speed improved during the first year after diagnosis, but then deteriorated over time and returned to baseline levels. Pain and grip strength initially improved, but then leveled off and remained stable throughout most of the follow-up period.

HAQ scores improved in men and women alike, but went in different directions during follow-up. Men had stable scores after initial improvement, whereas HAQ scores in women declined steadily.

**Table 1. Odds Ratios for Remission at 1 Year: Women Versus Men (N=6,668)**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI score &lt;2.8</td>
<td>0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DAS28 score &lt;2.6</td>
<td>0.65</td>
<td>0.003</td>
</tr>
<tr>
<td>ACR criteria*</td>
<td>0.89</td>
<td>0.49</td>
</tr>
</tbody>
</table>

ACR criteria=American College of Rheumatology criteria (no swollen or tender joints, normal erythrocyte sedimentation rate, and no morning stiffness, pain, or fatigue); CDAI=Clinical Disease Activity Index; DAS28=28-joint Disease Activity Scale.

Source: Adapted from Furst et al.1

**Emphasis on Quality of Life and Patient-Reported Outcomes**

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from the second year forward and had returned to baseline by year 8. Women also exhibited more disability with respect to grip strength, and men had greater deterioration of range-of-motion scores.

The findings show that patients with RA may have progressive disability despite effective control of disease activity. Disability in early RA appears similar in men and women, but shows a more progressive decline in women over time. Accordingly, clinical management strategies should include regular assessments of the degree of disability throughout follow-up, not just in the early phases of the disease.

**Impact of RA on Sexuality**

Sexuality is a neglected aspect of RA assessment and clinical management. As a consequence, relatively little is known about the impact of the disease on sexual function.

A group from France addressed the impact of RA on sexuality in a study involving 1,271 patients who responded to a mailed questionnaire. The survey instrument was designed to elicit information about demographics, current therapy, functional capacity, global health status, disease activity, pain, mood, and fatigue.

The patients had a mean age of 64 years and mean disease duration of 12 years, and 84% of respondents were women. All but 2% of the patients were receiving some form of RA therapy, and 41% of the patients were being treated with biologic agents.

The mean HAQ score was 1.2, but scores reflected a wide range of disability, including 20% of patients with HAQ scores of ≥2.0. All other assessments were based on 10-point VAS instruments and yielded the following mean scores: global health status, 5.5; pain, 4.7; disease activity, 4.6; and mood, 5.8. One fourth of the patients were receiving treatment for depression or anxiety, and 90% reported fatigue as a problem.

Responses showed that RA had a negative impact on affective relationships in 70% of patients and sexual relationships in 66%. Overall, 56% of patients reported being sexually active in the past year, and they had a mean sexual satisfaction score of 5.6. RA was cited as the principal reason for lack of sexual activity by 40% of patients, but 45% cited other factors in addition to RA.

Both sexually active and inactive patients cited similar difficulties related to sexual function: loss or absence of libido (~50%), vaginal dryness (~35%), and joint pain or stiffness (25%–35%). Additionally, 39% of sexually active and 26% of sexually inactive patients cited a lack of understanding by partners, feelings of guilt (39% and 25%, respectively), and frustration (36% and 24%, respectively).

Half of the respondents had not sought help to improve sexual function and relationships, 72% had never discussed sexual issues with a health care professional, 66% were unwilling to discuss the issues, and 62% did not see a need for help.

The results provide much-needed data regarding an issue of RA that has received little attention over the years. The study showed that sexual function and relationships of patients with RA are closely associated with disability, disease activity, pain, and mood. The findings clearly point to an area that clinicians need to address with their patients.

**Work Performance and Absenteeism**

Functional impairment related to RA often translates into decreased work performance and more workdays lost to sick leave. A substantial proportion of employed patients with RA eventually cannot work and must sustain on disability payments.

Two separate studies from Sweden examined RA-related absence from work and the impact of anti-TNF therapy on absenteeism. Both studies involved analysis of data from two large registries of patients with RA.

One of the studies included 6,347 patients, each of whom was matched with five individuals without RA in the general population. All of the patients started anti-TNF therapy between 1999 and 2007. Data on sick leave and disability were obtained from national databases.

The results showed that 42% of patients with RA were receiving part- or full-time disability payments when they started anti-TNF therapy, as compared to 12% of the general population. At the start of treatment with a TNF inhibitor, the patients with RA averaged 203 days of sick leave and disability compared to 54 days in the general population. In the year before initiation of anti-TNF therapy, the mean number of days of sick leave and disability increased by 27 in the RA group and 4 in the non-RA group.

During the first year of biologic therapy, the average number of days of sick leave and disability decreased by 3 in the RA group and increased by 5 in the control group. The overall rate remained increased in patients with RA (92 per 1,000 person-years) compared to the control group (13 per 1,000 person-years). However, initiation of anti-TNF therapy was associated with a stabilization of workdays lost because of RA.

Another study involved 365 patients with RA who started receiving anti-TNF therapy between 2004 and 2007. Each patient was matched with four non-RA controls from the general population.

Using national databases, the investigators calculated sick leave and disability days for patients with RA and the control group in the year before and year after starting anti-TNF therapy. A year before they began biologic therapy, more than 20% of patients with RA were on sick leave or disability compared to less than 10% of the control group. By the time the patients with RA began treatment with a TNF inhibitor, 38.6% of them were registered for sick leave.

Within 6 months of beginning biologic therapy, the proportion of patients with RA registered for sick leave had decreased to 28.5% (P<0.001) and remained stable for the rest of the year. The proportion in the control group did not change appreciably throughout the follow-up period.

The relative risk of sick leave for the patients compared to the control group declined from 6.6 at the start of anti-TNF therapy to 5.2 a year later. The relative risk of disability remained stable, beginning at 3.4 and ending at 3.2 after the first year of treatment.

Comparing changes in sick leave and disease duration, the investigators found that patients with the shortest disease duration (0–24 months) had the greatest declines in sick leave.

Collectively, these two studies show that patients with RA are considerably more likely to be on sick leave or disability than is the general population. They also show that treatment with TNF inhibitors can significantly reduce sick leave and disability requests, at least over the brief follow-up period of the studies. Additionally, one of the studies showed that patients with shorter RA duration...
derived the greatest benefit in terms of reducing the number of days of sick leave and disability, supporting early use of TNF inhibitors for the treatment of RA.

Comorbidity and RA
RA increases the risk of premature mortality, primarily mortality due to cardiorespiratory conditions. Although comorbidity is common among patients with RA, the extent of comorbid conditions and their impact on mortality in patients with RA has received little attention in the published literature.

A study from the United Kingdom addressed the lack of data by applying a validated comorbidity index to a cohort of patients with RA. The study included 1,460 consecutive patients from nine outpatient clinics in the United Kingdom, recruited into an inception cohort since 1987.

Investigators ascertained the date and cause of death by use of a national database, and comorbidity was assessed by means of the Charlson index, a weighted count of 17 comorbid conditions. Data derived from the index were used to calculate the annualized and 15-year incidence of comorbidity in the cohort, and Cox regression analysis was used to estimate the impact of baseline Charlson comorbidity on mortality.

Consistent with the known epidemiology of RA, 66% of the patients were female, and the mean age at onset of RA was 55 years. During a mean follow-up of 8.6 years, 573 patients died. Principal causes of death included cardiovascular disease (39.7%), respiratory conditions (22.6%), and malignancy (24.1%).

The analysis showed that 461 patients had one or more comorbid conditions at enrollment. The annualized incidence of comorbidity was 121.4 per 1,000 population, principally hypertension (26.7/1,000), cardiovascular and respiratory diseases (21/1,000 each), solid tumors (9.6/1,000), gastrointestinal disorders (8.5/1,000), thyroid disorders (7.5/1,000), and cerebrovascular disease (5.8/1,000).

The proportion of patients with a Charlson score of ≥2 was 17.5% at baseline, increasing to 53.7% by 15 years, resulting in an annualized incidence of 6.1%.

In a fully adjusted model, a Charlson score of >1 was associated with a 14% increase in the mortality hazard, and a score of >2 increased the hazard by 78%.

This study is one of the first to describe and quantify the impact of comorbid conditions on mortality risk in patients with RA. The results document a substantial comorbidity burden, even at diagnosis of RA. Comorbidity is associated with worse survival, suggesting that clinicians’ assessment of RA should take into account comorbid conditions to reflect true RA outcomes. Additionally, the results point to a need to recognize comorbidity conditions in patients with RA and to develop prevention strategies for the conditions.

Assessing the Value of Patient-Reported Outcomes
Clinicians and researchers rely on a variety of objective assessment tools to evaluate patients with RA. At one time, patient-reported outcomes were considered too subjective to reflect a patient’s true health status. Recent studies have helped sway opinion by showing good correlation between patient-reported outcomes and those derived from other types of validated instruments.

A group of investigators from Europe, Scandinavia, and Canada continued to refine the use of patient-reported outcomes in RA by comparing results obtained with a patient-oriented assessment tool with those from an instrument that relies on physician-reported outcomes. The RA Impact of Disease (RAID) is a patient-derived index that measures the impact of RA on patients’ lives. The index has seven weighted components: pain, fatigue, physical and emotional well-being, sleep, and coping. Assessment of physician-reported outcomes consisted of the DAS28 score, swollen joint count, and tender joint count.

Table 2

<table>
<thead>
<tr>
<th>Outcome</th>
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<tr>
<td>Emotional well-being</td>
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<td>Sleep</td>
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<tr>
<td>TJC (reference value)</td>
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<tr>
<td>Physical well-being</td>
<td>1.0</td>
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<tr>
<td>Coping</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>SJC</td>
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<td>HAQ</td>
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</tr>
<tr>
<td>Pain</td>
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<tr>
<td>DAS28</td>
<td>3.0</td>
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</table>

At baseline, the DAS28 scores averaged 4.0. Treatment changes involved a conventional disease-modifying antirheumatic drug (DMARD) in 32% of cases, a biologic agent in 47%, and corticosteroids in 42%.

Comparing patient-reported and physician-reported outcomes, the investigators found good correlation (Table 2).

The patient- and physician-reported outcomes demonstrated similar efficiency in detecting change in status, with the exception of the DAS28 score, which performed better than all other measures, whether physician or patient derived.

The findings show that patient-reported outcomes are reliable indicators of health status in patients with RA. Though the physician-derived DAS28 score performed best, the study showed that patient-reported outcomes, such as the RAID index, provide information that is complementary to information derived from conventional assessment tools used by clinicians.

Anti-TNF Therapy Improves Household Productivity
For many patients, RA severely limits the ability to perform routine activities at home and in the workplace. As a result, therapy that helps patients maintain function at home can have a substantial, positive impact.
Strand et al\textsuperscript{16} examined the effect of treatment with certolizumab pegol, a TNF inhibitor, on household productivity and daily activities in patients who completed 12 weeks of randomized therapy and then entered open-label treatment with the TNF inhibitor (400 mg every 4 weeks) and remained on treatment for a total of 2 years.\textsuperscript{16}

The study included 69 patients with a mean RA duration of 9.5 years. At the beginning of open-label therapy, the patients’ HAQ disability index values averaged 1.42 and the DAS28 scores averaged 5.76. The patients reported that RA substantially interfered with a wide range of daily activities.

Daily activities and household productivity were assessed every 4 weeks for the first 6 months and then every 3 months for the remainder of follow-up (Table 3).

Improvement in all areas occurred within 12 weeks after initiation of treatment with certolizumab pegol and continued to improve throughout the 2 years of treatment and follow-up. Patients reported fewer days of missed household activities, reduced household productivity, and missed family/social/leisure activities. Cumulative gains in days of household work averaged 20.5 at 12 weeks, 108.4 at 52 weeks, and 199.3 at 100 weeks. Similar increases were observed in household productivity and family, social, and leisure activities.

The small size of the study warrants caution in extrapolation of the results to larger or different populations of patients with RA. However, the results demonstrate a substantial, positive impact of treatment with certolizumab pegol on household productivity. The findings provide additional evidence that assessment of patient-oriented outcomes complement standard evaluations of the status of patients with RA.

### Summary

Patient-reported outcomes in RA have gained recognition and new respect for reflecting consequences of the disease process that may go overlooked by traditional means of assessing disease status. The impact of RA on a person’s ability to work, to perform routine activities, and to participate in family and social activities has as much meaning for the patient as clinically oriented assessment tools have for the physician. Patient- and physician-reported outcomes complement each other and provide a more comprehensive assessment of health status. Given the evidence that effective RA therapy favorably affects patient-reported outcomes, physicians have more reason than ever to implement aggressive therapy to prevent joint destruction and help preserve patients’ physical function and quality of life.

### References

3. Young A, Dixey J, Kulinskaia E, et al. Which areas of daily activities per month, mean (median) b 5.0 (2) 1.5 (0) 0.9 (0) 0.6 (0) 0.3 (0)

Table 3. Productivity at Home and Daily Activities in Certolizumab Pegol Monotherapy Patients Over 2 Years*  

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 52</th>
<th>Week 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household workdays missed per month, mean (median)</td>
<td>10.1 (7)</td>
<td>4.6 (0.5)</td>
<td>2.5 (0)</td>
<td>1.5 (0)</td>
<td>1.0 (0)</td>
</tr>
<tr>
<td>Household workdays with reduced productivity per month, mean (median)</td>
<td>12.1 (10)</td>
<td>4.7 (2)</td>
<td>2.5 (0)</td>
<td>1.9 (0)</td>
<td>1.1 (0)</td>
</tr>
<tr>
<td>Rate of RA interference with household productivity per month, mean (median)</td>
<td>5.8 (6)</td>
<td>3.7 (3)</td>
<td>2.5 (2)</td>
<td>2.7 (3)</td>
<td>2.0 (2)</td>
</tr>
<tr>
<td>Days missed of family/social/leisure activities per month, mean (median)</td>
<td>5.0 (2)</td>
<td>1.5 (0)</td>
<td>0.9 (0)</td>
<td>0.6 (0)</td>
<td>0.3 (0)</td>
</tr>
</tbody>
</table>

*Observed data. b 0–10 scale (0=no interference, 10=complete interference); n=67. Source: Strand et al\textsuperscript{16} Used with permission.
The Role of TNF Inhibitors in Evolving RA Strategies

The impact of add-on therapy on non-RA outcomes had not been carefully examined. Strand et al11 presented data to show that adding a TNF inhibitor to methotrexate led to significant improvement in one common and clinically important comorbidity of patients with RA—depression.

Investigators assessed the mental health of 397 patients with RA treated with methotrexate alone or in combination with adalimumab. The Beck Depression Inventory (BDI) and the 36-item Short Form Health Survey (SF-36) were administered at baseline and after 12, 24, and 52 weeks of treatment. Clinical depression was defined as a BDI score of >9.

At baseline, 39.5% of the patients were clinically depressed, and the proportion of depressed patients did not differ between treatment groups. The mean BDI score was significantly lower in the adalimumab group at all time points ($P<0.01$), reaching a maximum difference at 26 weeks (6.57 vs 8.79). The difference was maintained after 52 weeks (6.93 vs 8.79).

Similarly, the mean score on the mental health component of the SF-36 was significantly higher (improved) in patients treated with adalimumab plus methotrexate at all time points ($P<0.01$). The between-group difference was greatest at 52 weeks (50.51 vs 47.49).

After 52 weeks of treatment, 23.9% of the adalimumab group met the BDI definition of clinical depression compared with 37.8% of patients treated with methotrexate alone ($P=0.003$).

This study is one of the first to demonstrate a differential effect of RA therapies on depression and mental health in patients with RA. The results suggest that the combination of adalimumab and methotrexate may offer significant benefits related to depression and mental health, in addition to the combination’s proven positive effects on RA patients’ physical functioning and radiographic progression of RA.

Summary

Improved understanding of the RA disease process continues to provide direction for clinical strategies that can help limit the manifestations and consequences of the disease process. As the knowledge accumulates, the challenge will be to translate scientific discovery into clinical practice to optimize therapy. Optimizing the use of every available therapeutic tool will help ensure that patients obtain maximal benefit from the discovery process.

References


5. Fossati G, Nesbitt A. Certolizumab pegol has a different profile from the other anti-TNFs, including golimumab, in a variety of in vitro assays. Ann Rheum Dis. 2010;69(suppl 3):324.


Evidence-Based Guideline Development and Practical Application of Clinical Guidance

References


10. Soderlin M, Geborek P. Intensity of smoking (pack-years) is associated with poor therapy response in RA patients starting their first anti-TNF treatment: Data from SSATG, a biologic register in southern Sweden. Ann Rheum Dis. 2010;69(suppl 3):54.
CME Questions

Instructions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

1. What lifestyle factor was discussed as possibly having a role in the management of rheumatoid arthritis (RA)?
   A. Weight loss
   B. Dietary modification
   C. Smoking cessation
   D. Physical activity

2. Studies have shown that switching from one tumor necrosis factor (TNF) inhibitor to another drug in the same class:
   A. Offers no benefits in the management of RA
   B. Will lead to a response in a proportion of patients
   C. Poses a risk of potentially serious adverse effects
   D. Is the best strategy for maintaining long-term disease control

3. Data reviewed in this educational activity showed that TNF inhibitors:
   A. Differ at the molecular level
   B. Have similar means of achieving TNF inhibition
   C. Have substantial off-target effects
   D. Vary in the magnitude of immunosuppression

4. Adding a TNF inhibitor to methotrexate therapy:
   A. Had no effect on mental health compared with methotrexate alone
   B. Exacerbated symptoms of anxiety and depression
   C. Improved scores on standardized assessments of depression and mental health
   D. Led to new symptoms of mental health disturbance

5. Data from a clinical registry showed that remission of RA occurs:
   A. Equally in men and women
   B. More often in women than in men
   C. Less often than previously estimated in all patients with RA
   D. Less often in women than in men

6. In patients with RA, disability:
   A. May occur despite apparent disease control
   B. Is similar in men and women in early RA
   C. Is more progressive over time in women than in men
   D. All of the above

7. Treatment of RA with anti-TNF therapy is associated with:
   A. Fewer requests for sick leave and disability
   B. No effect on sick leave or disability among employed patients
   C. Increased sick leave resulting from infectious complications of treatment
   D. Increased requests for overtime to pay for the treatment

8. Information presented in this activity showed that patient-reported outcomes:
   A. Have little validity in the evaluation of patients with RA
   B. Should replace the use of conventional physician-directed assessments
   C. Are complementary to physician-derived outcomes
   D. Tend to exaggerate disease severity

9. Comparison of early and late outcomes in patients treated with anti-TNF therapy showed:
   A. No associations
   B. That lack of early response may help identify patients who are unlikely to achieve long-term disease control
   C. That early response may lead to false impressions about disease control
   D. That most patients respond to therapy later than previously estimated

10. North American and European clinical guidelines for the treatment of RA:
    A. Reflect polar opposite approaches to clinical management
    B. Emphasize delaying the use of anti-TNF therapy for as long as possible
    C. Recommend starting all patients’ therapy with TNF inhibitors or other biologic therapy
    D. Share a number of features consistent with early and aggressive treatment to achieve disease control
Anti-TNF Therapies: Improving Patient Outcomes in the Treatment of Rheumatoid Arthritis

EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type. All information is confidential. Please print.

Name:

Specialty:

Degree: MD DO PharmD NP RN BS PA Other:

Affiliation:

Address:

City: ___________________________ State: __________________ Zip: __________________

Telephone: ______________________ Fax: __________________

E-mail: ________________________

Signature: ___________________________________________________________________________________________________

CME CREDIT VERIFICATION

I verify that I have spent ______ hour(s)/_______ minutes of actual time working on this CME activity. No more than 2.0 CME credit(s) will be issued for this activity.

COURSE EVALUATION: GAPS

This activity was created to address the professional practice gaps listed below, please respond regarding how much you agree or disagree that the following gaps were met:

- Physicians need to assess and diagnose patients with RA in an early enough time frame to prevent joint damage.
- Treatment options are best evaluated and initiated early after diagnosis to yield better patient outcomes and improved quality of life.
- Clinicians need to monitor patients more frequently to ensure tight control of RA symptoms.
- By focusing more on the prevention of joint damage as well as the treatment of pain, clinicians can significantly improve quality of life for many patients.
- Physicians need to be more familiar with all agents in the pharmacologic armamentarium to provide a personalized therapeutic approach to each patient.
- Clinicians need a greater understanding as to when and how to switch patients from one anti-TNF to another.

Did participating in this educational activity improve your KNOWLEDGE in the professional practice gaps that are listed above?

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Please elaborate on your answer. ____________________________________________________________________________

Did participating in this educational activity improve your COMPETENCE in the professional practice gaps that are listed above?

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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<tr>
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<td>5</td>
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</table>

Please elaborate on your answer. ____________________________________________________________________________

CME INSTRUCTIONS

This educational supplement provides 2.0 free AMA PRA Category 1 Credits™. Access to http://louisville.edu/hsc/continuinged/earn-ce-credits/rheum and print your certificate online.