Recent Developments in Anti-TNF Therapy for Rheumatoid Arthritis

Highlights of Selected Clinical Presentations and Studies

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TOPIC HIGHLIGHTS

Evolving Concepts in Rheumatoid Arthritis and Clinical Use of Anti-TNF Therapy

Early Use of TNF Inhibitors in the Treatment of RA

Rapidity of Response to Anti-TNF Therapy

Exploring the Impact of Anti-TNF Switch

Functional Benefits and Quality of Life

RA, TNF Inhibition, and Cardiovascular Disease

CME Post-Test
This supplement is based on selected abstracts and clinical posters presented at the American College of Rheumatology Annual Meeting (ACR) held October 24-29, 2008, in San Francisco, California.

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Dr Mease is a clinical rheumatologist with Seattle Rheumatology Associates, clinical professor at the University of Washington School of Medicine, and chief of rheumatology clinical research at the Swedish Hospital Medical Center in Seattle. His primary research interests include pharmacotherapy of rheumatologic diseases and the methodology of disease assessment. He conducts clinical trials in emerging therapies for a number of conditions including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, fibromyalgia, systemic lupus erythematosus, osteoarthritis, and osteoporosis.

Dr Mease has published more than 100 articles in rheumatology and dermatology journals as well as numerous textbook chapters and is on the review boards of Arthritis & Rheumatism, The Journal of Rheumatology, The Annals of Rheumatic Diseases, and Seminars in Arthritis & Rheumatism. Dr Mease is on the medical advisory boards of several pharmaceutical and biotechnology companies, the Lupus Foundation, the Psoriasis Foundation, and the Northwest Arthritis & Osteoporosis Institute. He is a founding member of GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis), an international consortium of rheumatology and dermatology investigators, representatives of patient service leagues, the biopharmaceutical industry, and regulatory agencies. He is also chair/co-chair of three working groups of OMERACT (Outcome Measures in Rheumatology Clinical Trials): psoriatic arthritis, fibromyalgia, and single joint assessment.

Dr Mease received his BA and MD degrees from Stanford University. He completed his residency in internal medicine at the University of Washington School of Medicine, where he was subsequently chief resident and fellow in rheumatology.
LEARNING OBJECTIVES
This continuing education activity will address some of the latest developments in the use of anti-TNF therapy and in the management of RA in general. After completing the activity, readers should be able to:
• Summarize the associations between RA and cardiovascular disease
• Assess trends in the use of anti-TNF therapy in early RA
• Analyze quality-of-life issues that affect RA patients
• Appraise the rapidity with which RA can progress and the impact of aggressive therapy on disease progression
• Evaluate principles and potential outcomes of switching from one drug to another within the TNF inhibitor class.

TARGET AUDIENCE
This educational activity is designed for rheumatologists, primary care physicians, nurses, nurse practitioners, and other health care professionals involved in the care of patients with RA.

DISCLOSURES
Guest Editor: Dr Mease has disclosed that he serves as a consultant for Abbott Laboratories, Amgen, Inc., Bristol-Myers Squibb Company, Biogen Idec, Centocor, Inc., F. Hoffmann-La Roche LTD, Genentech, Inc., Wyeth Pharmaceuticals, and UCB Inc. He has also received grant/research support and has served on speakers’ bureaus for Abbott, Amgen, Bristol-Myers Squibb, Biogen Idec, Centocor, Genentech, and Wyeth.
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• Go to www.CEConcepts.net/RAHighlights and successfully complete the post-test (70% or higher).
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Collectively, these and other studies reported at the ACR meeting emphasized the value of early, aggressive intervention in RA, not only to minimize or prevent joint destruction, but also to afford protection against the increased risk of CVD and related clinical events seen in RA patients. Given the recognition that RA disproportionately affects women, the Swedish data suggest that early intervention with TNF inhibitors might reduce CVD risk in the majority of patients with RA.

**Anti-TNF Therapy in Early RA**

A large volume of data has demonstrated that joint destruction begins early in the course of RA. Increased appreciation of the early damage inflicted by RA has led to earlier use of aggressive therapy, including anti-TNF therapy.

Many patients derive a significant benefit with methotrexate as initial treatment for RA. However, among patients who do not achieve a good response with methotrexate, the optimal “next-step” strategy has been unclear. Van Vollenhoven et al reported data from a randomized, open-label study, suggesting that the addition of a TNF inhibitor to methotrexate provides superior disease control compared with the addition of the nonbiologic disease-modifying antirheumatic drugs (DMARDs) sulfasalazine and hydroxychloroquine.

A randomized clinical trial of golimumab—the newest member of the anti-TNF class—evaluated first-line use of a TNF inhibitor in patients with RA and no prior exposure to methotrexate. The data showed that initial treatment with methotrexate plus a TNF inhibitor led to a significantly higher ACR 50 response rate compared with methotrexate monotherapy.

New therapies usually are more costly than older therapies, so cost-effectiveness frequently is a major consideration in the use of newer therapies. Data from the Dutch Behandel Strategien (BeSt) trial provided the basis for a cost-effectiveness analysis of different approaches to first-line treatment of RA. Investigators used the data to compare the cost-effectiveness of initial therapy with a TNF inhibitor versus a nonbiologic DMARD.

Not surprisingly, the analysis showed that the upfront cost of anti-TNF therapy was greater. However, the higher early cost was offset over time by greater gains in quality-adjusted life years with a TNF inhibitor compared with a conventional DMARD. The findings demonstrated that a focus on prevention of structural damage and preservation of function can overcome the early cost disadvantage associated with anti-TNF therapy.

**Quality of Life**

The absence of a cure for RA places greater emphasis on preservation of quality of life. Numerous ACR presentations addressed various aspects of quality of life in patients with RA. A series of presentations involving treatment with certolizumab pegol effectively summarized quality-of-life issues.

The RA Prevention of Structural Damage (RAPID) 1 trial showed that certolizumab pegol as add-on therapy to methotrexate resulted in prompt and sustained improvement in physical function and pain.

A presentation at the ACR meeting revealed findings from an open-label extension phase of RAPID 1. The study showed that patients who received certolizumab pegol continuously for 2 years had sustained clinically meaningful improvement in pain and physical function.

Another analysis of data from RAPID 1 and RAPID 2 focused on work disability in patients with RA. In both RAPID trials, patients completed a work productivity survey every 4 weeks from baseline until end of study. The survey allowed investigators to examine both absenteeism and presenteeism (reduced productivity while at work).

The data showed that patients treated with certolizumab pegol had significant gains in number of days worked and number of productive work days compared with patients in the placebo group. Improvement was evident as early as 4 weeks and increased during 6 months of follow-up in RAPID 2 and persisted for a year in RAPID 1.

A third analysis of data from the RAPID trials involved the impact of therapy on household productivity. Participants in the two trials completed a standardized...
assessment of household functioning and productivity on a monthly basis. The results showed that patients randomized to certolizumab pegol had significant gains in household work days, productive household work days, and in family, social, and leisure activities.

Finally, data from an ongoing observational study in Finland demonstrated household productivity benefits with anti-TNF add-on therapy, even in patients already on intensive treatment for RA.17 Existing therapy consisted of three non-biologic DMARDs plus prednisolone, to which infliximab was added.

After 2 years, significantly more patients assigned to anti-TNF add-on therapy had achieved disease remission compared with the placebo group. The higher remission rate correlated with significantly fewer work-related absences.

Rapidity of Response
Response to therapy for RA is more than a "yes or no" proposition. How quickly a therapy leads to improvement is a meaningful clinical parameter for patients and clinicians alike.

Data from the RAPID trials afforded an opportunity to look at the timeframe of response. In RAPID 1, patients who did not achieve an ACR 20 response by weeks 12 to 14 withdrew from the study. Patients who withdrew from the trial because of lack of response had radiographic assessments at week 16.19 The results showed that patients treated with certolizumab pegol had less radiographic progression compared with patients assigned to placebo add-on therapy. The implication is that radiographic evidence of a benefit from anti-TNF therapy can be seen as early as 16 weeks.

Swedish investigators reported findings from a study that examined how soon after the start of therapy patients noticed improvement in activities of daily living, psychosocial status, and quality of life.20 Using a personal digital assessment, patients answered a 10-item questionnaire daily, beginning 1 week before the start of treatment and continuing through the first week of therapy. Results showed that patient responses after 1 week of treatment correlated with the change in disease activity score (DAS28) at 3 months.

Anti-TNF Switching
A proportion of patients with RA achieve inadequate responses to anti-TNF therapy. Optimal therapy for those patients has yet to be defined, but many clinicians will give patients a trial of a different anti-TNF therapy recognizing that loss of response to one drug in the class does not mean loss of response to the entire class. A substantial proportion of patients do respond to second- and third-line anti-TNF therapy, a fact that arthritis specialists have recognized for some time.

Rapidly widely used in clinical practice, the strategy of TNF switching had not been studied in the setting of a controlled clinical trial. Investigators addressed that shortcoming in a trial of golimumab, showing that patients could have meaningful clinical responses to a different TNF inhibitor after inadequate response or loss of response to prior anti-TNF therapy.21 Several studies reported at the ACR meeting reflected the ongoing exploration of TNF switching.

Registry data from a longitudinal cohort study were analyzed with regard to persistence with anti-TNF therapy.22 Almost 60% of patients remained on initial anti-TNF therapy during follow-up for almost 4 years. An additional 20% of the patients remained on second- and third-line TNF inhibition. Collectively, 80% of patients treated with a TNF inhibitor remained on some form of anti-TNF therapy during long-term follow-up.

Greenberg et al examined the CORRONA registry with respect to persistence with anti-TNF therapy among biologic-naïve and biologic-experienced patients.23 Among patients with no prior anti-TNF therapy, 80% remained on their initial TNF inhibitor at 6 months, 67% at 12 months, and 53% at 24 months. Among switched patients, persistence rates and response rates were lower compared with the biologic-naïve group.

Summary
This supplement to Rheumatology News reviews the previously discussed abstracts and other presentations from the 2008 ACR meeting. The information that follows provides clinicians with a summary of the current status of key issues in the management of RA, particularly issues related to optimal use of the expanding therapeutic class of TNF inhibitors. Readers will find the information relevant and readily applicable to clinical practice.

References
Recent advances in the treatment of rheumatoid arthritis (RA) have not minimized the value of methotrexate, which remains an important component of the therapeautic armamentarium. However, RA proves to be unresponsive to methotrexate in a substantial proportion of patients, raising the question of how best to proceed with treatment. Clinicians have several potential options, but little is known about the relative efficacy of these options. Van Vollenhoven and colleagues examined outcomes with two potential strategies after methotrexate failure: tumor necrosis factor (TNF) inhibition versus the addition of a conventional disease-modifying anti-rheumatic drug (DMARD).1

Methods
Patients with an RA symptom duration <1 year began therapy with methotrexate at a dose of 20 mg/week or less. After 3 to 4 months of treatment, patients who had not achieved a Disease Activity Score (DAS) 28 <3.2, but who could tolerate methotrexate, were randomized to open-label treatment with sulfasalazine and hydroxychloroquine or to the TNF inhibitor infliximab. Patients continued background methotrexate therapy. DMARD dosages could be adjusted for tolerance, and the frequency of infliximab infusion could be changed on the basis of response, but not the dose.

Within each treatment arm, one therapeutic switch was allowed in the event of intolerance. Cyclosporine could replace sulfasalazine-hydroxychloroquine, and etanercept could replace infliximab.

The primary outcome was good response applying European League Against Rheumatism (EULAR) criteria at 12 months, and secondary outcomes included moderate EULAR response and American College of Rheumatology (ACR) response.

Results
At the end of the study, 42% of the patients randomized to TNF inhibitor had a good EULAR response compared with 26% in the DMARD group (P<0.01). ACR 20, 50, and 70 responses were achieved in 33%, 16%, and 8% patients assigned to DMARD add-on therapy versus 49%, 29%, and 13% in the TNF-inhibition group (P<0.05 for ACR 20 and ACR 50).

Analysis in reference to methotrexate initiation revealed good EULAR responses in 34% of the patients randomized to conventional DMARDs and 50% of the TNF inhibitor group. ACR 20, 50, and 70 results also showed a significant advantage for TNF inhibition over DMARD add-on therapy (P=0.02 for all comparisons).

Conclusions
Following methotrexate failure with a TNF inhibitor leads to significantly better responses by EULAR and ACR criteria at 12 months, as compared with a strategy of add-on therapy with conventional DMARDs. Assuming that initial treatment with methotrexate is a reasonable approach, the subsequent addition of anti-TNF therapy leads to superior clinical outcomes compared with conventional DMARDs.

Key Point
After methotrexate failure, patients with early RA achieve better responses with a TNF inhibitor than with conventional DMARDs.

Does Disease Activity Level Affect Response to TNF Inhibition?
Randomized clinical trials of TNF inhibitors have generally had RA disease activity inclusion criteria. In the United States, clinicians broadly prescribe TNF inhibitors to patients with lower RA disease activity than required in clinical trials. Some evidence has suggested that TNF inhibitors are more effective in patients who have low or moderate disease activity versus high disease activity. Keystone et al continued the examination of TNF inhibitor effectiveness by baseline disease activity in a comparison involving patients with moderate or severe RA disease activity.2

Methods
Based on data from a US registry, the analysis included patients with no prior exposure to biologic therapy for RA. The patients were followed for 5 to 10 minutes after initiation of anti-TNF treatment. The study group was stratified by baseline disease activity, using Clinical Disease Activity Index (CDAI) criteria to define moderate (CDAI 10 to 22) and high (CDAI >22) disease activity.

The principal outcomes were the proportion of patients achieving remission (CDAI ≤2.8), low disease activity (CDAI ≤10), and modified ACR 20 and ACR 50 (mACR) responses requiring four of six ACR criteria, including tender and swollen joint counts. Additional analyses included response by DAS28 criteria for moderate and high disease activity among patients with erythrocyte sedimentation rates, DAS28 remission (<2.6), and DAS28 low disease activity (<3.2).

Results
The study population comprised 172 patients with high disease activity and 124 patients with moderate disease activity. The groups did not differ with respect to baseline demographics. TNF inhibition led to CDAI remission in a similar proportion of patients with moderate (13.6%) and high (14.9%) disease activity. Significantly more patients with moderate disease activity achieved a low disease activity state (45.8% vs 32.9%, P=0.03).

Analyses by mACR response criteria revealed mACR 20 responses in a similar proportion of patients with moderate (34.5%) and high (41%) disease activity. The mACR 50 response rates also did not differ significantly between patients with moderate (26.7%) and high (30.8%) disease activity. Use of DAS28 criteria did not significantly alter the results, although the DAS28 remission rate was numerically greater in patients with moderate (33.3%) versus high (22.7%) disease activity.

Conclusions
Results from this US-based registry of patients from clinical practices showed comparable or superior outcomes with TNF inhibitor therapy in patients with moderate versus high RA disease activity. The findings provided support for use of TNF inhibitors in patients with moderate disease activity. The results also suggested expansion of clinical trial entry criteria to improve generalizability of results with no falloff in the ability to achieve remission and response endpoints.

Abstract 1656, Keystone E et al.2

Key Point
TNF inhibitors achieve at least comparable response rates in patients with moderate versus high RA disease activity.
Recent Developments in Anti-TNF Therapy for Rheumatoid Arthritis

**TNF Inhibitor Active in First-Line RA Therapy**

Golimumab, the newest member of the anti-TNF class, is administered subcutaneously once every 4 weeks. The drug’s effectiveness has been evaluated in a variety of RA patient populations. The safety and efficacy of golimumab as initial therapy for RA was evaluated in a multicenter, randomized clinical trial involving patients with active RA and no history of exposure to methotrexate.3

**Methods**

The trial involved patients with active RA, as defined by the presence of at least four tender and swollen joints. None of the patients had a history of treatment with methotrexate. They were randomized to four treatment groups: placebo plus methotrexate; placebo plus golimumab 100 mg; golimumab 50 mg plus methotrexate; and golimumab 100 mg plus methotrexate. The primary endpoint was the proportion of patients who achieved an ACR 50 response at 24 weeks.

**Results**

Patients randomized to golimumab 50 mg had a significantly higher ACR 50 response rate compared with patients assigned to the placebo-methotrexate group (40.3% vs 29.4%, P=0.042) (Table 1). The placebo-golimumab and golimumab 100 mg-methotrexate groups had numerically higher ACR 50 response rates (32.7% and 36.5%, respectively) but did not differ significantly from the placebo-methotrexate group.

The primary outcome was assessed by intention-to-treat (ITT) analysis. A post hoc modified ITT analysis also was performed, excluding three patients who were randomized but withdrew before receiving the first dose of therapy. Limiting the analysis to patients who actually received assigned therapy resulted in a significantly higher ACR 50 response rate in patients assigned to golimumab 50 mg plus methotrexate (40.5%, P=0.038) and in the combined group of patients who received golimumab and methotrexate (38.5%, P=0.049).

A combined analysis of patients randomized to golimumab 50 mg plus methotrexate and golimumab 100 mg plus methotrexate revealed a strong trend toward superiority versus the placebo-methotrexate arm (38.4%, P=0.053). A noninferiority comparison of the two placebo groups showed that golimumab 100 mg was superior to methotrexate.

The proportion of patients who had one or more serious adverse events was 6% to 7%, except in the placebo-golimumab group, which had a rate of 3.2%. Serious infections occurred in 1% to 2% of patients, except in the 100-mg golimumab group (4.4%). Malignancies were diagnosed in two patients in the placebo-methotrexate group and in one patient each in the remaining three groups. Two patients died, and one patient had a cardiac arrest after surgery.

**Conclusions**

Although the primary endpoint (ACR 50 by ITT analysis) was not achieved, the modified ITT analysis showed that the combination of golimumab 50 mg and methotrexate achieved a significantly higher response rate compared with methotrexate alone. The findings suggest that adding golimumab 50 mg to methotrexate is more effective than an initial treatment strategy of methotrexate alone.

**Key Point**

Adding golimumab to methotrexate leads to a better response rate compared with methotrexate alone as initial therapy for patients with active RA.

**Predicting Sustained Remission to TNF Inhibition**

Recent studies have established remission as a reasonable and attainable goal for treatment of RA with TNF inhibitors. For patients who achieve the goal of remission, the subsequent approach to clinical management remains unclear, as clinical guidelines provide little direction. The ability to identify predictors of sustained remission would result in more informed decision making about whether to continue TNF inhibition or discontinue treatment.

Studies of patients treated with conventional DMARDs have identified specific immunologic markers associated with sustained remission. Which similar biomarkers can predict sustained response after discontinuation of TNF inhibitors was examined in a study reported by Saleem et al.4

**Methods**

The study involved patients who had achieved remission, defined as a DAS28 <2.6, with the combination of a TNF inhibitor methotrexate. Inclusion criteria required patients to be in remission for at least 6 months and to be in sustained

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<th>Table 1. Efficacy Outcomes After 24 Weeks</th>
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<td>Number of patients</td>
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<td>ACR 50 (primary endpoint; ITT)</td>
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<td>ACR 20</td>
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M=methotrexate; P=placebo; G50=golimumab 50 mg; G100=golimumab 100 mg; ACR 50-m=modified ACR 50; ITT=intention to treat; mITT=modified intention to treat.

Adapted from: Fleischmann RM et al.3
remission since receiving the last dose of a TNF inhibitor. Disease flare was defined as a DAS28 >2.6 or an increase in DAS28 of 1.2 or more during a median follow-up of 12 months.

Exploration of potential biomarkers of sustained remission was performed by use of flow cytometry to measure CD25+ regulatory T cells and inflammation-related cells and use of an enzyme-linked immunosorbent assay (ELISA) for cytokine analysis.

**Results**

Investigators studied 20 patients with early RA in remission following combination therapy with a TNF inhibitor and methotrexate. The patients discontinued anti-TNF therapy, but remained on methotrexate. During 1 year of follow-up, 11 patients remained in remission.

Sustained remission after stopping anti-TNF therapy was associated with a shorter RA symptom duration prior to the start of therapy (6 vs 9 months, P=0.016). Only one of 11 patients with symptom duration >9 months achieved sustained remission. Time to remission after starting therapy did not differ (4 vs 5 months).

Several immunologic parameters were associated with sustained remission (Table 2): lower levels of inflammation-related cells (29% vs 45% of CD4+ T cells, P=0.03), higher levels of naïve CD4+ T cells (7.7% vs 3.3%, P=0.01), lower levels of T-regulatory cells (1.4% vs 3.2%, P=0.001), and higher levels of thymic T-regulatory cells expressing CD62L (70% vs 34% of T-regulatory cells, P=0.005).

Levels of two circulating cytokines also predicted an increased likelihood of sustained remission after stopping anti-TNF therapy: interleukin-10 (12.8 vs 3.4 pg/mL, P=0.003) and lower levels of interleukin-12 (0.4 vs 2.2 pg/mL, P=0.01).

**Conclusions**

The results suggested that sustained remission after cessation of anti-TNF therapy is possible in more than 50% of patients with early RA. Sustained remission was associated with a shorter duration of symptoms for the start of anti-TNF therapy, higher levels of functional T cells, and higher levels of interleukin (IL)-10 and lower levels of IL-12.

The findings further suggested the existence of an immunologic state with characteristics of sustained remission and provided an argument in favor of initiating anti-TNF therapy earlier in the course of RA.

Abstract L4, Saleem B et al.

**Key Point**

Earlier initiation of anti-TNF therapy increases the chances of sustained remission, which may be associated with specific immunologic changes.

**Cost-Effectiveness of Initial Treatment With a TNF Inhibitor**

Treatment of RA has evolved from symptom-directed treatment to the use of therapies that have the potential to limit disease progression. However, as newer, more effective therapies have become available, questions related to the cost and cost-effectiveness of these therapies have arisen.

The Dutch Behandel Strategien (BeSt) trial provided an opportunity to examine the relative cost-effectiveness of various strategies for the treatment of early RA. Patients with RA symptom duration <2 years were randomized to four treatment groups: sequential monotherapy with conventional DMARDs; step-up combination therapy; initial combination therapy with tapered high-dose prednisone; and initial combination therapy that included the TNF inhibitor infliximab. The results demonstrated the clinical superiority of anti-TNF-based therapy over the other strategies.

Ganz et al used BeSt data to compare the cost-effectiveness of initial combination therapy with infliximab versus sequential DMARD monotherapy.

**Methods**

Two-year data on Health Assessment Questionnaire (HAQ)-based clinical outcomes were used to create a statistical model with a 5-year time horizon. Clinical findings were extrapolated from other published literature.

**Medical resource use and drug costs (in 2006 British £) were based on the British National Formulary and two systematic reviews. The base case represented the United Kingdom and a third-party payer perspective.**

Model outcomes included the cost per 1-point improvement in the HAQ score and the cost per quality-adjusted life-year (QALY). HAQ scores were translated into QALYs using formulas from the systematic reviews. Sensitivity analyses assessed the impact of drug cost, HAQ improvement, and the translation between HAQ and QALY.

**Results**

The BeSt results showed that initial combination therapy with prednisone or infliximab resulted in early HAQ improvement as compared with sequential monotherapy and step-up combination therapy. Cumulative costs with initial prednisone combination therapy increased from £1,155 to £15,875. Costs associated with initial infliximab-containing combination therapy increased from £8,131 to £22,151.

QALYs improved more with initial infliximab combination therapy (0.70 to 3.30) than in the group treated with initial combination therapy with prednisone (0.62 to 2.91). The cost-effectiveness of initial anti-TNF combination therapy versus sequential monotherapy increased over time, as the cost-per-QALY decreased from £592,764 in the first year to £15,965 in year 5. Results were not sensitive to changes in drug cost, HAQ, or the conversion algorithm.

**Conclusions**

The authors concluded that the higher costs associated with earlier use of anti-TNF therapy are offset by the regimen’s greater clinical benefit over time. They speculated that delaying the use of anti-TNF therapy could increase costs by allowing progression of structural damage that could have been prevented.


**Key Point**

The higher costs of earlier use of anti-TNF therapy are offset by the clinical benefit that accrues over time versus other treatment strategies.

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**Table 2. Cessation of Anti-TNF Therapy: Flare Versus Sustained Remission**

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<td>RF</td>
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RF=rheumatoid factor; CCP=cyclic citrullinated peptide antibody; DAS28=Disease Activity Scale using 28 joint counts; RAQoL=Rheumatoid Arthritis Quality-of-Life questionnaire; HAQ=Health Assessment Questionnaire.

Adapted from: Saleem B et al.
Rapidity of Response to Anti-TNF Therapy

Early Inhibition of Radiographic Progression

The speed with which a therapy improves RA is meaningful for patients and clinicians alike. TNF inhibitors prevent radiographic progression of RA, independently of their effects on disease activity. How soon the inhibitory effects on progression begin has yet to be determined. A post hoc analysis of data from the two Rheumatoid Arthritis Prevention of Structural Damage (RAPID 1 and RAPID 2) randomized clinical trials of certolizumab pegol provided the basis for exploration of the issue of onset of action.7

Methods

The two trials included a total of 1,600 patients with RA, randomized to one of two doses of certolizumab pegol or to placebo as add-on therapy to methotrexate. Patients were followed for 24 weeks in one trial and 52 weeks in the other. Patients who did not achieve an ACR 20 response at weeks 12 and 14 discontinued the study at week 16. Radiographs were obtained at baseline, week 24, and week 52, or at withdrawal. Patients who withdrew from the two studies formed the basis for the post hoc analysis. Joint damage was determined by modified Total Sharp Score (mTSS) and erosion score (ES) and joint space narrowing (JSN) subscores. Data from both certolizumab pegol dose groups were combined for each study.

Results

A total of 266 patients from RAPID 1 and 196 patients from RAPID 2 withdrew at week 16. Baseline values for mTSS, ES, and JSN were similar in the certolizumab pegol and placebo groups in both studies. Changes in all three measures of disease progression were significantly lower in the certolizumab pegol groups (P≤0.05) (Table 3). Moreover, the proportion of patients who had at least 20% improvement in swollen and tender joint counts at weeks 12 and 14 was two to three times greater in patients randomized to certolizumab pegol.

Conclusions

This analysis supports previous observations that TNF inhibition prevents radiographic progression, independently of its effect on RA disease activity. Certolizumab pegol as add-on therapy to methotrexate led to inhibition of radiographic progression of RA as early as 16 weeks. Such early inhibition of radiographic changes supports a shorter interval between imaging studies in patients with RA.

Abstract 982, van der Heijde D et al.7

Key Point

The addition of certolizumab pegol to methotrexate led to rapid inhibition of radiographic progression of RA, independently of the effect on disease activity.

TNF Inhibition After DMARD Failure

The focus of clinical investigation of any therapy is appropriately concentrated on safety and efficacy. However, certain qualitative factors can be clinically important to patients and provide a means of distinguishing multiple agents within the same class. Toward that end, Fleischmann and colleagues examined the rapidity of response to certolizumab as monotherapy and in combination with methotrexate.8

Methods

Data for the study came from two randomized clinical trials of certolizumab pegol as treatment for RA. One trial evaluated the TNF inhibitor as monotherapy in patients who had a history of one or more DMARD failures. Patients were randomized to certolizumab pegol 400 mg (N=111) or to matching placebo (N=109). The second trial involved patients who had an inadequate response to methotrexate and received certolizumab pegol as add-on therapy. Patients were randomized to certolizumab pegol 200 mg (N=393), 400 mg of the TNF inhibitor (N=390), or placebo (N=199). The primary endpoint of both studies was ACR 20 response at 24 weeks. In the current analysis, investigators examined ACR 20, 50, and 70 responses at 1, 2, and 4 weeks after beginning randomized therapy.

Results

Treatment with certolizumab pegol was associated with a faster onset of response in both studies. In the monotherapy trial, a significant difference in ACR 20 response between the TNF inhibitor and placebo was evident after one week. At weeks 1, 2, and 4, patients randomized to 400 mg of certolizumab pegol had ACR 20 response rates of 36.7%, 43.0%, and 44.5%, all of which were significantly different from placebo (P≤0.05).

In the study of TNF inhibitor add-on therapy, patients assigned to the 200-mg dose of certolizumab in addition to methotrexate had ACR 20 responses of 22.9% at week 1, 33.5% at week 2, and 43.6% at week 4 (P≤0.05 vs placebo at all time points). Results were similar for certolizumab pegol 400 mg plus methotrexate.

ACR 50 responses with certolizumab pegol monotherapy significantly exceeded those of the control group by week 1 and by week 2 in the trial of add-on therapy (P≤0.05 for all comparisons). The ACR 70 response rate was significantly higher than placebo by week 8 in the monotherapy trial (P≤0.05) and by weeks 4 to 6 in the trial of combination therapy (P≤0.05). Additionally, significant improvement in all core components of ACR response was observed by week 1 in both trials.

Conclusions

Treatment with the TNF inhibitor certolizumab pegol resulted in rapid relief of RA signs and symptoms, as assessed by ACR response criteria. Rapid improvement was observed whether certolizumab pegol was used as monotherapy or as add-on therapy to methotrexate.

Abstract 1650, van Baarsen LGM et al.8

Key Point

Treatment with certolizumab pegol leads to rapid improvement in RA signs and symptoms, irrespective of a patient’s treatment history.

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Table 3. Outcomes After Withdrawal at Week 16

<table>
<thead>
<tr>
<th></th>
<th>RAPID 1</th>
<th>RAPID 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO+MTX</td>
<td>CZP*+MTX</td>
</tr>
<tr>
<td>mTSS, mean change</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>ES, mean change</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>JSN, mean change</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*CZP=200 and 400 mg treatment arms; PBO=placebo; MTX= methotrexate; CZP=certolizumab pegol; mTSS=modified Total Sharp Score; ES=erosion score; JSN=joint space narrowing score.

Adapted from: van der Heijde D et al.7

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continued on page 11
Clinical Outcomes After One or More Anti-TNF Therapies

Switching patients with RA from one TNF inhibitor to another agent in the class is thought to be commonplace in clinical practice. However, only recently have investigators begun to examine the clinical implications of switching anti-TNF therapies. Unanswered questions exist with respect to both the safety and efficacy of following one TNF inhibitor with another. Glass et al used data from a patient registry to compare functional status, disease activity, and fatigue among patients continued on an initial anti-TNF therapy versus patients who were switched from one TNF inhibitor to another.10

Methods

Investigators analyzed data from a longitudinal cohort study that included retrospectively collected patient medication history and prospective annual medication use, disease activity, functional status, and fatigue. Disease activity was assessed by DAS28-C reactive protein (DAS28-CRP), functional status by multidimensional HAQ (MDHAQ), and fatigue by a visual analog scale of 0 to 100.

On the basis of the most recent follow-up visit, patients were categorized as still being treated with their initial anti-TNF therapy, still using a second or third anti-TNF therapy, stopped after one anti-TNF regimen, or stopped after a second or third anti-TNF regimen.

Results

Of the 982 patients included in the registry, 532 (54%) patients had a history of anti-TNF therapy, and 421 patients remained on anti-TNF therapy at the time of the analysis. Follow-up averaged 44 months. Among patients with a history of anti-TNF therapy, 22% had used two agents in the class and 6% had been treated with three anti-TNF regimens. Almost 60% of the patients remained on their initial anti-TNF agent. Of the 111 patients who had discontinued anti-TNF therapy, 65% stopped after one drug, 30% after two drugs, and 5% after three drugs.

Although the mean DAS remained in the moderate level (3.2 to 5.1) for all patients with anti-TNF exposure, scores were lower among patients who were still being treated with their initial anti-TNF regimen (3.3 vs 3.7 to 4.5) (Table 4). Mean fatigue scores were higher for current users of a second or third anti-TNF agent (40 vs 53).

Overall, 47% of the patients had used methotrexate and 46% used nonsteroidal anti-inflammatory drugs (NSAIDs); rates did not differ among groups. However, prednisone use was significantly lower among patients still on their initial anti-TNF therapy (32%) compared with patients who were on a second or third anti-TNF regimen (50%), who stopped after one anti-TNF regimen (49%), or who stopped after multiple anti-TNF regimens (67%, P<0.0001).

Conclusions

Almost 80% of patients treated with anti-TNF therapy remained on therapy after 44 months, suggesting that a majority of patients with RA benefit from the therapies and tolerate them. The higher DAS and fatigue scores among patients currently taking a second or third anti-TNF agent could indicate that they derived less benefit from the therapy or that they had more severe disease and required additional RA therapies.

Abstract 974, Glass RJ et al.10

Table 4. Mean Outcomes: Anti-TNF Switch Versus No Switch

<table>
<thead>
<tr>
<th>Anti-TNF Treatment Category</th>
<th>N</th>
<th>Months</th>
<th>DAS</th>
<th>HAQ</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx ongoing, 1 Anti-TNF</td>
<td>312</td>
<td>44</td>
<td>3.3</td>
<td>1.4</td>
<td>40</td>
</tr>
<tr>
<td>Tx ongoing, &gt;1 Anti-TNF</td>
<td>109</td>
<td>46</td>
<td>3.7</td>
<td>1.4</td>
<td>53</td>
</tr>
<tr>
<td>Stopped After 1 Anti-TNF</td>
<td>72</td>
<td>21</td>
<td>4.1</td>
<td>1.5</td>
<td>44</td>
</tr>
<tr>
<td>Stopped After &gt;1 Anti-TNF</td>
<td>39</td>
<td>31</td>
<td>4.5</td>
<td>1.2</td>
<td>51</td>
</tr>
</tbody>
</table>

DAS=Disease Activity Scale; HAQ=Health Assessment Questionnaire. Adapted from Glass RJ et al.10

Anti-TNF Therapy in Biologic-Naive and Experienced Patients

Clinical trials of anti-TNF therapy typically excluded patients who had prior exposure to a TNF inhibitor. In clinical practice, clinicians often encounter patients with RA who have been treated with one or more agents in the anti-TNF class. The efficacy of TNF inhibitors in biologic-experienced patients with RA has not been studied extensively. Greenberg et al performed a retrospective analysis of data from an RA registry that included biologic-naive and experienced patients.11

Methods

Registry patients who had one or more prescriptions for a TNF inhibitor were stratified into three groups: biologic-naive patients (1,395); first-switch patients (630); second-switched patients (163). The groups were compared with respect to response, remission, and persistency with anti-TNF therapy. Response was defined by modified ACR 20 (mACR 20) criteria and remission by a Clinical Disease Activity Index (CDAI) score <2.8. Because of limited sample size, outcomes for infliximab versus other TNF inhibitors involved only biologic-naive and first-switch patients. Investigators excluded patients who were in CDAI remission at baseline and those who discontinued anti-TNF therapy because of toxicity.

Results

The persistency rate for biologic-naive patients was 80.2% at 6 months, 67.5% at 12 months, and 52.8% at 24 months. Anti-TNF experienced patients had hazard ratios for discontinuation of 1.43 (first switch) and 1.42 (second switch) compared with biologic-naive patients. Biologic-naive patients were less likely to discontinue anti-TNF therapy with infliximab compared with the other anti-TNF agents (hazard ratio [HR] 0.74), but not first-switch patients.

Modified ACR 20 response rates for biologic-naive patients were 29.7% at 6 months, 26.9% at 12 months, and 23% at 24 months. In contrast, first-switch patients had significantly lower mACR 20 response rates at 6 months (odds ratio [OR] 0.58), at 12 months (OR 0.50), and at 24 months (OR 0.51). Second-switch patients also had lower mACR 20 rates.
Recent Developments in Anti-TNF Therapy for Rheumatoid Arthritis

Compared with biologic-naive patients at all three time points (OR 0.20-0.32).

Remission rates for biologic-naive patients were 15.8% at 6 months, 15% at 12 months, and 15.5% at 24 months. Compared with naive patients, first switch was associated with significantly lower remission rates at 6 months (OR 0.46), 12 months (OR 0.51), and 24 months (OR 0.44). Similarly, the second-switch group had reduced odds ratios for remission at all time points, ranging from 0.20 at 6 months to 0.33 at 12 months to 0.32 at 24 months.

The investigators observed no significant differences in response or remission between first- and second-switch patients.

**Conclusions**
Persistence, response, and remission rates were consistently higher for biologic-naive versus switched patients. None of the outcomes differed significantly between first- and second-switch patients. The only significant difference among the TNF inhibitors was a decreased likelihood of discontinuation with infliximab among biologic-naive patients.

Abstract 971, Greenberg J et al.12

**Key Point** Biologic-naive patients treated with TNF inhibitors have higher persistency, response, and remission rates compared with first- and second-switch patients.

**TNF-Inhibitor Switching and Immunogenicity**

TNF inhibitors confer at least a theoretical potential for immunogenicity, which might alter the therapeutic activity of the agents. In the case of infliximab, a chimeric antibody containing mouse sequences, antibody formation has been documented, although concomitant methotrexate can suppress the antibodies. However, the impact of these antibodies on therapeutic efficacy has remained unclear. A study reported at the ACR meeting continued the examination of TNF inhibitors' immunogenic potential in patients treated with adalimumab, either as the first anti-TNF therapy or as a therapeutic switch from infliximab.12

**Methods**
The study involved 226 patients with active RA, reflected in a mean DAS28 of 5.2. The patients were treated with adalimumab in a prospective observational cohort study. The study population consisted of 51 patients previously treated with infliximab and 175 patients with no prior exposure to anti-TNF therapy. Blood samples were obtained at baseline and after 28 weeks of therapy. Antibodies against adalimumab and infliximab were measured by means of a radioimmunoassay. Clinical response was assessed by the DAS28 at 28 weeks.

**Conclusions**
Anti-TNF switch patients who formed antibodies against infliximab were more likely to develop antibodies against adalimumab. Antibody formation adversely affected response to treatment.

Abstract 1647, Bartelds GM et al.12

**Key Point** Patients with RA treated with infliximab and who develop anti-infliximab antibodies have a greater likelihood of developing antibodies against another TNF inhibitor, adalimumab, which may affect clinical response.

**Rapidity of Response to Anti-TNF Therapy**

**Improved Hand Function Predicts Response to Anti-TNF Therapy**
Recognition of early signs of response to anti-TNF therapy would greatly aid clinical decision making regarding the treatment of patients with RA. The TNF inhibitor adalimumab results in documented benefits related to clinical outcomes and health-related quality of life in patients with RA. However, the day-to-day evolution of the disease course had not been studied extensively. Swedish investigators sought to determine whether patient-recorded assessments of disease activity, activities of daily living, psychosocial variables, and quality of life after 1 week of treatment with adalimumab correlated with clinical outcome at 3 months, as defined by change in DAS28.9

**Methods**
The study involved 46 patients with early, active RA. They had physician assessments prior to starting adalimumab and after 3 months of treatment. By using a personal digital assistant, the patients recorded their responses to a 10-item assessment daily for 1 week before the start of treatment and for one week afterward, then once weekly until the last week of the study, when patients again recorded their responses daily.

**Results**
Correlational analyses of changes after 1 week of treatment and the change in DAS28 showed that the best predictors of the 3-month outcome were global assessments of emotional well-being (P=0.003) and ability to use the hands (P=0.004). Neither global disease activity nor pain predicted the 3-month outcome.

**Conclusion**
Emotional well-being and hand function after 1 week of adalimumab therapy predicted a favorable outcome at 3 months. The findings demonstrated the potential for identifying patients after just 1 week of treatment who are destined to have favorable outcomes at 90 days with anti-TNF therapy.

Abstract 1649, Augustsson J et al.9

**Key Point** Improved hand function and emotional well-being after 1 week of anti-TNF therapy (adalimumab) correlated with favorable outcomes at 90 days.
Recent Developments in Anti-TNF Therapy for Rheumatoid Arthritis

Functional Benefits and Quality of Life

Anti-TNF Add-On Therapy Reduces Work Absences

Accumulating evidence suggests that aggressive treatment of early RA leads to functional benefits, including fewer absences from work. In a series of studies, Finnish investigators have explored the impact of aggressive treatment regimens on clinical, function, and quality-of-life outcomes in patients with early RA. One recent study showed that the combination of methotrexate, sulfasalazine, and hydroxychloroquine plus prednisolone was associated with fewer absences from work. At the ACR meeting, the Finnish group presented data from a study that assessed the work-related impact of adding a TNF inhibitor to the triple DMARD combination plus prednisolone.

Methods

Investigators at 15 centers enrolled 100 patients with untreated early RA, defined by a symptom duration of 12 months or less. All of the patients received the previously described combination therapy consisting of three DMARDs and prednisolone. The patients were randomized to receive infliximab or placebo at weeks 4, 6, 10, 18, and 26. Doses of methotrexate and sulfasalazine were tailored to individual patient requirements to achieve remission. Doses of hydroxychloroquine and prednisolone remained constant throughout follow-up. In the event of intolerance, a different DMARD could be substituted, but all patients remained on three DMARDs and prednisolone at all times. Days of RA-related absences from work were recorded during 2 years of follow-up.

Results

At 2 years, 62% of the placebo group and 70% of the infliximab group were in remission (Table 5). The infliximab regimen was associated with higher remission rates over time compared with the placebo regimen (OR 1.97, P=0.04). Patients in the placebo group had a median of 31 RA-related work absences during follow-up compared with a median of 2.5 RA-related work absences in the infliximab group, resulting in an age- and sex-adjusted incidence ratio of 1.65 per patient-observation year (P=0.001). Five patients in the placebo group became permanently disabled during the study compared with one in the infliximab group.

Conclusion

The investigators concluded that 6 months of infliximab add-on therapy resulted in a “remarkable” decrease in work disability days during 2 years of follow-up.

Arthritis Rheum. 2005, Puolakka K et al.

Table 5

<table>
<thead>
<tr>
<th>Table 5. Combination Therapy for RA: Effect on Work Absences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Remission</td>
</tr>
<tr>
<td>Disability Days (median)</td>
</tr>
<tr>
<td>Permanent Disability</td>
</tr>
</tbody>
</table>

Adapted from: Puolakka K et al.

Sustained Improvement in Physical Function and Pain

Unchecked progression of RA adversely affects physical functioning and can lead to permanent disability. Therapy that preserves patients’ functional capacity and relieves pain can have a profound effect on physical and emotional well-being. In the RAPID 1 trial, treatment of RA with certolizumab pegol resulted in prompt, sustained, and meaningful improvement in physical function and pain. An ongoing open-label extension of RAPID 1 is assessing the long-term safety and efficacy of certolizumab pegol as add-on therapy to methotrexate. Two-year follow-up data on physical function and pain were reported at the ACR meeting.


Key Point

Methotrexate and anti-TNF add-on therapy achieved sustained, long-term, clinically meaningful improvements in physical function and pain in patients with early, active RA. The benefits were similar with the two doses of certolizumab pegol.


Key Point

The addition of infliximab to three DMARDs plus prednisolone for 6 months substantially reduced work absences over 2 years among patients with early, active RA.

Methods

Patients who completed the 52-week RAPID 1 study could enroll in the open-label extension study. RAPID 1 evaluated two doses of certolizumab pegol (200 mg and 400 mg), but all participants in the extension received 400 mg of certolizumab pegol plus methotrexate every 2 weeks. Patients who completed 2 years of continuous certolizumab therapy (RAPID 1 and open-label extension combined) were included in an evaluation of physical function and pain. Investigators assessed physical function by means of the HAQ Disability Index (HAQ-DI), and an arthritis-specific visual analog scale was used to assess pain. The analysis included changes from baseline for all outcomes, as well as the proportion of patients who had minimum clinically important differences (MCID) in the HAQ-DI, defined as improvement of ≥0.22.

Results

The analysis included 168 patients who originally received certolizumab pegol 200 mg plus methotrexate in RAPID 1 and 177 patients who received certolizumab pegol 400 mg. Sustained improvement in physical function was observed throughout 100 weeks of treatment. The proportion of patients who had MCID responses in the HAQ-DI was 72.4% in the certolizumab pegol 200-mg group and 70.1% among patients originally assigned to 400 mg. Pain relief averaged 38 to 39 points for both doses of certolizumab pegol. The threshold for meaningful improvement on the pain scale is 10 points.

Conclusions

Methotrexate plus certolizumab pegol add-on therapy achieved sustained, long-term, clinically meaningful improvements in physical function and pain in patients with early, active RA. The benefits were similar with the two doses of certolizumab pegol.


Abstract 980, Mease P et al.
Impact of TNF Inhibition on Work Performance

Work disability is a common and serious consequence of RA. Work disability comprises absenteeism and presenteeism (reduced productivity at work). In the RAPID clinical investigation program, certolizumab pegol as add-on therapy to methotrexate reduced signs and symptoms of active RA and inhibited progression of joint damage. Data collection in RAPID included assessments of RA therapy’s impact on work productivity.17

Methods

Participants in the RAPID trials completed the Work Productivity Survey (WPS-RA) every 4 weeks from baseline until trial completion. Investigators compared mean changes in absenteeism, presenteeism, and self-rated impact of RA on work productivity (on a scale of 0 to 10) among treatment groups, which included a placebo control.

Results

RAPID 1 included 982 patients and RAPID 2 had 619 patients. About 35% to 40% of the participants were employed at baseline. Absenteeism averaged 3.26 days at baseline in RAPID 1 and 3.92 days in RAPID 2, and work productivity averaged 5.22 and 5.46 at baseline in RAPID 1 and 2, respectively. Presenteeism averaged 7.11 days in RAPID 1 and 8.79 days in RAPID 2 and was associated with reduced productivity in both trials.

In both trials, patients treated with certolizumab pegol gained work days and productive work days compared with placebo-treated patients, and the degree to which RA interfered with work productivity decreased in the certolizumab pegol groups (Table 6). Improvement was noted as early as 4 weeks and increased over 6 months of follow-up. In RAPID 1, the improvements persisted for as long as 1 year.

Conclusion

Certolizumab pegol, when added to methotrexate, improved work performance among patients with active RA, including reductions in absenteeism, presenteeism, and the extent to which RA interfered with work. Abstract 978, Smolen J et al.17

Daily Activities Maintained With TNF Inhibition

Recognition of RA’s impact on household productivity continues to increase. The recognition has led to greater emphasis on evaluation of household activities as an essential aspect of determining RA’s impact on a patient’s overall functional ability. In the RAPID clinical trial program for certolizumab pegol, patient assessment included regular evaluation of household work and daily activities and the impact of treatment on those outcomes, as reported at the ACR meeting.18

Methods

The RAPID trials incorporated the Work Productivity Survey (WPS-RA) into patient assessment. The WPS-RA measures RA’s impact on household work and daily activities and the change in those outcomes attributable to treatment of RA. Patients completed the WPS-RA every 4 weeks, responding to questions about missed days of household work, days with reduced household productivity, missed days of family/social/leisure activities, and self-rated impact of RA on household work productivity (on a scale of 0 to 10).

Results

At baseline, the burden of RA on household performance averaged 10 to 11 days per month of reduced productivity, and the rate of RA interference with household activities and productivity averaged 5 to 6. RA caused the patients to lose 7 to 8 days per month of household work and 5 to 6 days of family/social/leisure activities.

As compared with placebo treatment, certolizumab pegol was associated with gains in household work days, in productive household work days, and in family/social/leisure activities. The improvements were evident as early as week 4 and continued to improve for 6 months. RA’s interference with household duties began to decrease as early as week 4 and continued to improve for 6 months. The improvements were maintained for as long as 1 year.

Conclusion

The addition of certolizumab pegol to methotrexate was associated with a reduction in RA’s impact on household productivity and improvement in patients’ ability to participate in family, social, and leisure activities. Abstract 977, Emery P et al.18

Table 6. Monthly Gain in Household Productivity: 24 Weeks

<table>
<thead>
<tr>
<th></th>
<th>RAPID 1</th>
<th>RAPID 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P+M</td>
<td>C200+M</td>
</tr>
<tr>
<td>Household Work Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.54</td>
<td>4.67**</td>
</tr>
<tr>
<td>Productive Household Work Days</td>
<td>2.85</td>
<td>5.68**</td>
</tr>
<tr>
<td>Family/Leisure Days</td>
<td>2.55</td>
<td>3.9</td>
</tr>
<tr>
<td>Reduction in RA Interference (0-10)</td>
<td>0.7</td>
<td>2.72**</td>
</tr>
</tbody>
</table>

**P-value<0.01,*P-value<0.05 versus P+M.
P=placebo; M=methotrexate; C200=certolizumab pegol 200 mg; C400=certolizumab pegol 400 mg.
Adapted from: Emery P et al.18

Key Point

Certolizumab pegol add-on therapy was associated with significant improvement in work performance.

Key Point

Anti-TNF add-on therapy improved household productivity and patients’ ability to participate in family and leisure activities.
RA Significantly Increases the Risk of Cardiovascular Disease

RA increases the risk of CVD, and the magnitude of the increase versus populations without RA appears comparable to that of type 2 diabetes mellitus (DM). However, CVD risk in patients with RA has been ascertained primarily from cross-sectional studies that had limited longitudinal data. In an attempt to provide greater context to CVD risk assessment in patients with RA, Peters et al compared the incidence of CVD in patients with type 2 DM and in patients with RA versus the general population.19

Methods

Investigators determined 3-year CVD incidence in a prospective cohort that included 335 outpatients with RA. The incidence derived from that evaluation was compared with the incidence of CVD in 1,852 participants in a population-based cohort study. Fatal and nonfatal CVD were determined on the basis of The International Classification of Diseases, Ninth Revision (ICD-9) criteria. The investigators used Cox proportional hazards models to compare the incidence of cardiovascular events in patients with RA, in patients with type 2 DM, and in the general population.

Results

Patients with RA had a CVD incidence more than double that of the general population (9% vs 4.3%). The percentages translated into an incidence of 3.30 per 100 patient-years for patients with RA and 1.51 per 100 person-years for the general population. Compared with the general population, patients with RA had an age- and sex-adjusted relative risk for CVD of 2.00 (P=0.003). Further adjustment for cardiovascular risk factors did not substantively change the results. Compared with individuals without RA and type 2 DM, patients with RA had a risk ratio for CVD of 2.02 (P=0.021), and patients with type 2 DM had a risk ratio of 2.22 versus healthy individuals (P=0.002).

Conclusions

The findings suggest that RA itself could be an independent risk factor for CVD, according to the investigators.

Abstract 691, Peters MJ et al.19

Key Point
The study confirmed that RA increases the risk of CVD by the same extent as type 2 DM. The results could not be explained by conventional cardiovascular risk factors, raising the possibility that RA itself is a risk factor for CVD.

Anti-TNF Therapy and Risk of MI and Stroke

Inflammation is a trait common to RA and cardiovascular disease (CVD). Moreover, patients with RA have an increased risk of CVD, including clinical events. TNF inhibitors reduce inflammation, and experimental and observational data suggest TNF inhibition may decrease the risk of CVD events. To expand the study of TNF inhibition and CVD, Jacobsson et al examined the long-term risk of CVD events in patients treated with TNF inhibitors.20

Methods

Investigators examined a cohort of 67,208 Swedish patients with RA, using data from three national registries of hospital admission, outpatient visits, and early RA. Analysis of data from the Swedish Biologics Registry identified 5,299 patients who started anti-TNF therapy during 1998 through 2005. Each of these patients was matched with four controls randomly selected from the national RA cohort.

The primary outcomes were first hospitalization for a primary diagnosis of CVD, acute myocardial infarction (MI), or stroke, as determined by ICD coding. Patients were censored at death, emigration, or end of study. Investigators also evaluated the relationship between EULAR response to TNF inhibition and the risk of CVD, MI, and stroke, adjusting for age, sex, comorbidities, antiinflammatory medication, quality of life (HAQ), and disease activity (DAS28).

Results

During follow-up, 2,778 CVD events occurred, along with 492 acute MIs, and 338 strokes. Comparison of patients treated with anti-TNF therapy and the RA controls revealed a statistically significant reduction in the relative risk of CVD among women, but not in men or in the overall cohort (Table 7). A trend toward reduced risk of MI and stroke was found among women treated with TNF inhibitors.

Comparison of EULAR response and nonresponse yielded an adjusted relative risk of 1.03 for any CVD event, 0.86 for acute MI, and 0.81 for stroke. None of the differences achieved statistical significance.

Conclusions

Anti-TNF therapy did not significantly influence CVD risk overall. However, the analysis provided evidence of a lower risk of CVD, acute MI, and stroke among women treated with TNF inhibitors. Response to anti-TNF therapy did not emerge as a strong predictor of overall CVD risk, although a trend toward a lower risk of stroke was in evidence.

A definitive answer to the issues addressed by this analysis likely would require a randomized, controlled clinical trial.

Abstract 1997, Jacobsson LT et al.20

Key Points

Anti-TNF therapy did not influence the overall risk of CVD. However, women appeared to derive a benefit, including a statistically significant reduction in the risk of CVD events.

Table 7. Anti-TNF Therapy and Cardiovascular Events

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>0.90 (0.78-1.03)</td>
<td>1.02 (0.81-1.29)</td>
<td>0.82 (0.69-0.98)</td>
</tr>
<tr>
<td>Acute MI</td>
<td>1.02 (0.78-1.32)</td>
<td>1.17 (0.80-1.72)</td>
<td>0.92 (0.65-1.32)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.76 (0.55-1.05)</td>
<td>1.51 (0.80-1.72)</td>
<td>0.68 (0.41-1.12)</td>
</tr>
</tbody>
</table>

CVD=cardiovascular disease; MI=myocardial infarction. Adapted from: Jacobsson LT et al.20
Cardiovascular Outcomes in Patients Treated With TNF Inhibitors

Cardiovascular disease (CVD) makes a substantial contribution to overall morbidity and mortality in patients with RA. Some data have suggested that treatment with methotrexate reduces the risk of CVD, but the relationship between anti-TNF therapy and CVD has remained controversial. Solomon (Brigham & Women’s Hospital, Boston) et al evaluated the risk of cardiovascular events (MI, stroke, or transient ischemic attack) among patients with RA treated with various disease-modifying antirheumatic drugs (DMARDs).21

Methods

Data for the analysis came from the Consortium of Rheumatology Researchers of North America (CORRONA) registry. Investigators identified patients whose rheumatologist reported a new cardiovascular event and confirmed the event during follow-up. Rheumatologists’ medication reports formed the basis of a longitudinal assessment of exposure to therapy. The analysis included three medication categories: TNF inhibitors, methotrexate, and all other nonbiologic DMARDs.

Use of NSAIDs and steroids were incorporated as covariates in Cox proportional hazards regression models, which also accounted for cardiovascular risk factors and markers of RA disease activity (Disease Activity Score, Health Assessment Questionnaire, RA duration, antibody status, and nodules).

Results

The analysis included 10,870 patients with a median follow-up of 24 months in CORRONA and a median RA duration of 7 years. Three fourths of the patients tested positive for rheumatoid factor or anti-CCP antibodies.

During follow-up, 71 patients had confirmed cardiovascular events, consisting of 26 MIs and 45 strokes/transient ischemic attacks (TIAs). Solomon and colleagues found a statistically significant reduction in cardiovascular events among patients treated with TNF inhibitors compared with nonbiologic DMARDs, not including methotrexate (HR 0.3, 95% confidence interval [CI] 0.1-0.6). Methotrexate therapy was associated with a trend toward a lower risk of cardiovascular events versus other nonbiologic DMARDs (HR 0.6, 95% CI 0.3-1.2).

Separate analyses yielded similar findings with respect to MI and stroke/TIA.

Variables associated with a trend toward an increased risk of cardiovascular events were older age, male sex, modified HAQ score, DAS28, nodules, hyperlipidemia, current smoking status, and current prednisone dose.

Conclusions

Treatment with a TNF inhibitor was associated with a significant reduction in the risk of cardiovascular events. A trend toward reduced risk was observed in patients treated with methotrexate. Several RA-associated variables increased the risk of cardiovascular events, as did the use of prednisone, which increased the risk in a dose-dependent manner.

Abstract 1016, Solomon DH et al.21

References


10. Glass RJ, Shadick NA, Cui J, Maher N, Weinblatt M. Methotrexate therapy was associated with a trend toward a lower risk of cardiovascular events versus other nonbiologic DMARDs (HR 0.6, 95% CI 0.3-1.2).


Key Point

RA-related clinical characteristics are associated with an increased risk of cardiovascular events. Treatment with TNF inhibitors significantly reduces the risk, and treatment with methotrexate reduces the risk to a lesser extent.
INSTRUCTIONS: Review the learning objectives for this activity and read the supplement carefully. Read each question and circle the correct answer. Retain a copy of your answers for your records. Complete and submit your answer sheet as directed online at www.CEConcepts.net/RAHighlights. You will receive your statement of credit immediately upon successful completion (correctly answering 70% of the questions).

1. According to the studies summarized, rheumatoid arthritis (RA):
A. Increases the risk of cardiovascular disease
B. Has no association with cardiovascular disease
C. Is associated with reduced left ventricular volume
D. A & C

2. Studies reported at the ACR meeting showed that anti-TNF therapy:
A. Increases the risk of stroke
B. Increases the risk of myocardial infarction
C. Has a neutral or favorable effect on the risk of cardiovascular events
D. A & B

3. After methotrexate failure in patients with early RA, what type of treatment led to better outcomes?
A. TNF inhibition
B. A higher dose of methotrexate
C. Combination DMARDs
D. Injectable steroids

4. A cost-effectiveness study of therapy for early RA showed that initial combination treatment with a TNF inhibitor versus sequential DMARD therapy:
A. Had a higher initial cost that was never recouped over time
B. Cost at the outset and remained more cost-effective throughout follow-up
C. Had a higher initial cost that was offset by increased gains in quality-adjusted life years
D. Cost about the same when averaged over five years

5. Which phrase best describes the effect of TNF inhibition on radiographic progression of RA?
A. Dependent on control of disease activity
B. Independent of disease activity control
C. Not evident until at least 6 months of treatment
D. Direct correlation between disease activity and radiographic progression

6. In studies of patients with RA that was unresponsive to conventional DMARDs, TNF inhibition:
A. Was effective as monotherapy or in combination with methotrexate
B. Was effective only when used in combination with methotrexate
C. Was less effective than methotrexate alone
D. None of the above

7. According to the data reported, switching from one TNF inhibitor to another:
A. Is not feasible
B. Can restore or maintain disease control in some patients
C. Predisposes patients to infection
D. Is ineffective

8. A comparison of anti-TNF therapy in biologic-naïve and experienced patients showed that response rates:
A. Were higher in biologic-experienced patients, suggesting a “priming effect”
B. Were similar, but biologic-experienced patients had more side effects
C. Initially were lower in biologic-experienced patients but increased over time
D. Were consistently higher in biologic-naïve patients

9. The evidence presented suggested that anti-TNF add-on therapy for early RA:
A. Had no effect on work absences
B. Was equivalent to a strategy of multiple DMARDs plus prednisone
C. Decreased the number of days missed from work
D. Decreased RA-related work absences but increased absences related to other conditions

10. How did the addition of a TNF inhibitor to methotrexate affect work performance?
A. Decreased absenteeism but not presenteeism
B. Decreased presenteeism but not absenteeism
C. Decreased absenteeism, presenteeism, and the degree to which RA interfered with work
D. Was associated with fewer on-the-job accidents

Name: ____________________________
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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.

POST-TEST ASSESSMENT: Please rate your current knowledge of TNF inhibition on a scale of 1 to 5, with 1 being the lowest and 5 the highest. 1 2 3 4 5

COURSE EVALUATION: Please evaluate the effectiveness of this activity by circling your choice on a scale of 1 to 5, with 1 being the lowest and 5 the highest.

Objective #1. Summarize the associations between RA and cardiovascular disease. 1 2 3 4 5
Objective #2. Assess trends in the use of anti-TNF therapy in early RA. 1 2 3 4 5
Objective #3. Analyze quality-of-life issues that affect RA patients. 1 2 3 4 5
Objective #4. Appraise the rapidity with which RA can progress and the impact of aggressive therapy on disease progression. 1 2 3 4 5

Objective #5. Evaluate principles and potential outcomes of switching from one drug to another within the TNF inhibitor class. 1 2 3 4 5
How do you rate the overall quality of the activity? 1 2 3 4 5
How do you rate the educational content of the activity? 1 2 3 4 5
After participation in this activity, have you decided to change one or more aspects in the treatment of your patients? □ Yes □ No
If yes, what change(s) will you make?

If no, why not?

Was the presented information fair, objective, balanced, and free of bias in the discussion of any commercial product or service? □ Yes □ No
If no, please comment:

Suggested topics for future activities:

Suggested authors for future activities:

Would you be willing to participate in postactivity follow-up surveys? □ Yes □ No
Would you be willing to participate in a phone, e-mail, or in-person discussion exploring ways to improve our CME activities? □ Yes □ No

CEC thanks you for your participation in this CME activity. All information provided improves the scope and purpose of our programs and your patients’ care.