

What's New From ACR/EULAR: Translating Research Into Clinical Practice

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A Publication for Rheumatology
Nurse Practitioners and Physician Assistants



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Target Audience

Nurse practitioners (NPs) and physician assistants (PAs) in the practice of rheumatology.

Activity Goal

To familiarize NPs and PAs with the latest research findings from recent scientific meetings in rheumatology regarding the early diagnosis of RA and implementation of available treatment options.

Learning Objectives

After completing this activity, participants should be better able to:

1. Integrate new criteria for diagnosing RA into the initial evaluation of patients who present with signs of rheumatologic disease.
2. Assess the need for treatment adjustments by using a quantitative scale to monitor disease activity in patients with RA during follow-up visits.
3. Translate clinical data on advances in RA therapies into practical strategies for patient care.

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The fundamental concept governing today's approach to treating rheumatoid arthritis (RA) is minimization of cumulative inflammation.¹ Core principles of RA management identified by practicing rheumatologists include early diagnosis and referral for treatment, immediate treatment with conventional or biologic disease-modifying antirheumatic drugs (DMARDs), frequent assessments to maintain tight control of inflammation, and treatment tailored to individual patient needs.¹ The importance of early recognition and management of RA is highlighted by the advent of clinical remission as a feasible goal since the introduction of biologic therapy² and emerging evidence of sustained benefits with combination therapy.^{3,4}

Few areas of medicine are changing as rapidly as rheumatology.

Potentially practice-changing developments were reported at the 2009 scientific meetings of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). This issue of *PCE Updates in Rheumatology* focuses on the results of the cutting edge research presented at EULAR 2009 and ACR 2009 and strategies for translating these developments into clinical practice.

Early Recognition and Treatment

Lessons From CATCH

Numerous studies have shown that the early initiation of therapy, aggressive in some cases, can prevent erosions and may induce remission.^{1,5} Even in patients with early mild disease,

aggressive therapy may be needed to prevent disease progression. In the Canadian Early Arthritis Cohort (CATCH), a significant number of patients presented with very low disease activity at baseline. One third of these patients had progressive disease during a 1-year follow-up period, despite DMARD therapy. One reason may be that patients presenting with remission at baseline received significantly less aggressive treatments (methotrexate [MTX], parenteral MTX, and DMARD combinations). They also received delayed MTX treatment compared with patients presenting with high disease activity (53% vs 16%, $P = .006$). These results suggest patients with early arthritis and a poor prognosis must be identified early so that more aggressive treatments can be initiated.⁶

Katchamart W, Boire G, Pope J, et al. The clinical course, outcomes, and treatment of early inflammatory arthritis: results from CATCH (Canadian Early Arthritis Cohort) [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):369.⁶

Table 1. Proposed New RA Diagnostic Criteria

Domain	Point Score ^a
Joint Involvement	0-5
1 medium-large joint	0
2-10 medium-large joints	1
1-3 small joints	2
4-10 small joints	3
>10 small joints	5
Serology	0-3
Not positive for RF or anti-CCP antibody	0
≥1 of these 2 tests (RF or anti-CCP antibody) are positive at low titer, defined as more than the upper limit of normal, but not >3 times the upper limit of normal	2
≥1 test (RF or anti-CCP antibody) is positive at high titer, defined as >3 times the upper limit of normal	3
Duration of Synovitis	0-1
<6 weeks	0
≥6 weeks	1
Acute Phase Reactants	0-1
Neither CRP nor ESR is abnormal	0
Abnormal CRP or abnormal ESR	1

Anti-CCP = anti-cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor.

^aPatients receive the highest point level they fulfill within each domain. A diagnosis of RA requires a total point score ≥6.

Hawker GA.⁷

New RA Diagnostic Criteria From EULAR/ACR

To facilitate early recognition of patients with RA, EULAR and ACR have collaboratively developed new diagnostic criteria for RA.⁷ According to the new criteria, patients are rated on a scale of 0 to 10 points, with points assigned in 4 domains of signs and symptoms: joint involvement, serology, duration of symptoms, and acute phase reactants. Patients who tally 6 or more points are considered to have definite RA (Table 1). The new diagnostic criteria bring official policy on the diagnosis of RA in line with current treatment practice of early recognition and management.¹

Hawker GA. Developing new RA classification criteria: reaching a consensus. Presented at: ACR 2009 Annual Scientific Meeting; October 18, 2009; Philadelphia, PA.⁷

Commentary

Martin J. Bergman: Early treatment and aggressive management have consistently led to better patient outcomes. Knowing which regimen is best for an individual patient remains an issue. Patients with the appearance of minimal disease are still at risk for worsening findings over time. Knowing the current state of disease activity, preferably through the use of a quantitative scale, such as the Disease Activity Score 28 (DAS28), Clinical Disease Activity Index (CDAI), or Routine Assessment of Patient Index Data 3 (RAPID3), should help to differentiate patients who “appear” to be doing well from those who are truly doing well. Early diagnosis and beginning treatment as soon as the diagnosis is made should also benefit patients. The new diagnostic criteria should aid in this process.

Rick Pope: The results from the CATCH study present a challenge to all clinicians in rheumatology. My experience in clinical practice led me to believe that patients with RA with low disease activity required less aggressive therapy. However, based on the CATCH study, “low disease activity” may be lulling us into a false sense of security. Recently, a patient with RA who was serologically positive for anti-CCP and RF presented for a follow-up examination. For the past year, he had been receiving MTX therapy at a weekly dosage of 15 mg. I ordered a set of hand and foot radiographs because his previous images were more than 1 year old. The radiographs showed subchondral cysts and frank erosions had developed in 3 joints in his hands. As I reviewed his record, I noted that his biomarker positivity had been known to me and the rheumatologist. He had been “doing well,” without stiffness and without pain. Two of the joints that now

showed radiographic progression had been enlarged but not frankly synovitic. After a negative tuberculosis skin test and chest x-ray, he started treatment with a tumor necrosis factor (TNF) inhibitor. The patient previously had been resistant to adding a biologic for multiple reasons. However, his case provides a strong reminder that tools are now available to assist in recognition of patients who are likely to develop more severe disease.

The new early RA scoring system being developed by ACR and EULAR is potentially useful and may allow clinicians to identify RA patients more quickly and accurately. Higher scores of RF and anti-CCP are more heavily weighted, which makes sense now that we comprehend how these biomarkers relate to disease aggressiveness. The scoring system would also better accommodate the clinical picture, with joint involvement being an important part of the evaluation.

Predicting RA Progression Role of Clinical Assessment Tools

The ACR core data set, DAS28, and the Health Assessment Questionnaire-Disability Index (HAQ-DI) are the most frequently used indices for measuring RA disease activity in clinical trials, but their use in routine clinical practice is limited by their complexity and practice time constraints. Several simplified disease assessment tools have been developed, including the self-administered Rheumatoid Arthritis Disease Activity Index (RADAI). Among the Study of New-Onset Rheumatoid Arthritis (SONORA) cohort, RADAI was found to show changes over time similar to those shown by the DAS28-CRP (a modification of the DAS28 that uses the CRP level instead of the ESR in score calculation) and the HAQ-DI.⁸

The correlations between RADAI and DAS28-CRP were 0.44 at baseline and 0.45 at 1 year (both $P < .0001$); the correlations between RADAI and HAQ-DI were 0.64 at baseline and 0.65 at 1 year (both $P < .0001$). When patients were classified into mild, moderate, or severe disease categories, agreement between RADAI and either DAS28-CRP or HAQ-DI was low. RADAI is a valid measure of disease progression over time and has the potential to become a practical tool in clinical practice.⁸

Li X, Chen MH, Bombardier C. Validation of Rheumatoid Arthritis Disease Activity Index (RADAI) in a North American cohort of patients with early rheumatoid arthritis (RA) [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):965.⁸

In a study population derived from the MTX arm of the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO), 169 patients were evaluated at week 12 of MTX therapy to identify possible prognostic markers of radiographic progression at 52 weeks. CRP level, ESR, tender joint count (TJC), swollen joint count (SJC), and HAQ scores at week 12 were significant ($P < .05$) predictors of radiographic progression at 52 weeks. Furthermore, patients with a CRP serum level >0.67 mg/dL and a SJC >1 , or a CRP level ≤ 0.67 mg/dL and SJC >10 at week 12 were likely to have the worst radiographic progression at week 52. These findings suggest that CRP and SJC after 12 weeks of MTX therapy are the best predictors of radiographic progression at week 52 in patients with RA.⁹

Weinblatt ME, Keystone EC, Cohen MD, et al. Predictors of radiographic progression in rheumatoid arthritis patients treated with methotrexate [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):350.⁹

Commentary

MB: It is my practice to use a clinical measure at every visit. There are many available, including CDAI, DAS28, RAPID3, and RADAI. All have strengths and weaknesses, but all provide a quantifiable method for measuring disease activity. While no single measure is perfect, some measure is better than no measure. Which measurement tool is chosen should be left to the clinician.

The conclusion of the TEMPO analysis is that patients who have persistent disease, as measured by persistently elevated CRP and persistently abnormal joint examinations, will most likely have disease progression. If these patients are still showing signs of disease activity at 12 weeks, a change in medications should be considered.

RP: The use of clinical assessment tools is increasingly necessary in day-to-day practice. These measurements provide the clinician with valuable input as to how the patient is responding to therapy. Assessment of disease activity and functional status of the patient are part of the 7 ACR RA quality indicators that have been instituted and, as of 2009, have implications for Medicare reimbursement. This will likely continue in the future.

The TEMPO trial analysis provides insight into what an early clinical response means. How the patient responds at 3 months is an indication of what we are likely to see at 52 weeks on radiographic scores. The take-home lesson is that such early indicators should be heeded, and if patients are not responding, alternative treatments should be considered at the 12-week time point.

New Findings on Biomarkers

The presence of RA-related autoantibodies (IgM-RF and anti-CCP) prior to diagnosis suggests that there is a

pre-clinical period in RA. Prospective analysis of individuals with such serologic findings prior to the development of RA may provide a better understanding of early disease pathogenesis. As part of the Studies of the Etiology of RA (SERA), a prospective cohort of first-degree relatives of probands with RA was created. In relatives without RA by ACR criteria, IgM-RF positivity was associated with ≥ 1 TJC (odds ratio [OR], 2.50; 95% confidence interval [CI], 1.27-4.89) and elevated CRP (OR, 5.31; 95% CI, 1.45-19.52). Follow-up of these individuals with very early signs of clinical disease will be valuable to understanding factors associated with transition to a phenotype that meets full ACR criteria.¹⁰

Kolfenbach JR, Deane KD, Derber LA, et al. Association of rheumatoid arthritis (RA)-related autoimmunity and joint findings in unaffected at-risk populations [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):371.¹⁰

Although anti-CCP and IgM-RF positivity status predicts RA development, recent data indicate that the levels of anti-CCP antibody and IgM-RF appear to be better predictors of persistent arthritis than just negativity or positivity status.¹¹ Among a cohort of 376 patients from the Norwegian Very Early Arthritis Clinic (NORVEAC) who had undifferentiated arthritis, the likelihood of developing persistent arthritis increased as the levels of anti-CCP antibody and RF increased (Table 2). Thus, in making risk assessments, clinicians should stratify patients according to the levels of these antibodies and not just antibody positivity or negativity.¹¹

Mjaavatten MD, van der Heijde DMFM, Uhlig T, et al. Levels of anti-CCP and IgM RF predict persistent arthritis in patients with very early undifferentiated arthritis (UA) [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):334.¹¹

In patients with established RA, anti-CCP positivity is associated with a greater disease burden.¹² New data indicate that higher levels of anti-CCP and RF antibodies are associated with greater disease burden. In a cohort of US veterans, per 100 unit increments of anti-CCP and RF concentrations at baseline were associated with reduced remission and greater area under the curve for DAS28, after adjustment for age, sex, race/ethnicity, education, disease duration, follow-up time, smoking status, comorbidity, pharmacologic interventions, and disease status (DAS28 ≤ 2.6 vs DAS28 > 2.6).¹³ This association, however, appears to be related to concomitant elevations in RF levels. In anti-CCP+/RF- patients, higher anti-CCP concentrations were associated with an increased likelihood of achieving remission (OR, 1.10; 95% CI, 1.00-1.20); among anti-CCP-/RF+ patients, higher RF concentrations trended toward a decreased likelihood of achieving remission (OR, 0.81; 95% CI, 0.58-1.13).¹³

Miriovsky BJ, Michaud KD, Thiele GM, et al. Associations of anti-CCP and rheumatoid factor concentrations with future disease activity in rheumatoid arthritis [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):332.¹³

Another study showed that anti-CCP antibody status was not a significant predictor of erosion-free status in RA.¹⁴ In this study of patients with disease duration of < 10 years, 46% of those who were erosion-free at recruitment and at 2-year follow-up were anti-CCP+. In contrast, younger age, male gender, and shorter RA duration were independent predictors of erosion-free status.¹⁴

Liao KP, Weinblatt ME, Cui J, et al. Clinical factors that predict erosion-free status in rheumatoid arthritis [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):372.¹⁴

Commentary

MB: Biomarkers play an important and helpful role in the diagnosis and prognosis of RA. However, we should not be lulled into using biomarkers as the sole determinant of disease activity and severity. Patients with active disease are at high risk for erosions and disability, regardless of their serologic status. Knowing what to expect in the future, based on serologies, is a benefit. However, close monitoring of patients, regardless of serologies, remains the best approach.

RP: These studies contribute to our expanding knowledge of the prognostic value of biomarkers in RA. Higher level positivity for anti-CCP antibody and RF increases the likelihood of severe disease. However, patients who do not have these markers can still progress, making close clinical observation and functional health assessments our best prognostic tools available to date.

RA Therapies: What's New? Abatacept

Abatacept Plus MTX in Early RA: Clinical Remission and Radiographic Nonprogression

Adding abatacept to MTX in patients with early RA is effective against clinical symptoms and joint erosion, according to results from the 1-year open-label extension (OLE) phase of the Abatacept Study to Gauge Remission and Joint Damage Progression in Methotrexate-Naïve Patients With Early Erosive Rheumatoid Arthritis (AGREE). The OLE followed a 1-year double-blind phase. More than half of the patients who were MTX-naïve (55.2%) and received continuous abatacept plus MTX over the 2-year period achieved disease remission (DAS28 <2.6) at 2 years.¹⁵ Among those who received MTX alone in the double-blind phase, close to 45% achieved remission at 2 years in the OLE. Serious adverse events (SAEs)/100 patient years (100-PY) in the OLE and double-blind

phases were similar (6.42 vs 8.35), as were serious infection events (SIEs)/100-PY (1.73 vs 2.04).¹⁵

Westhovens R, Robles M, Nayiager S, et al. Disease remission is achieved within two years in over half of methotrexate naive patients with early erosive rheumatoid arthritis (RA) treated with abatacept plus MTX: results from the AGREE Trial [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):638.¹⁵

Reduction of radiographic progression also was greater and sustainable at 2 years in patients treated early with both abatacept and MTX.¹⁶ Patients originally randomized to the abatacept and MTX experienced less progression of structural damage from baseline through year 2, as measured by a change in the mean total Sharp (TS) score (0.84 vs 1.75). In addition, there was a greater proportion of nonprogressors at year 2 in the original combination arm compared with the MTX monotherapy arm (56.8% vs 43.8%). The inhibition of radiographic progression was greater year 2 than year 1

Table 2. Anti-CCP and RF-IgM Levels Predict Persistent Arthritis^a

Serum Protein Variable (U/mL)	OR (95% CI)	P Value	Positive Likelihood Ratio	Negative Likelihood Ratio
Anti-CCP				
≤25	1.0			
>25-100	4.4 (1.6-12.54)	.005	4.1 (1.5-11.0)	0.9 (0.9-1.0)
>100-250	9.4 (2.1-42.92)	.004	8.7 (2.0-38.2)	0.9 (0.8-1.0)
>250	13.64 (4.04-46.04)	<.001	11.4 (3.5-37.0)	0.8 (0.8-0.9)
IgM-RF				
≤25	1.0			
>25-75	4.6 (2.0-10.6)	<.001	4.0 (1.9-8.7)	0.9 (0.8-0.9)
>75	19.2 (4.5-82.5)	<.001	16.2 (3.9-67.2)	0.8 (0.8-0.9)

^aUnivariate logistic regression analyses with persistent arthritis as dependent variable. Mjaavatten MD, et al.¹¹

(mean change in TS = 0.18 vs 0.66, $P < .0001$), and 91.1% of year 1 nonprogressors in the original abatacept and MTX arm remained nonprogressors in year 2.¹⁶

Bathon J, Genant H, Nayiager S, et al. Reduced radiographic progression in patients with early rheumatoid arthritis (RA) treated with abatacept + methotrexate compared to methotrexate alone: 24 month outcomes [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):639.¹⁶

These results support early aggressive use of combination therapy with abatacept and MTX in MTX-naïve patients with early RA.

Abatacept: 5-Year Sustained Clinical Efficacy

In patients whose RA failed to respond to MTX therapy, sustained disease modification and restoration of normal physical function are feasible with abatacept.¹⁷ In the long-term extension arm of the Abatacept in Inadequate Responders to MTX (AIM) study, two thirds of RA patients with inadequate response to MTX who received abatacept experienced sustained clinical remission, radiographic nonprogression, and normalization of physical function and health-related quality of life during 5 years of continuous treatment.

Westhovens R, Dougados M, Hall S, et al. Disease remission, radiographic non-progression and normalization of function achieved at year 1 are sustained long-term in a majority of patients: 5-year outcomes with abatacept in biologic-naïve patients [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):1657.¹⁷

Adalimumab

Adalimumab Dose Escalation in Partial Responders: Durable Response

Dose escalation of adalimumab from 40-mg subcutaneously (SC) every other week to 40-mg SC weekly in

patients with moderate to severe RA who responded only partially to the initial regimen induced durable response and is safe.¹⁸ In 43 patients with inadequate response to adalimumab every other week, who were then given adalimumab 40 mg weekly for 17 months, 56% achieved a new good EULAR response that began within 7.5 months and lasted more than 12 months. In 71% of the adalimumab weekly group, the good EULAR response persisted to the end of the observation period. Although more flares occurred in the weekly group than in the every other week group (OR, 3.6; 95% CI, 0.9-13.9; $P = .07$), the rate of serious infections were similar in the 2 groups (5.5/100-PY vs 4.9/100-PY, respectively).¹⁸ These results suggest that in partial responders to adalimumab 40-mg every other week, dose escalation to weekly might be a worthwhile option.

Karpouzas GA, Broumand A, Bagheri S, et al. Adalimumab dose escalation induces durable remissions and is safe in minorities with moderate to severe rheumatoid arthritis (RA) [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):1702.¹⁸

Adalimumab Plus MTX: Sustained Clinical Efficacy Over 8 Years

The efficacy of adalimumab (40-mg every other week) and MTX combination therapy in maintaining clinical efficacy in patients with RA was evaluated in a long-term extension study.¹⁹ After 8 years of combination therapy, 60% of patients experienced disease remission (DAS28 <2.6) and 55% radiographic nonprogression. Improvements in physical function also were noted; mean HAQ scores decreased from 1.33 at baseline to 0.65 at 8 years.¹⁹ The sustained efficacy of adalimumab plus MTX supports the long-term use of this regimen in patients with RA.

Keystone EC, Kavanaugh A, van der Heijde DMFM, Sinisi S, Hall J, Guertel B. Long-term impact of adalimumab plus methotrexate on radiographic, clinical, and functional progression of rheumatoid arthritis [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):1679.¹⁹

Adalimumab Plus MTX: Window of Opportunity in Early RA

An analysis of data from 2 long-term trials involving patients with long-standing RA (study DE019: 5 years of treatment) or early RA (PREMIER study: 2 years of treatment) who received combination therapy with adalimumab and MTX found that patients with moderate disease (whether early or long-standing) have a great likelihood of regaining normal physical function. However, in patients with severe disease, the efficacy of combination therapy is greater in those with early RA. By 1 year in the DE019 study, >60% of patients with moderate disease had achieved normal population HAQ scores compared with 34% of patients with severe disease; this difference was maintained during a 5-year period. In the PREMIER study, 70% of patients in the moderate group and 61% of patients in the severe group had reached normal functioning at 1 year. Thus, there is a window of opportunity for preventing irreversible loss of function in severe RA, but this opportunity is greater for patients with early RA than with long-standing RA.²⁰

van Vollenhoven R, Cifaldi M, Roy S, Chen N, Gotlieb L, Malaise M. Ability to regain normal function in moderate vs. severe rheumatoid arthritis: analysis from long-standing and early RA patient populations [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):1013.²⁰

Etanercept

Therapeutic Strategy in Early RA: Where Does Etanercept Fit In?

The optimal therapeutic strategy in early RA has not been established.

The Treatment of Early Aggressive RA (TEAR) study, a 2-year randomized, double-blind study, compared 4 treatment strategies in early RA: immediate MTX plus etanercept, immediate triple DMARD therapy (MTX, sulfasalazine, and hydroxychloroquine), step-up from MTX to MTX plus etanercept, or step-up from MTX to triple DMARD therapy.²¹ This study found no significant differences in the DAS28 scores among the treatment groups during weeks 48 to 102 of treatment. However, patients receiving immediate therapy with either regimen were more likely to achieve ACR 20/50/70 responses at 6 months than patients receiving either step-up therapy, but, again, there was no difference among all 4 strategies at 2 years. Based on these results, the authors concluded that initial use of MTX monotherapy with the addition of sulfasalazine/hydroxychloroquine or etanercept if necessary after 6 months is a reasonable therapeutic strategy for early RA.²¹

Moreland LW, O'Dell JR, Paulus H, et al. TEAR: Treatment of early aggressive RA; A randomized, double-blind, 2-year trial comparing immediate triple DMARD versus MTX plus etanercept to step-up from initial MTX monotherapy [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):1895.²¹

Infliximab

Addition of Infliximab to MTX Reduces Radiographic Progression in Early RA

In the Swedish Pharmacotherapy (SWEFOT) study, patients with early RA who failed to achieve a DAS28 <3.2 after 3 to 4 months of MTX monotherapy were randomized to the addition of conventional DMARDs, sulfasalazine (2000 mg/d) plus hydroxychloroquine (400 mg/d), or infliximab (3 mg/kg). At 2 years, there was significantly less radiographic progression in the infliximab arm

compared with the conventional therapy arm as measured by total Van der Heijde-Sharp score ($P = .009$), erosion score ($P = .039$), and joint-space narrowing ($P = .026$). In patients with early RA insufficiently responsive to MTX monotherapy, the addition of infliximab yielded significantly better radiologic results through 24 months than the addition of conventional DMARDs.⁴

van Vollenhoven RF, Albertsson K, Forslind K, et al; SWEFOT Study Group. In early RA with insufficient response to MTX, the addition of anti-TNF results in less radiological progression over 24 months than the addition of conventional DMARDs: results from the SWEFOT trial. Presented at: ACR 2009 Annual Scientific Meeting; October 20, 2009; Philadelphia, PA. Abstract LB6.⁴

MTX

High Starting Doses Are Safe

MTX at a dose of 25 mg/wk is clinically effective, but therapy usually is started at a lower dose (7.5 mg/wk) and titrated up gradually, probably because of safety concerns. To evaluate the safety of high-dose MTX, Medley and colleagues matched pharmacy records of 86 patients with RA receiving MTX prescriptions with their blood tests and liver function tests (LFTs) from the hospital pathology system. Approximately 30% of patients assessed had received a MTX dose of 25 mg/wk and the rest, a dose of ≤ 15 mg/wk. There were 4 neutropenic episodes: 1 in the high-dose group and 3 in the low-dose group. An abnormal LFT result was seen in 60% of patients in the high-dose group compared with 44% of patients in the low-dose group (RR, 1.35; $P < .2$). In the high-dose group, 32% of patients had abnormal alanine transferase (ALT) levels, including 1 patient with an ALT level 3 times the upper limit of normal. In comparison, abnormal ALT levels occurred in 31% of

patients in the low-dose group, with 2 patients having ALT levels 3 times the upper limit of normal. These data indicate that starting MTX at a maximum dose of 25 mg/wk appears safe.²²

Medley SEJ, Dolan AL, Coakley G. How safe is starting high dose methotrexate? [abstract]. *Ann Rheum Dis.* 2009;68(suppl 3):591.²²

Rituximab

Rituximab Plus MTX in Early RA: Inhibition of Joint Damage and Improved Clinical Outcomes

Starting rituximab with MTX in patients with early RA improves response. In patients with early RA naïve to MTX, greater clinical and radiographic benefits are achieved with initial rituximab (2×1000 mg at days 1 and 15) plus MTX combination therapy than with MTX monotherapy. In patients receiving the combination therapy for 1 year, 30% achieved remission, 18% achieved major clinical response (ACR 70 maintained for at least 6 months), and 64% had radiographic nonprogression; all responses were significantly superior to those in patients receiving MTX alone. Patients who were randomized to a lower dose of rituximab (2×500 mg) plus MTX also had a significantly better clinical response than patients receiving MTX alone; but no difference in the radiographic response between the 2 treatment groups was seen. The rate of SAEs and SIEs were similar among the 3 treatment groups.²³

Tak PP, Rigby W, Rubbert A, et al. Inhibition of joint damage and improved clinical outcomes with a combination of rituximab (RTX) and methotrexate (MTX) in patients (pts) with early active rheumatoid arthritis (RA) who are naive to MTX: a randomised active comparator placebo-controlled trial [abstract]. *Ann Rheum Dis.* 2009;68(suppl 3):75.²³

Periodontitis Is Common in RA Patients

Periodontitis is more common among individuals with RA than among the general population. A prospective 6-month observational study found that RA patients with either localized or generalized aggressive periodontitis have higher levels of inflammatory (CRP, ESR) and immune (anti-CCP) abnormalities. Significant positive correlations among periodontitis, disease activity, and anti-CCP levels were noted.

After 6 months of anti-TNF therapy, statistically significant improvement in periodontal status occurred in RA patients. Results indicate that the 2 diseases, both of which are inflammatory diseases that lead to bone loss, may share common mechanisms and that anti-TNFs are potentially able to modulate the inflammatory process in the periodontium.

Practice point: Patients with 1 disease may benefit from screening for the other.

Ancuta C, Iordache C, Ancuta E, Iordache O, Chiriac R. Periodontal status in patients with rheumatoid arthritis [abstract]. *Ann Rheum Dis.* 2009;68(suppl 3):413.

Commentary

MB: Using MTX in an appropriate fashion is important. Too often MTX is “dripped” into the patient, while multiple studies, including the Medley study, have shown that higher dosages can be attained rapidly without increased toxicity. Once a patient fails to respond to MTX, deciding on what constitutes the next best option is unclear. The biologics—anti-TNFs, anti-B-cell therapy, and anti-T-cell therapy—have been shown to be effective and result in durable responses. This is true at a clinical/functional level and a radiologic level. The TEAR study supports the notion that aggressive management in early disease can lead to a good outcome, whether it is biologic-based or DMARD-based. Many questions remain with respect to this study, including the radiologic (x-ray) outcomes and long-term durability of the results (>35% of study patients dropped out of all study arms). Still, knowing there are many options that will help our patients is important.

RP: For many years we had evidence

that the addition of biologics to MTX prevents damage to joints better than MTX alone. Of interest to me is that after nearly 30 years of use, MTX continues to be the cornerstone of therapy. In Europe, there is evidence that starting MTX at maximum doses appears to be safe, but this concept has not caught on in the 2 offices where I practice. The Medley study suggests that early use of MTX at higher doses is safe.

The analysis of data from the adalimumab DE019 and PREMIER trials is intriguing. It suggests that function can improve in a patient with long-standing moderate disease when MTX is added to adalimumab. Many of our patients with well-established RA believe their disease is too far advanced for functional improvement, but for those with moderate disease activity, this study offers them hope for regaining function.

Timing of Treatment Switching

Therapy adjustment is recommended at least every 3 months for patients with persistent disease; however, the efficacy of currently available therapies

increases over time, at least during the first year. This raises 2 questions: How long should clinicians wait before considering a treatment ineffective and switching therapy? Is the time to reach this decision the same regardless of the treatment used? Using data from the PREMIER study, Dougados and colleagues calculated the probability of achieving remission at 1 year at each level of DAS28 (<2.6, 2.6 to <3.2, 3.2 to <5.1, and ≥5.1) and for DAS28 improvements of ≤0.6 or >0.6 at weeks 4, 8, 12, 26 in patients receiving adalimumab plus MTX or MTX alone. Patients treated with MTX alone who present with non-significant improvement in DAS28 of ≤0.6 at week 8, a DAS28 ≥5.1 at week 12, or a DAS28 ≥3.2 at week 26 are candidates for switching therapy as they had the lowest probability of remission at 1 year. In patients receiving adalimumab plus MTX, a suitable waiting period prior to treatment switching is ≥6 months.²⁴

Dougados M, Keystone EC, Guerette B, Patra K, Lavie F. How early can we predict remission at 1 year in early rheumatoid arthritis? A subanalysis of PREMIER [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):1607.²⁴

Commentary

MB: MTX is an effective medication and can lead to remission in a significant number of patients. However, keeping patients on an ineffective therapy is of no benefit, so knowing when to switch therapies is of paramount importance. In my opinion, this is best accomplished by measuring disease activity using 1 of the quantitative scales mentioned previously. It is necessary to give whatever therapy is chosen a reasonable amount of time to work. From the research findings presented here, it would appear that this timeframe is between 3 and 6 months. If patients have no response

at 3 months, it is probably wise to move to a different agent. However, if there is some response, albeit incomplete, waiting for a longer period, such as 6 months, also can be considered. Having a predefined target, such as the targets proposed in this study, will help decide which patients need to stay on the current therapy and who needs to switch.

RP: In my clinical practices, RA flares often are treated by increasing the dose of MTX, adding an NSAID, or adding steroids injected locally or given orally. The PREMIER study suggests that switching to another anti-TNF agent or to a T-cell or B-cell targeted therapy should be considered for a patient whose RA is not responding after 6 months of treatment. However, the degree to which sleep, subtle increases in activity, and stress can play a role in flares always impresses me. Although RA activity can wax and wane independently of such factors, we should not forget to discuss these issues with our patients to pinpoint possible reasons for flares. Nonetheless, the study suggests that at some point, switching therapies can be important for longer-term outcomes. The clinician must define what factors constitute the need for switching and when to discuss these issues with the patient.

No New Safety Issues With RA Treatments

An analysis of data from the Rheumatoid Arthritis DMARD Intervention and Utilization Study (RADIUS) registry was performed to assess the safety profiles of biologics and traditional DMARDs. RADIUS comprises 2 prospective, 5-year, multi-center observational registries of more than 10,000 patients with RA. Investigators found no unexpected safety signals and no trends of concern through December 2008. Across

multiple therapies, the rates of SAEs, SIEs, and events of interest (malignancy and cardiovascular) were comparable to rates observed with MTX treatment.²⁵

Gibofsky A, Palmer W, Keystone EC, et al. Safety profiles of disease-modifying anti-rheumatic drugs and biologics in patients with rheumatoid arthritis: observations from the RADIUS Registry [abstract]. *Arthritis Rheum.* 2009;60(suppl 10):1593.²⁵

Commentary

MB: Our current medications, specifically the anti-TNF agents studied in this analysis, have the theoretical risk of significant side effects. The lack of “unexpected safety signals” is reassuring. However, the lack of “unexpected signals” does not mean the lack of any risk. Careful monitoring of our patients for conventional and opportunistic infections as well as other potential toxicities is essential, lest we fall into a false sense of security.

RP: The lack of any long-term safety signals emerging from this analysis of the RADIUS registry data gives us some continued level of confidence as we recommend TNF inhibitors to our patients. My concern in the safety arena continues to be longer term safety, and

as practitioners we should continue to be vigilant looking for and reporting safety issues to our colleagues and manufacturers of these drugs.

References

1. Kiely PD, Brown AK, Edwards CJ, et al. Contemporary treatment principles for early rheumatoid arthritis: a consensus statement. *Rheumatology (Oxford)*. 2009;48:765-772.
2. Valesini G, Di Franco M, Spinelli FR, Scrivo R. Induction of remission in rheumatoid arthritis: criteria and opportunities. *Rheumatol Int*. 2008;29:131-139.
3. Rantalaiho V, Korpela M, Hannonen P, et al; FIN-RACo Trial Group. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. *Arthritis Rheum*. 2009;60:1222-1231.
4. van Vollenhoven RF, Albertsson K, Forslind K, et al; SWEFOT Study Group. In early RA with insufficient response to MTX, the addition of anti-TNF results in less radiological progression over 24 months than the addition of conventional DMARDs: results from the SWEFOT trial. Presented at: ACR 2009 Annual Scientific Meeting; October 20, 2009; Philadelphia, PA. Abstract LB6.

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PCE Takeaways

- Early and aggressive treatment of RA can help improve patient outcomes. Low disease activity does not preclude disease worsening over time.
- Disease activity should be monitored at each follow-up examination using a quantitative clinical assessment tool, such as DAS28, CDAI, RAPID3, or RADAI.
- Treatment switching should be considered if disease activity persists after 12 weeks.
- MTX therapy for RA can be initiated at 25 mg/wk without increasing toxicity.
- The long-term efficacy and safety of biologic therapies for RA, alone or in combination with MTX, continue to be supported by recent research.

CASE STUDY: 47-Year-Old Man With Joint Pain, Swelling, and Stiffness

by Rick Pope, MPAS, PA-C, DFAAPA

Presentation and History

Evan, a 47-year-old man, presented with a 3-month history of pain, swelling, and stiffness in his feet, hands, knees, and shoulders. His joints were stiff for more than 1 hour in the morning. A cortisone injection into one of his metacarpophalangeal joints helped for a few weeks. His wife accompanied him and was clearly anxious about her husband. Evan was tired, worried, and said, "I just wish this joint pain would go away." During the interview there were several uncomfortable moments as Evan and his wife argued over how much he smoked and had been drinking. He admitted to drinking 12 mixed drinks per week and to smoking 1 to 2 packs of cigarettes per day. He had been smoking since age 16. He also drinks 3 cups of coffee per day. He was a self-employed contractor and had been having difficulty using his hands; he had been unable to work several days during the past 3 months. His father has cardiovascular disease. His aunt has RA, and his niece has juvenile idiopathic arthritis.

Review of Systems

The patient had sinus congestion and a history of bronchitis, but no pneumonia. He denied shortness of breath on exertion. He had no rashes and no history of Raynaud's phenomenon, alopecia areata, pleuroserositis, clotting abnormalities, oral ulcers, iritis, dry eye, or dry mouth. He denied a history of melena or rectal bleeding and had no history of hepatitis, liver function test abnormalities, sexually transmitted disease, or HIV infection. The patient had no constitutional symptoms of weight loss, fever, sweats, change in appetite, or change in bowel or bladder function.

Physical and Laboratory Findings

- Height: 5 ft 9 in; weight: 168 lb; blood pressure: 128/72 mm Hg; pulse: 82 beats/min and regular; afebrile
- Smoke-stained teeth in fair repair
- Mild conjunctival injection, no uveal disease
- Mild maxillary sinus tenderness; inspiratory rhonchi noted
- Skin: no nail pitting, onycholysis, or ridging; no rashes noted
- TJC: 8
- SJC: 10 (mild effusion right knee, warm but not red)
- Other findings: unremarkable
- ESR: 22 mm/h
- CRP: 2.8 mg/dL
- RF: +63 IU/mL (negative <14 IU/mL)
- Anti-CCP antibody titer: + >250 (strong positive >50)
- Antinuclear antibody titer: negative
- Lyme titer: equivocal, but Western blot negative for both immunoglobulin M (IgM) and IgG
- Hemoglobin, hematocrit, and platelet count: all within normal limits

Radiographic Findings

- Hands (bilateral, anteroposterior view): no evidence of erosions or collapse of the carpal joints

- Feet (bilateral): normal alignment, no erosions, no soft-tissue swelling, no extra-articular calcifications

Diagnosis: Early RA

Clinical Commentary

Evan's history, physical and radiographic findings, and serologic status provide a clear-cut rationale for early, aggressive intervention. Positivity in RF and anti-CCP, both in high titers, points to the likelihood of persistent and aggressive disease. The art of rheumatology lies in educating the patient on the expected path of his disease and providing a treatment plan that matches his prognosis.

Treatment Decision

Evan's alcohol use and smoking and his wife's clear dislike of these behaviors offered a challenge and an opportunity to intervene on multiple levels. We discussed the advisability of stopping these behaviors, and Evan agreed to stop drinking and to cut down on his smoking. The pros and cons of MTX and TNF inhibitors also were discussed.

Influenza, H1N1, and pneumococcal vaccinations were administered. A tuberculosis skin test, chest x-ray, and serologic tests for hepatitis B and hepatitis C virus infections were ordered. After a review of Evan's laboratory test results and a discussion reinforcing his need to discontinue alcohol and stop smoking, treatment was instituted with MTX (15 mg orally) and folic acid supplementation (1 mg/d). The addition of supplemental calcium and vitamin D also was recommended because Evan's RA and smoking history are risk factors for developing osteoporosis in his later years. Regular appointments for laboratory monitoring and follow-up visits were scheduled, and Evan was referred to his primary care clinician for assistance with smoking cessation. Particularly because of his father's history of CV disease and the increased CV risk posed by RA, a lipid profile test also was suggested.

3-Month Follow-up

Evan was willing to stop alcohol use, but smoking cessation proved to be difficult. Evan's wife accompanied Evan to each visit. Her attitude changed from one of disgust to one of support, as she watched her husband make positive strides to help himself. At 3-month follow-up, Evan's clinical progress was rapidly moving forward. His TJC and SJC decreased, and now only his right wrist was affected. His joint stiffness still persisted for about 30 minutes in the morning, but he had not missed a day of work since starting MTX. His ESR and CRP had normalized.

At this point, we discussed treatment with TNF inhibitors, and he was willing to move ahead after a careful explanation of the side effect profile. Additionally, he was willing to accept the latest data of disease burden associated with high-titer RF and anti-CCP and clearly understood the importance of prevention in light of his occupation as a contractor.

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5. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2007;66:34-45.
6. Katchamart W, Boire G, Pope J, et al. The clinical course, outcomes, and treatment of early inflammatory arthritis: Results from CATCH (Canadian Early Arthritis Cohort) [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):369.
7. Hawker GA. Developing new RA classification criteria: reaching a consensus. Presented at: ACR 2009 Annual Scientific Meeting; October 18, 2009; Philadelphia, PA.
8. Li X, Chen MH, Bombardier C. Validation of Rheumatoid Arthritis Disease Activity Index (RADAI) in a North American cohort of patients with early rheumatoid arthritis (RA) [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):965.
9. Weinblatt ME, Keystone EC, Cohen MD, et al. Predictors of radiographic progression in rheumatoid arthritis patients treated with methotrexate [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):350.
10. Kolfenbach JR, Deane KD, Derber LA, et al. Association of rheumatoid arthritis (RA)-related autoimmunity and joint findings in unaffected at-risk populations [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):371.
11. Mjaavatten MD, van der Heijde DMFM, Uhlig T, et al. Levels of anti-CCP and IgM RF predict persistent arthritis in patients with very early undifferentiated arthritis (UA) [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):334.
12. Pinheiro GC, Scheinberg MA, Aparecida da Silva M, Maciel S. Anticyclic citrullinated peptide antibodies in advanced rheumatoid arthritis. *Ann Intern Med*. 2003;139:234-235.
13. Miriovsky BJ, Michaud KD, Thiele GM, et al. Associations of anti-CCP and rheumatoid factor concentrations with future disease activity in rheumatoid arthritis [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):332.
14. Liao KP, Weinblatt ME, Cui J, et al. Clinical factors that predict erosion-free status in rheumatoid arthritis [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):372.
15. Westhovens R, Robles M, Nayiager S, et al. Disease remission is achieved within two years in over half of methotrexate naive patients with early erosive rheumatoid arthritis (RA) treated with abatacept plus MTX: results from the AGREE Trial [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):638.
16. Bathon J, Genant H, Nayiager S, et al. Reduced radiographic progression in patients with early rheumatoid arthritis (RA) treated with abatacept + methotrexate compared to methotrexate alone: 24 month outcomes [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):639.
17. Westhovens R, Dougados M, Hall S, et al. Disease remission, radiographic non-progression and normalization of function achieved at year 1 are sustained long-term in a majority of patients: 5-year outcomes with abatacept in biologic-naïve patients [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):1657.
18. Karpouzas GA, Broumand A, Bagheri S, et al. Adalimumab dose escalation induces durable remissions and is safe in minorities with moderate to severe rheumatoid arthritis (RA) [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):1702.
19. Keystone EC, Kavanaugh A, van der Heijde DMFM, Sinisi S, Hall J, Guerette B. Long-term impact of adalimumab plus methotrexate on radiographic, clinical, and functional progression of rheumatoid arthritis [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):1679.
20. van Vollenhoven R, Cifaldi M, Roy S, Chen N, Gotlieb L, Malaise M. Ability to regain normal function in moderate vs. severe rheumatoid arthritis: analysis from long-standing and early RA patient populations [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):1013.
21. Moreland LW, O'Dell JR, Paulus H, et al. TEAR: Treatment of early aggressive RA; A randomized, double-blind, 2-year trial comparing immediate triple DMARD versus MTX plus etanercept to step-up from initial MTX monotherapy [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):1895.
22. Medley SEJ, Dolan AL, Coakley G. How safe is starting high dose methotrexate? [abstract]. *Ann Rheum Dis*. 2009;68(suppl 3):591.
23. Tak PP, Rigby W, Rubbert A, et al. Inhibition of joint damage and improved clinical outcomes with a combination of rituximab (RTX) and methotrexate (MTX) in patients (pts) with early active rheumatoid arthritis (RA) who are naive to MTX: a randomised active comparator placebo-controlled trial [abstract]. *Ann Rheum Dis*. 2009;68(suppl 3):75.
24. Dougados M, Keystone EC, Guerette B, Patra K, Lavie F. How early can we predict remission at 1 year in early rheumatoid arthritis? A Subanalysis of PREMIER [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):1607.
25. Gibofsky A, Palmer W, Keystone EC, et al. Safety profiles of disease-modifying anti-rheumatic drugs and biologics in patients with rheumatoid arthritis: observations from the RADIUS Registry [abstract]. *Arthritis Rheum*. 2009;60(suppl 10):1593.