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Looking Beyond Joint Damage in Rheumatoid Arthritis: Managing Extra-articular Manifestations and Comorbidities

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Survival among patients with rheumatoid arthritis (RA) has not improved despite a decline in overall mortality rates in the United States during the last 4 to 5 decades.¹ Life expectancy is significantly lower in patients with RA than in the general population; the strongest predictors of poor survival are the extra-articular manifestations of the disease and presence of comorbidities.² In addition to its joint manifestations, systemic inflammation in RA can manifest in a wide range of extra-articular tissues and organs, including the heart, lungs, eyes, kidneys, and skin.³ Extra-articular RA (ExRA) is associated with increased comorbidity and premature mortality.³⁻⁵ Thus, clinicians need to consider ExRA and comorbidities when managing patients with RA. Although treatment options for specific ExRA manifestations are limited, biologic therapies targeted at the pathogenic mechanisms responsible for ExRA may help reduce morbidity and mortality.^{6,7}

This issue of PCE Updates in Rheumatology reviews the extra-articular manifestations of RA as well as the comorbid conditions that may exist with RA and their management. Nicole M. Furfaro, MSN, ARNP, presents a case study of a patient with ExRA, with clinical commentary (page 6).

Needs Assessment

Although mortality rates in the United States have declined during the last 40 to 50 years, survival among patients with rheumatoid arthritis (RA) has not improved.¹ The strongest predictors of poor survival are the extra-articular manifestations of the disease and the presence of comorbidities.² The systemic inflammation of RA can manifest in a wide range of tissues and organs, including the heart, lungs, eyes, kidneys, and skin.³ Cardiovascular disease is the most common comorbid condition in patients with RA.⁴ Clinicians must consider extra-articular manifestations and comorbidities when managing RA. Although treatment options for specific extra-articular manifestations are limited, biologic therapies targeted at pathogenic mechanisms may help reduce morbidity and mortality.⁵

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Target Audience

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

Learning Objectives

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

- Recognize the manifestations of extra-articular RA and their impact on clinical outcomes.
- Translate the clinical evidence on RA-associated comorbidities into preventive care for patients with RA, including appropriate monitoring and lifestyle modifications.
- Incorporate disease-modifying antirheumatic drug therapy into an overall management plan for reducing cardiovascular comorbidity risk in patients with RA.

(continued on page 2)

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Perspectives From Nicole M. Furfaro, MSN, ARNP

What screening tests are recommended for assessing extra-articular manifestations and comorbidities in RA patients?



Most patients who exhibit extra-articular manifestations have high rheumatoid factor (RF) levels and/or long-standing erosive disease. These patients should be monitored closely. Some extra-articular manifestations, such as subcutaneous rheumatoid nodules or secondary Sjögren syndrome dryness, do not require specific treatment; however, other manifestations, such as vasculitis, scleritis or episcleritis, and pulmonary nodules, require thorough evaluation and possibly input from the rheumatology physician and/or other specialists. Ask patients about signs and symptoms of concern at every visit. If time is limited, ask them to fill out a Review of Systems form. This information can be reviewed quickly and used to guide pertinent history taking and physical examination.

The primary issue in comorbidity assessment is education. While rheumatology specialists are aware of the increased risks for comorbidities associated with RA, it typically is the primary care clinician who is charged with performing the annual physical examination and providing care during the work-in “sick visits.” It is important that we educate primary care physicians, nurse practitioners (NPs), and physician assistants (PAs) on the latest risk factor data. Fortunately, most comorbidities seen in patients with RA (eg, infection, cardiovascular disease [CVD], and lymphoma) are similar to those seen in the general population, only more prevalent.

Therefore, clinicians are aware of the need to monitor patients closely and limit modifiable CV risk factors (eg, smoking, obesity, sedentary lifestyle, dyslipidemia, diabetes). Screening can be performed by the specialist or the primary care provider. In addition to evaluation of any presenting symptoms, assessment can include blood cell counts; chest radiographs (when appropriate); and bone density testing to screen for osteoporosis in patients receiving glucocorticoids, menopausal women, and other patients as dictated by individual risk factors.

What are the biggest challenges faced by NPs and PAs in managing RA patients' CV risks?

The situation described in the case study (page 6) is not uncommon in rheumatology practices. The NP or PA often is faced with many primary care issues, especially when the lines of patient management become blurred between treatment for joint issues and general health assessment. One of the biggest issues is getting patients to “buy” into caring for themselves with diet, exercise, weight loss, and blood pressure management. This issue is not specific to rheumatology patients, but is becoming increasingly important in our population of patients as evidence regarding the role of inflammation grows. If a need exists for screening, educating, or treating a comorbid condition, and it is not being addressed at the primary care office, I will address it. As key members of the healthcare team for patients with RA, NPs and PAs in rheumatology practices should feel comfortable participating in comorbidity management and raising awareness of how inflammation in RA impacts a patient's risk for CVD and other conditions.

ExRA Manifestations

The incidence or frequency of ExRA is difficult to estimate; it varies among studies depending on the study design (clinic, population, or community-based), disease severity, classification criteria for ExRA used, and inclusion of comorbidities as ExRA manifestations.^{8,9} Nonetheless, ExRA is common. In a community-based cohort of patients with RA, the 30-year cumulative incidence of ExRA was found to be 46.0% (standard error, 3.4%).⁸ Across published studies, rheumatoid nodules are the most common extra-articular feature and are present in $\leq 30\%$ of patients with RA.⁹ Sjögren syndrome and pulmonary manifestations (pulmonary fibrosis) are also relatively common, occurring in 6% to 10% of patients with RA. Many other ExRA features occur in $\leq 1\%$ of patients with RA in normal clinic settings. Some patients may develop severe ExRA manifestations including pericarditis, pleuritis, Felty syndrome (splenomegaly, leukopenia), and vasculitis (Table 1).⁹

Nodules are common and generally painless, asymptomatic, and benign. However, at pressure points such as the elbows, toes, or sacrum in bedridden patients, they can cause problems when they ulcerate and become infected. In other tissues, nodules can cause flexor tendon deformities and scleral thinning. Nodules may also occur, albeit uncommonly, in pleura, lung, pericardium, or myocardium, where they may pose diagnostic problems.⁹ Methotrexate (MTX) therapy is associated with

Table 1. ExRA Manifestations

Rheumatoid nodules	Glomerulonephritis ^a
➤ Subcutaneous	Episcleritis, scleritis, kerato-conjunctivitis perforans ^a
➤ In other locations	Vasculitis
Raynaud phenomenon	➤ Severe cutaneous ^a
Secondary Sjögren syndrome	➤ Systemic ^a
Pulmonary fibrosis	➤ Benign cutaneous and nail-fold
Pericarditis ^a	Lymphadenopathy
Pleuritis ^a	Weight loss, cachexia
Felty syndrome ^a	Malaise, fatigue, fever
Polyneuropathy, mononeuropathy, mononeuritis multiplex ^a	Amyloid
Myopathy, polymyositis ^a	

^aSevere ExRA according to Malmö criteria (Turesson C et al.³).

Adapted from Young A et al.⁹

rheumatoid nodulosis, and discontinuing MTX usually leads to regression of some nodules. Case reports have also suggested an association between anti-tumor necrosis factor (TNF)- α therapy and accelerated nodulosis.¹⁰

ExRA onset is independent of the duration of RA, and extra-articular manifestations can occur in recently diagnosed RA.³ There are no reliable predictors for ExRA features in early RA. However, there is some evidence that male gender; tobacco use; presence of more severe joint disease; worse functional status; and presence of high levels of inflammatory markers, RF, antinuclear antibodies (ANA), and the RA HLA-related shared epitope (HLA DRB1) could predict ExRA features in early RA.^{9,11} (See *Fast Facts: Proposed Pathogenic Mechanisms and Potential Therapeutic Targets in ExRA*, page 5.)

The type of ExRA feature may predict the clinical course and clinical outcome of patients with RA. For instance, the presence of nodules has been related to erosive disease and functional impairment; pulmonary fibrosis, with mortality and functional impairment; and Sjögren syndrome, with functional impairment.⁹ Presence of severe ExRA or multiple ExRA features may also predict poor survival.^{3,4,12} In a cohort of patients with RA followed for a median period of 11.8 years, the presence of any ExRA feature increased mortality risk (adjusted hazards ratio [HR], 2.20; 95% confidence interval [CI], 1.73-2.82), and the presence of an additional ExRA feature further increased the risk (adjusted HR, 1.91; 95% CI, 1.36-2.69). The presence of 1 severe ExRA manifestation was associated with the greatest risk of premature death (adjusted HR, 4.45; 95% CI, 3.29-6.00).¹²

Major Comorbidities

Broadly considered, RA comorbidity includes conditions that (1) coexist with but are unrelated to RA; (2) increase an outcome of RA; (3) are increased by an RA outcome; (4) are caused (at least in part) by RA; (5) are caused by or related to RA treatment; or (6) share a common cause with RA.¹³

The pattern of comorbidity in RA has not changed during the last 20 years. A prospective cohort study found that 43% of patients with early RA (N = 183) had at least 1 comorbid condition at RA diagnosis, and 81% developed at least 1 additional comorbidity during the 16- to 20-year follow-up period.¹⁴ The most common comorbid conditions at diagnosis were CVD (hypertension, 11%; ischemic heart disease and cerebrovascular incident, 6%), malignancy (6%), and thyroid disease (5%). During follow-up, CVD (38%), malignancies (15%), severe infections (15%), and diabetes (7%) were the most common comorbid conditions.¹⁴

CVD

The rates of myocardial infarction (MI) and stroke in patients with RA are nearly double those in persons without RA.¹⁵ The CVD risk conferred by RA is about the same order of magnitude as that conferred by diabetes.¹⁶ Prognosis after MI is significantly worse in patients with RA.¹⁷ The risks for hospitalized or unrecognized MI and sudden cardiac death (SCD) are significantly higher in patients with RA than in non-RA patients. The higher MI risk exists even

before the clinical onset of RA, but patients with RA are less likely to have anginal symptoms.¹⁸ Patients with RA are also at increased risk of ischemic stroke (odds ratio [OR], 2.66; 95% CI, 1.24-5.70) as well as all categories of stroke (OR, 1.64; 95% CI, 1.16-2.30).¹⁹ Patients with RA have twice the risk of congestive heart failure (CHF) compared with patients without RA.

The increased risk of CVD in patients with RA is beyond what can be explained by traditional CVD risk factors (such as smoking, body mass index [BMI], diabetes, and male gender).²⁰ Thus, RA is an independent risk factor for CVD. A recent study showed that increased CVD risk in RA could be related to the presence of severe ExRA manifestations. In this study, presence of severe ExRA features was found to be associated with an increased risk of first-ever CV events and new-onset coronary artery disease in patients with RA.²¹ As the underlying systemic inflammation in RA is responsible for ExRA manifestations, it is likely that inflammation contributes to the increased CVD risk in RA.²²⁻²⁴

The increased risk of CV events increases the risk of CV mortality in RA. CVD is one of the major causes of excess mortality in RA.⁹ The rate of CV death is increased by 30% in patients with RA compared with those without RA.¹⁵ These data highlight the need for aggressive reduction of CV morbidity and mortality in patients with RA.

Infection

ExRA significantly increases the risk of infection in patients with RA. In a population-based cohort analysis, the strongest predictor of serious infection (requiring hospitalization) was ExRA (HR 2.38; 95% CI, 1.58-3.60; *P* < .001) followed by chronic lung disease (HR 2.05; 95% CI, 1.53-2.74; *P* < .001) and leukopenia (HR, 1.92; 95% CI, 1.37-2.67; *P* < .001).²⁵ Specific ExRA manifestations associated with serious infection in this analysis included Felty syndrome (HR, 2.19; 95% CI, 1.15-4.18), Sjögren syndrome (HR, 2.33; 95% CI, 0.99-5.49), rheumatoid lung disease (HR, 2.68; 95% CI, 1.54-4.68), and vasculitis (HR, 6.19; 95% CI, 3.20-12.00).²⁵

The risk of serious infection is also increased by RA treatments, including corticosteroids^{26,27} and anti-TNF- α agents.^{28,29} The increased risk of serious infections with corticosteroid use is well documented.^{26,27} In a large observational study of patients with RA (N = 16,788) followed for 3.5 years, prednisone use increased the risk of pneumonia hospitalization (HR, 1.7; 95% CI, 1.5-2.0). The increased risk was dose-related with higher doses conferring a greater risk (<5 mg/d: HR, 1.4; 95% CI, 1.1-1.6; >5-10 mg/d: HR, 2.1; 95% CI, 1.7-2.7; >10 mg/d: HR, 2.3; 95% CI, 1.6-3.2).²⁶

The increased risk of infections with the anti-TNF- α agents, infliximab and adalimumab, was reported in a meta-analysis of placebo-controlled randomized trials of these 2 agents. In this study, the pooled OR for serious

infections was 2.0 (95% CI, 1.3-3.1) with the anti-TNF- α agents (N = 3439) compared with placebo (N = 1512).²⁸ However, the risk of serious infections associated with anti-TNF- α agents is not greater than that observed with traditional disease-modifying antirheumatic drug (DMARD) therapy. Data from the British Society for Rheumatology Biologics Register involving 7664 patients treated with an anti-TNF- α agent (infliximab, adalimumab, or etanercept) found no increased risk of all-site serious infections in these patients compared with patients treated with traditional DMARD therapy (N = 1354).³⁰ Recently, the US Food and Drug Administration has alerted healthcare professionals of possible systemic fungal infections associated with anti-TNF- α therapy that require prompt recognition and treatment.³¹

Lymphoma

Patients with RA are at increased risk of lymphoma and the risk ratio for lymphoma is 1.8 to 2.0 in large epidemiologic studies.¹³ Male gender, age, and RA activity all have been associated with increased risk of lymphoma.¹³ Evidence regarding the impact of anti-TNF- α agents on lymphoma risk has been contradictory. Apart from a meta-analysis of randomized controlled trials of anti-TNF- α agents that showed an increased risk of malignancies (including lymphomas) with these agents,²⁸ recent studies indicate that the risk of lymphoma in RA is related to disease severity (inflammation), not anti-TNF- α

treatment.³²⁻³⁵ A matched case-control study of patients with RA found that compared with low overall disease activity, medium overall disease activity was associated with an 8-fold increase and high overall disease activity with a 70-fold increase in lymphoma risk.³³ In a population-based cohort study of patients with RA (1 prevalent cohort [n = 53,067], 1 incident cohort [n = 3703], and 1 anti-TNF- α treated cohort [n = 4160]), after adjusting for age, sex, and disease duration, the

adjusted relative risk (RR) of lymphoma in the anti-TNF- α -treated cohort was marginally higher than in the other RA cohorts: prevalent cohort, 1.0 (reference); incident cohort, 0.8 (95% CI, 0.4-1.4); anti-TNF- α -treated cohort, 1.1 (95% CI, 0.6-2.1). The authors of this study pointed out that the marginally augmented lymphoma risk should be judged in the light of a higher disease activity among patients who were offered anti-TNF- α treatment.³⁴

Fast Facts:

Proposed Pathogenic Mechanisms and Potential Therapeutic Targets in ExRA

Many ExRA manifestations as well as RA comorbidities are associated with increased disease activity and with markers of inflammation, such as high levels of RF and antibodies to cyclic citrullinated peptides (anti-CCP).^{9,11} Increased disease activity and elevated levels of markers of inflammation could be attributed to immune system abnormalities such as T-cell and B-cell abnormalities as well as to proinflammatory cytokines (eg, TNF- α , IL-1, and IL-18).⁵

Thus, it is conceivable that specific therapies targeted at immune mediators of inflammation potentially may modify immune system abnormalities and reduce ExRA manifestations and comorbidities.⁵ These would include currently available biologic therapies for the treatment of RA such as anti-TNF- α agents, rituximab, anakinra, and abatacept. However, there is limited evidence for the role of biologic therapies in the treatment of ExRA.⁹

Proposed Pathogenic Mechanisms	Potential Targets	Potential Therapies
Circulating immune complexes and antibodies	B cells	Anti-CD20 antibodies
Circulating proinflammatory cytokines	TNF, IL-1, IL-18	Anti-TNF antibodies TNF receptor fusion proteins
T-cell abnormalities	T-cell activation and migration T-cell costimulation	Antibodies to leukocyte functional antigens CTLA-4 Ig fusion protein
Systemic endothelial activation	MHC class II expression	Statins

Ig = immunoglobulin; IL = interleukin; MHC = major histocompatibility complex.

Adapted from Turesson C et al.⁵

Case Study: Managing Comorbidity Risk in a 50-Year-Old Man With RA

Nicole M. Furfaro, MSN, ARNP

History

John is a 50-year-old man with a 10-year history of RA. Initially presenting with RF seronegativity, a minimally elevated C-reactive protein (CRP) level, and a normal erythrocyte sedimentation rate (ESR), he was treated with a combination of hydroxychloroquine, nonsteroidal anti-inflammatory drugs, and, rarely, corticosteroids. Methotrexate therapy was initiated 5 years ago, when he began experiencing morning stiffness of 1-hour duration and aching in his metacarpophalangeal joints, wrists, and metatarsophalangeal joints. His rheumatologist repeated serologic testing and ordered bilateral x-ray films of hands, wrists, and feet.

Physical Examination

- Height: 70 in
- Weight: 200 lb
- Blood pressure: 140/90 mm Hg
- Pulse: 84 bpm
- BMI: 28.7 kg/m²
- Tender joint count: 20
- Swollen joint count: 12

Laboratory Findings

- RF: 90 IU/mL (positive) (normal value: <60 IU/mL)
- Anticyclic citrullinated peptide antibody titer: negative

- CRP: 2.0 mg/dL (elevated) (normal value: <0.8 mg/dL)
- ESR: 60 mm/h (elevated) (normal value: 0-20 mm/h)
- Fasting blood glucose level: 98 mg/dL

Radiographic Findings

Wrists: 1 mild erosion in each radiocarpal joint
Hands and feet: normal

Family History

John's father died of a cerebrovascular accident at age 65. His mother, alive at age 90, has coronary artery disease, type 2 diabetes mellitus (DM), osteoarthritis, and osteoporosis. He has a sister, age 55, with hypothyroidism and obesity, and a brother, age 53, who has "borderline" type 2 DM but is otherwise well.

Current Status

Although John remained active until his RA was diagnosed, pain has caused him to become more sedentary. Other than mowing the lawn and doing light housework, he does not exercise regularly. He works in sales and spends several hours daily commuting by car. Because his blood pressure is elevated and his blood glucose levels are borderline high, he is being treated with lisinopril (10 mg/d). He has been smoking since college and reports now smoking "only in my car" when traveling, which amounts to 2 packs per week. Given his MTX use, he limits alcohol intake to "1 beer weekly." During his last physical examination, his primary care provider told him to lose 20 lb.

Management Strategies

ExRA Manifestations

Treatments for specific ExRA manifestations are limited.⁹ In general, therapeutic principles for the management of severe RA are applicable for the treatment of ExRA.⁵ Thus, effective suppression of RA disease activity with DMARDs is of paramount importance.⁹ However, there is some

anecdotal evidence and data from small case series that DMARDs, corticosteroids, and immunosuppressive drugs may be beneficial in the treatment of certain types of severe ExRA (Table 2).⁵

Traditionally, short-term high doses of corticosteroids have been the treatment of choice for RA-associated interstitial lung disease (pulmonary fibrosis).⁵ However,

therapy with cyclosporine and infliximab may be beneficial in some patients, compatible with the role of T-cell abnormalities and cytokine-driven fibrosis.^{36,37} However, the use of anti-TNF- α therapy also may be associated with fulminant respiratory failure.³⁸ RA pulmonary fibrosis has a poor prognosis.⁹

Large pleural effusions in patients with RA-associated pleuritis usually

Clinical Decision Point

Other than treating John's slowly progressive RA, what should be the first focus of care for the NP or PA?

- Reducing osteoporosis risk
- Advising on exercise and weight loss
- Recommending smoking cessation
- Managing infection risk (related to RA and immunomodulatory therapy)

Clinical Commentary

Although all the care points listed are important to the comprehensive management of RA, the single most important modifiable risk factor for John is smoking. Smoking dramatically increases John's CVD risk and may worsen his RA.^{8,40}

John also should be advised to start an exercise program to lose weight, lessen his osteoporosis risk, and improve joint stability by strengthening muscles and tendons around joints. It is important to work with his primary care provider to recommend physical therapy or a general approach of "start low and go slow." John should be educated about the importance of stretching to warm up; he could start exercising by walking or biking for a few minutes on most days of the week and then gradually increase his activity level. Progression of exercise intensity (eg, duration, frequency, activity) can be modified for each patient based on response and individual preferences. The most important task is to get

patients moving and committed to an activity they enjoy.

Other issues to consider in this case are John's progressive joint damage despite MTX therapy (which is seen in some patients treated with monotherapy).

Treatment Decision

The decision is to prescribe an anti-TNF- α agent because John's RA symptoms are increasing (with RF seropositivity, mild erosive disease, and elevations in the ESR and CRP level) and because his elevated fasting blood glucose level, a strong family history of diabetes, and high BMI make oral corticosteroid use undesirable.

1-Year Follow-up

After 1 year, repeated radiographic evaluation demonstrates no progression in erosive changes. The ESR and CRP level have normalized. John experienced 2 upper respiratory tract infections during the past year, 1 of which was diagnosed as sinusitis and treated with antibiotics. He reports feeling much better, with a lessening of fatigue and morning stiffness. He stopped smoking. He still does not exercise regularly because of his "hectic schedule," but plans to try walking soon. He has lost 10 lb with diet modification, and his fasting glucose levels have improved.

are treated with high-dose corticosteroids. Alternatively, thoracocentesis or continuous suction drainage also may be used. If treatment-resistant pleural effusions occur, adequate drainage followed by intralesional prednisolone may be beneficial.^{5,9}

Moderate doses of corticosteroids (15-20 mg) usually are effective for the treatment of pericarditis in RA.

Intensive immunosuppressive treatment with cyclophosphamide or other agents may be necessary when pericardial effusions recur. For treatment-resistant effusions, intralesional prednisolone may be beneficial therapy, after adequate drainage. Patients with RA who have pericarditis are at risk of chronic constrictive pericarditis, leading to chronic heart failure.

Thus, echocardiographic evaluation is important, especially because constrictive pericarditis occurs in the absence of major systolic dysfunction.⁵

Systemic vasculitis in RA has been shown to respond to pulsed intravenous cyclophosphamide or daily oral cyclophosphamide in combination with high-dose corticosteroids. In the case of cutaneous

vasculitis, azathioprine in combination with high-dose prednisolone, as well as MTX treatment may be effective.⁵

MTX is the treatment of choice for neutropenia associated with Felty syndrome in RA, although other DMARDs such as parenteral gold and leflunomide also are effective. In patients who respond to these treatments, splenectomy usually is not required.⁵

There is no satisfactory treatment for rheumatoid nodules—the most common ExRA feature. Case reports have suggested a treatment benefit with hydroxychloroquine, colchicine, sulfasalazine, azathioprine, or D-penicillamine—each of which have been shown to lead to regression of nodules.³⁹

Comorbidities

Patients with ExRA and patients with RA who are receiving immunosuppressive therapy should be closely monitored for infections.⁵ If an infection does occur, it should be promptly treated.

Patients with ExRA also should be monitored for CVD. These patients should be encouraged to adopt preventive measures, eg, lifestyle modifications, to reduce modifiable CV risk factors. In addition, patients should be monitored regularly for the presence of traditional CV risk factors, such as hypertension, diabetes, and lipid abnormalities. If a patient is diagnosed with any of these risk factors, appropriate treatment should be initiated to reduce CVD risk. Smoking is a risk factor for CVD as well as the development of seropositive

Table 2. Treatment for ExRA

ExRA Manifestation	First-Line Treatment
Isolated pericarditis or pleuritis	Corticosteroids + DMARD
Interstitial lung disease	Corticosteroids + cyclosporine or cyclosporine and MTX
Systemic vasculitis	High-dose corticosteroids + cyclophosphamide (pulsed or continuous)
Cutaneous vasculitis	MTX or azathioprine
Felty syndrome	MTX

Adapted from Turesson C et al.⁵

erosive RA and severe ExRA, and patients should be strongly encouraged to stop smoking.^{5,8,40}

To reduce CVD risk as well as the morbidity and mortality associated with CVD, aggressive DMARD therapy should be used to reduce RA inflammation. Current evidence indicates that anti-TNF- α agents may reduce CVD risk in patients with RA.⁶ A community-based study found a decreased incidence and RR for the development of a severe first-time CVD event in patients with RA treated with

anti-TNF- α therapy (etanercept or infliximab) compared with patients not treated with anti-TNF- α therapy, after controlling for age, sex, and disease severity. The age-sex adjusted incidence rates were 14 and 35.4 events per 1000 patient-years, respectively, corresponding to a RR of 0.62 (95% CI, 0.34-1.12, $P = .111$). Controlling for disease severity (1 variable at a time), the age-sex adjusted RR was further reduced in patients treated with anti-TNF- α (range, 0.4-0.60) compared with patients not treated with

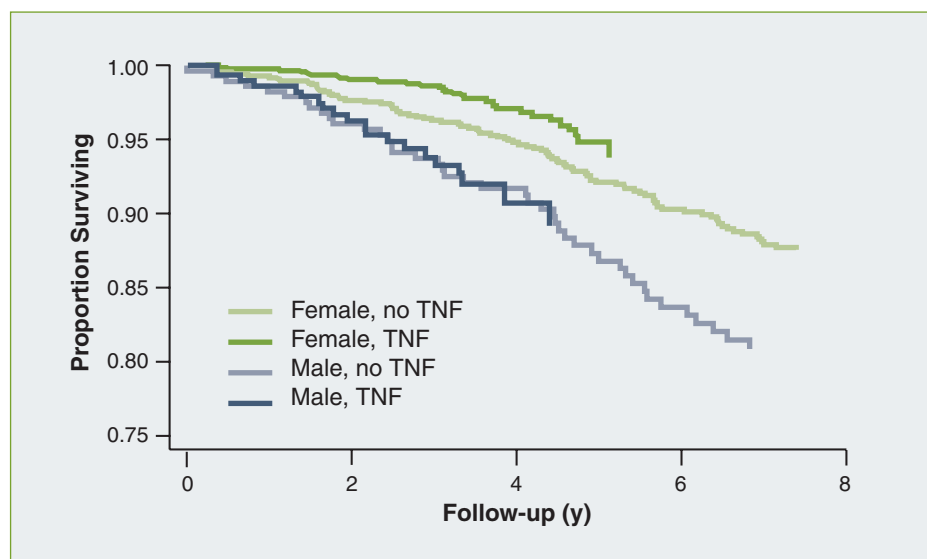


Figure 1. Survival curves for patients with RA treated with anti-TNF- α agents versus those not treated, adjusted for age, disability, and comorbidity, stratified by gender. Reproduced from Jacobsson LTH et al.⁷ © 2007 with permission from BMJ Publishing Group Ltd.

anti-TNF- α therapy; the RR was significant for disability and visual analog scale patient global assessment ($P \leq .017$). These findings suggest the risk of developing CVD is lower in patients with RA treated with anti-TNF- α agents and consistent with the hypothesis that inflammation contributes to the development of CVD events and reducing inflammation reduces CVD risk.⁶

Anti-TNF- α agents have been shown to reduce arterial stiffness in patients with RA or other arthropathies (ankylosing spondylitis or psoriatic arthritis). Using pulse wave velocity (PWV) to measure arterial stiffness, a study showed that in patients treated with anti-TNF- α , there was a significant reduction in PWV from baseline ($P = .001$), whereas there was no change in patients who did not receive anti-TNF- α therapy; the difference in arterial stiffness between the two groups was significant ($P = .002$). Thus, anti-TNF- α agents may ameliorate functional parameters of early atherosclerosis in treated patients, thereby reducing the risk of CVD.⁴¹

Anti-TNF- α agents may also reduce premature mortality risk in some patients with RA.⁷ A community-based register study found that after controlling for age, sex, disability, and baseline comorbidity, the adjusted HR for death was 0.65 (95% CI, 0.46-0.93) in patients treated with anti-TNF- α versus patients who were not treated. The treatment effect was significant in women (HR, 0.52; 95% CI, 0.33-0.82), but not in men (HR, 0.95; 95% CI, 0.52-1.71) (Figure 1). These findings are compatible with the hypothesis that

inflammation is a critical factor in RA-associated premature mortality.⁷

Prolonged use of some nonbiologic DMARDs is associated with a reduced risk of CVD in patients with RA as revealed by the Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis Program (QUEST-RA), a multinational study that included 4363 nonselected consecutive outpatients with RA.⁴² In this patient cohort, the lifetime prevalence for MI was 3.2%, stroke 1.9%, and for any CV event (MI, angina, coronary disease, or stroke) 9.3%. After adjusting for age, gender, disease activity/severity, RF positivity, ExRA manifestations, and traditional CV risk factors (hypertension, hyperlipidemia, diabetes, smoking, and obesity), prolonged use of MTX (HR, 0.85; 95% CI, 0.81-0.89), leflunomide (HR, 0.59; 95% CI, 0.43-0.79), or sulfasalazine (HR, 0.92; 95% CI, 0.87-0.98) was found to significantly reduce the risk of all CV morbidity in these patients ($P < .01$). In addition, exposure to glucocorticoids (HR 0.95; 95% CI, 0.92-0.98) and anti-TNF- α agents (HR, 0.42; 95% CI, 0.21-0.81) was significantly associated with all CV risk reduction ($P < .01$). Use of anti-malarial agents or gold was not associated with CV risk reduction.⁴²

In addition to reducing CV risk, MTX therapy has been associated with reducing CV mortality in patients with RA. In a cohort of patients with RA treated in an outpatient RA facility, those treated with MTX were found to have worse prognostic factors for mortality. In spite of this, there was a 60% reduction in risk of mortality

(HR, 0.4; 95% CI, 0.2-0.8) compared with no MTX use (after adjusting for prognostic factors for mortality). In this study, other DMARDs (sulfasalazine, penicillamine, hydroxychloroquine, or intramuscular gold) did not have a significant effect on mortality. MTX use was also associated with a 70% reduction in the risk of CV mortality (HR, 0.3; 95% CI, 0.2-0.7), and a 40% reduction in the risk of noncardiovascular deaths (HR, 0.6; 95% CI, 0.2-1.2). These results indicate that MTX may provide a substantial survival benefit, largely by reducing CV mortality.⁴³

PCE Takeaways

- Extra-articular manifestations and comorbidities are common in RA.
- Severe ExRA and comorbidities, particularly, CVD and serious infections, are significant predictors of mortality in patients with RA.
- The underlying systemic inflammation in RA is likely responsible for severe ExRA manifestations and CVD morbidity.
- Treatment options for severe ExRA are limited, although corticosteroids, MTX, cyclosporine, or azathioprine may be beneficial in certain settings; the role of anti-TNF- α therapy in the treatment of severe ExRA has not been demonstrated.
- Anti-TNF- α therapy and nonbiologic DMARD therapy may reduce the risk of CVD and CV mortality.

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About PCE Updates in Rheumatology...

Welcome to the third of 4 issues of 2008 *PCE Updates in Rheumatology*, Volume 2 developed for those NPs and PAs who serve patients in rheumatology practices throughout the country. "The demands for rheumatologic services are increasing exponentially with the aging population, while the number of physicians entering the rheumatology specialty is shrinking," according to the Society of Physician Assistants in Rheumatology (SPAR). Rheumatologists treating patients with rheumatoid diseases increasingly rely on specialist NPs and PAs to take an active management role in the frequent clinical contacts these patients require.

As healthcare professionals, NPs and PAs collectively provide a vital and increasing role in the diagnosis and management of acute and chronic illness. As clinicians, you spend more time with patients than most physicians, with your emphasis being patient disease state counseling and preventive care. Most importantly, NPs and PAs report that their roles have evolved from assisting physicians to treating and following their own patients. This increased role includes writing prescriptions,

monitoring patient progress, and seeing patients in your own examination rooms. As NPs and PAs, you are rapidly emerging as key providers of patient care. You practice with greater autonomy and prescribe more medication than ever before.

Approximately 286 NPs and 188 PAs see patients in rheumatology practices that provide ongoing care for patients with rheumatoid diseases. Therefore, you need to be thoroughly familiar with the latest therapeutic advances. This issue of *PCE Updates in Rheumatology* reviews the extra-articular manifestations and comorbidities associated with RA and their management.

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