Proceedings of the Fifth Annual Permanente Rheumatology Association Symposium, Sonoma, California, April 3-6, 2003

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Abstract

The new diagnostic tools and treatments developed for rheumatologic disease entities make rheumatology one of the most dynamic areas of medicine. Permanente rheumatologists attend the annual Permanente Rheumatology Association (PRA) meeting as an essential mechanism for exchanging information relevant to practicing this dynamic specialty at Kaiser Permanente (KP). The structure of the PRA meeting encourages high-level scholarship, education, and collaborative work between KP Regions. Alternating between Southern and Northern California, the annual PRA meeting was held this year in Sonoma and was attended by 38 physicians from seven KP Regions; in addition, assistance was provided by academic advisors representing Stanford University, the University of Colorado, and the Mayo Clinic. The 2003 meeting focused on polymyalgia rheumatica/giant cell arteritis (PMR/GCA), scleroderma, systemic lupus erythematosus (SLE), and the current, changing role of tumor necrosis factor (TNF) in inflammatory disease.

A major change in rheumatology practice is the shift from an organ-based approach to disease (ie, as taught in medical school) to more fundamental understanding of immune modulators that underlie disease. Dramatic new forms of therapy, including anti-TNF agents, are being used in many diseases. Rheumatologists' specialized knowledge of immunology will improve the care of patients who are not traditionally considered as "rheumatology patients."

Introduction: The Fifth Annual Permanente Rheumatology Association Symposium, Sonoma, California, April 3-6, 2003

Gerald Levy, MD MBA and Stanford Shoor, MD

The Annual Permanente Rheumatology Association (PRA) meeting has become indispensable for Permanente physicians who practice the rapidly changing field of rheumatology, which remains one of the most dynamic areas of medicine with its new diagnostic tools and treatments. The structure of the PRA meeting encourages high-level scholarship, education, and collaborative work between KP Regions. Alternating between Southern and Northern California, the annual PRA meeting was held this year in Sonoma: Thirty-eight KP physicians from seven KP Regions attended the meeting and were assisted by academic advisors representing Stanford University, the University of Colorado, and The Mayo Clinic (Table 1). The 2003 meeting focused on polymyalgia rheumatica/giant cell arteritis (PMR/GCA), scleroderma, systemic lupus erythematosus (SLE) and the current, changing role of tumor necrosis factor (TNF) in inflammatory disease.

The study group of Drs Miller-Blair and Schwartz examined the growing consensus that GCA and PMR are distinct manifestations within one disease spectrum. New information was presented on the pathogenesis, diagnosis, and evidence-based treatment of GCA. The role of temporal artery biopsy as well as appropriate treatment regimens were discussed.

Scleroderma is no longer called progressive systemic sclerosis (PSS) but simply systemic sclerosis (SS). New studies confirm that only a few SS patients have a progressive disease course and that severe disease becomes apparent in most patients within three years after onset. Drs Zelman and Schoen's study group also presented exciting new data on treatment of pulmonary fibrosis and Raynaud's phenomenon—two of the most troublesome aspects of SS.

Dr Venkat's group elucidated the major manifestations of SLE and presented new information on how hormonal levels influence production of proinflammatory cytokines. Improved tools for monitoring disease are now used to assess new forms of therapy, such as use of mycophenalate mofetil for treating SLE.

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Under the leadership of Drs Dillon and Bulpitt, the rheumatoid arthritis (RA) group focused on the growing understanding of how TNF functions in inflammatory disease. TNF agents are now used in ankylosing spondylitis, psoriatic arthritis, psoriasis, and other conditions. The long-term efficacy and tolerability of TNF agents remain excellent, but caution remains concerning the risk of tuberculosis and other types of infection. The RA study group recommends that KP develop and implement a registry to track management of chronic disease and responses to therapy in patients with RA.

In recognition of the dramatic change taking place in the field of rheumatology, Dr Levy presented a thought-provoking talk challenging the traditional view of that field: The organ-based approach taught in medical school is being replaced by enhanced understanding of the underlying immune modulators. One example of this shift is the growing role of anti-TNF agents in treatment of psoriasis, sepsis, and inflammatory bowel disease. Other cytokines have been shown to play a role in autoimmune eye and ear diseases, asthma, and other conditions. Rheumatologists' specialized knowledge of immunology will lead to opportunities for cross-specialty collaboration to improve the care of patients not traditionally considered "rheumatology patients."

Giant Cell Arteritis and Polymyalgia Rheumatica Study Group
Dana Miller-Blair, MD and Nina Schwartz, MD

GCA and PMR are manifestations of one disease entity and are driven by the same antigen. In addition to having the classic symptoms of PMR, patients with this disease may complain of myalgia, peripheral arthritis, distal tenosynovitis, or swelling of the distal extremities with pitting edema. Such manifestations raise the question of whether relapsing seronegative symmetrical synovitis with pitting edema (RS3PE) can coexist with seronegative rheumatoid arthritis. Clinical presentation of GCA includes classic cranial presentation, fever of unknown origin, and large vessel GCA. Clinical features of large vessel GCA include claudication, paresthesia, Raynaud's phenomenon, and frequently include negative results of temporal artery biopsy. GCA complicated by aortitis can be associated with aneurysm and with possible vascular rupture.

In one proposed model of pathogenesis, an exogenous antigen (perhaps an infectious agent) leads to priming of specific CD4+T cells in the lymph nodes.[1] These cells undergo clonal expansion and migration to sites of antigen deposition in the adventitia of muscular arteries. Interaction between these T cells and specialized macrophages (which also are localized to the adventitia) results in changes both in the media and in the intima. Why GCA develops in some patients and PMR develops in others is unclear, although a critical factor appears to be production of interferon gamma in the arterial wall in GCA but not in PMR.[1] Also poorly understood is the mechanism by which immune events in the adventitia direct the inflammatory, destructive, and ischemic changes which occur in other vessel layers. The tendency for GCA and PMR to develop in older persons also remains unexplained.

Table 1. 2003 Permanente Rheumatology Faculty Members and Academic Advisors
Steering Committee:
Stanford Shoor, MD (Chair)
Gerald Levy, MD MBA (Co-Chair)
Aileen Dillon, MD
Dana Miller-Blair, MD
Nina Schwartz, MD
Erick Schoen, MD
Kumar Venkat, MD
David Zelman, MD
Jackie Nagy
Polymyalgia Rheumatica/Giant Cell Arteritis (PMR/GCA):
Christine Fernando, MD
Jeffery Fong, MD
Paul Lambie, MD
Alan Lash, MD
Dana Miller-Blair, MD (Co-Chair)
Nina Schwartz, MD (Co-Chair)
Systemic Lupus Erythematosus (SLE):
Kumar Venkat, MD (Chair)
Eduardo Baetti, MD
Canagasundaram Balakrishnan, MD
Chee C Chow, MD
Alan Cohen, MD
Faculty Advisors:
Gene Hunder, MD, Mayo Clinic (PMR/GCA)
Mark Genovese, MD, Stanford (TNF)
Woody Emlen, MD, University of Colorado (SS)
Doug Monroe, PharmD, Kaiser Permanente (TNF)
Systemic Sclerosis (SS):
David Zelman, MD (Chair)
Eric Schoen, MD (Co-Chair)
Linda Atkinson, MD
Rick Erickson, MD
Wayne Yee, MD
Steve Orkand, MD
Amy Starr, MD
John Scavulli, MD
Tumor Necrosis Factor (TNF):
Aileen Dillon, MD
Ken Bulpitt, MD
Maurice Kinsolving, MD
James McKoy, MD
Mark Roberts, MD
Joseph Ruderman, MD
Jennifer Smith, ANP
Chronic Rheumatoid Arthritis:
Aileen Dillon, MD

The organ-based approach taught in medical school is being replaced by enhanced understanding of the underlying immune modulators.

The initial diagnosis of GCA is usually made on clinical grounds and confirmed by temporal artery biopsy.[2] However, when the clinical probability of GCA is high and the benefits of therapy outweigh the risks, a clinical diagnosis may suffice. Temporal artery biopsy remains the standard method of diagnosis and is most helpful when the probability of GCA is intermediate. Pathology specimens should be at least 2 cm in length. For patients in which corticosteroid therapy is begun before biopsy, positive results of biopsy decline with continued treatment. Biopsy may still yield positive results for as long as one to two weeks after initiation of corticosteroid therapy.[3] Sensitivity of the biopsy analysis can be as high as 91%.[4] Bilateral biopsy may be an option if the optimal side for biopsy cannot be determined with certainty and negative results of unilateral biopsy would be ignored by the clinician.[4] Laboratory studies can support a diagnosis of GCA. Determination of erythrocyte sedimentation rate (ESR) is the method traditionally used to diagnose and monitor disease activity. A few patients present with a normal ESR; paradoxically, these patients may have a higher risk for ischemic events. The C-reactive protein has a similar sensitivity in patients with PMR and GCA and may be considered an alternative test. Measurement of IL-6 activity may be a more sensitive test than determination of ESR but currently has limited availability. Anticardiolipin (aCL) antibodies may be associated with a higher risk of severe vascular complications in GCA. Vascular imaging is rarely used in diagnosis, except where extracranial arteritis of large vessels is suspected. Color duplex ultrasonography may prove helpful in diagnosis of GCA but still has limited clinical applicability.

Corticosteroid therapy with initial daily oral doses of 40 to 60 mg is standard treatment for GCA.[5] Little evidence supports intravenous pulse therapy with corticosteroid agents, although this therapy is preferred by some ophthalmologists. No randomized studies support a specific protocol for tapering the corticosteroid dose, and most clinicians recommend treatment duration of 12 to 30 months.[6,7] Steroid regimens in patients with GCA do not prevent late-onset morbidity related to persistent or recurrent vasculitis. Steroid-related side effects can be clinically significant after prolonged exposure to steroid drugs and have stimulated interest in use of steroid-sparing agents. Conflicting evidence has been reported regarding efficacy of methotrexate in patients with GCA.[8] Neither azathioprine or cyclosporine A have proved useful as steroid-sparing agents. Treatment using infliximab is an intriguing pos-

> **Genetic, sex, and environmental factors play an important role in the pathogenesis of SLE.**

sibility, but controlled studies must first be done before widespread use of this agent is indicated. Aspirin suppresses interferon gamma in the inflamed arterial wall and therefore may be useful for preventing irreversible cranial ischemic complications.

Systemic Lupus Erythematosus Study Group
Kumar Venkat, MD

Systemic lupus erythematosus (SLE) is a chronic multisystem disease with unknown neuroendocrine etiology. Genetic, sex, and environmental factors play an important role in the pathogenesis of SLE. Two major characteristics are seen in patients with SLE: 1) They produce pathogenic subsets of autoantibodies, immune complexes, and T cells and 2) they cannot properly regulate production and clearance of autoantibodies, immune complexes, and activated T cells. Abnormal immune responses occur in these patients because of interaction between susceptibility genes and environmental factors. Virtually every regulatory network that influences antibody and immune complex production and metabolism is abnormal both in mice with SLE and in humans with SLE. Hyperactivated B cells and T helper cells are the main factors in patients whose genome makes them susceptible to SLE. The disease originates in the genome and becomes clinically important only when multiple factors interact to sustain production of harmful products of the immune response and thus cause tissue damage.[9]

That most postpubertal patients who present with SLE are female suggests a role for the X chromosome in development of the disease. Present evidence suggests that estrogens or feminizing steroids exacerbate SLE. Disease activity in SLE is influenced by the level of gonadal steroid compounds measured during the menstrual cycle and during pregnancy. By the mechanism of estrogen receptor transcripts, sex hormones regulate the activity of several factors: cytokines released by T helper cells, genes related to autoimmunity, apoptosis in the human thymus, and function of T and B cells. Sex hormones could affect the immune system by modifying T cell receptors, thereby signaling and regulating expression of T cell surface signals, autoantigens, translation or transcription of cytokine genes, or lymphocyte homing. Low estrogen levels along with prolactin acting through T_H1 cells lead to production of proinflammatory cytokines (IL-2, IFN-γ, and LT) and are also important in the pathogenesis of RA and multiple sclerosis (MS). High levels of estrogen, progesterone, and testosterone acting through T_H2

cells lead to production of antiinflammatory cytokines (IL-4, IL-5, IL-6, IL-10, TGF-beta) and are important in the pathogenesis of SLE.[10]

Modern studies have led to the hypothesis that a neuroendocrine-immune loop (NEI) is essential for modulation of immune and inflammatory responses and for eventually restoring normal physiologic homeostasis. Defects that involve any components of the NEI loop as a result of genetic, infectious, toxic, or pharmacologic factors could influence susceptibility, contribute to development of chronic inflammatory and autoimmune disease, or alter responses and susceptibility to infection.[11]

SLE is diagnosed and monitored on the basis of medical history, physical examination results, and serological tests. Adequate monitoring of disease activity is achieved by a combination of these elements. Appropriate initial laboratory tests include routine studies, specific immunologic tests, and a variety of cytokines that can be measured in selected settings. No single test can predict exacerbation in SLE. Disease activity is most usefully and cost-effectively assessed by measuring levels of anti ds-DNA antibody and serum complement (C3, C4, CH50). Other tests, such as measurement of IL-2 receptor activity, have less predictive value, are difficult to interpret, and are expensive. Monitoring of renal function is essential for assessing disease activity and response to therapy.[12,13] In some patients, immunologic markers may remain abnormal during clinical remission.

SLE is a chronic disease characterized by remission and exacerbation. The cornerstone of treatment is prompt, appropriate therapy, achieved in large part through careful monitoring to detect flares of disease activity. Although rheumatologists have not reached a consensus on the best method of monitoring SLE activity, three recently developed indices—the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), the BILAG (British Isles Lupus Assessment Group Scale), and the SLAM (Systemic Lupus Activity Measure)—appear useful for monitoring disease activity as well as efficacy of treatment for SLE. Predictors of poor outcome in SLE are serum creatinine level >1.5 mg/dL (114.4 μmol/L), proteinuria in the nephrotic range, arterial hypertension, pulmonary involvement, thrombocytopenia, anemia, and SLEDAI score >20 at presentation. The mortality rate is nearly 50% for patients with SLE who present with acute pneumonitis or acute abdomen. Infection and thrombosis contribute equally to mortality in patients with SLE. Prolonged corticosteroid therapy increases the risk of infection and contributes to a higher incidence of coronary artery disease.[14,15]

The goal of therapy for SLE is to reduce the extent of organ involvement. Standard forms of therapy for SLE include corticosteroid agents, nonsteroidal antiinflammatory agents (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, antimalarial agents, and immunosuppressive drugs. Newer and experimental forms of therapy include hormonal therapy, intravenous immune globulin (IVIg), immunosuppressive drugs, plasmapheresis, and stem cell transplantation.[16] Types of hormonal therapy include dehydroepiandrosterone (DHEA), androgen, gonadotropin-releasing hormone (GnRH), bromocriptine, selective estrogen receptor modulators (SERMs), and progestogen. Immunotherapeutic agents under study include mycophenalate mofetil, cyclosporine, leflunonamide, arsanilic acid, cladarabine, and fludarabine. Building on the success of using biologic agents in other rheumatic diseases, agents such as Anti CD-40 ligand, LJP 394 (B cell tolerogen that reduces ds-DNA titers), Anti IL-10 antibody, and rituximab (Anti CD-20 monoclonal antibody) are now being used in small trials. Mycophenalate mofetil has shown promise in treatment of lupus nephritis in several small studies; the drug selectively inhibits lymphocyte proliferation (activated lymphocytes) and inhibits mesangial proliferation. In mouse models, mycophenalate mofetil reduces severity and progression of renal damage. When administered as treatment for SLE, mycophenalate mofetil has been shown to improve clinical manifestations and results of serology tests as well as SLEDAI scores. Mycophenalate mofetil may be useful for treating other SLE manifestations as well as a range of other autoimmune diseases, including dermatomyositis, vasculitis, RA, and uveitis.[17] Newer modalities are expensive and are currently limited to research protocols.

Scleroderma Study Group
David Zelman, MD and Eric Schoen, MD

Systemic sclerosis is a multisystem disease with diverse clinical manifestations and outcomes. Probably initiated by microvascular and immune events, systemic sclerosis can ultimately lead to fibrotic and atrophic sequelae in critical organ systems. Therapy for systemic sclerosis is complicated by the heterogeneity of its clinical manifestations and mechanisms, which are based on organ-specific intervention instead of a fundamental approach based on root causes. Identification of patients at highest risk will help clinicians to give highest priority to treating these patients, who are the most likely to benefit from aggressive intervention.

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If it develops at all, severe organ involvement is most likely to develop within the first three years after diagnosis.[18,19] Diffuse skin involvement, anemia, high sedimentation rate, visceral involvement, presence of specific autoantibodies (antitopoisomerase I and antiRNA polymerase) all portend worse prognosis. This early window probably represents a period of increased disease activity in which pharmacologic intervention can limit progression of the fibrotic damage that is the hallmark of systemic sclerosis.[20] Disease severity scales have been developed by international consensus to facilitate classification of systemic sclerosis and communication about the disease for study purposes.

Clinical trials of systemic sclerosis therapy have been notoriously difficult because sample sizes have been small and because the medications have had limited efficacy. Use of immunosuppressive drugs, immune-response modulators, antifibrotic agents (such d-penicillamine), minocycline, methotrexate, cyclosporine, gamma interferon, and chlorambucil have all led to equivocal results. Current forms of therapy remain directed at involvement of specific organs.[21-23] Systemic sclerosis often presents with Raynaud's phenomenon as well as morbidity which can range in severity from bothersome episodes to critical digital ischemia and gangrene. Factors contributing to perfusion include innate vessel size, alpha-2-adrenoreceptor reactivity, and endothelial factors such as prostacyclin, endothelin-1, and nitric oxide; and platelet-derived factors such as serotonin and thromboxane A2. Each of these factors may provide intriguing targets in treatment of Raynaud's phenomenon. Treatment of mild cases of Raynaud's phenomenon includes warming strategies as well as control of anxiety and stress. When medication is required, calcium channel blockers are the preferred choice,[23] but sympatholytic agents, such as prazosin, may be used for some patients. Controlled medical trials have shown modest benefit for both types of drug. Limited evidence supports the benefit of topical nitroglycerin, direct vasodilators, fluoxetine, antioxidant drugs, and anticoagulant agents.

Severe Raynaud's phenomenon with digital ischemia and gangrene requires aggressive treatment. Unfortunately, evidence-based studies provide little clinical guidance, leaving clinicians to rely on interventions supported only by small, inadequately controlled studies. Treatment options include maximization of calcium-channel blockers; anticoagulation with heparin; and use of alprostadil (PGE1), epoprostenol (prostacyclin), and bosentan (antiendothelin). Surgical treatment options include digital artery sympathectomy and revascularization with adventitial stripping.

Interstitial lung disease (ILD) in patients with scleroderma has become the most frequent cause of death now that renal involvement is effectively managed with ACE inhibitors.[19] Patients with these conditions present with a dry cough, dyspnea, and "velcro" crackles heard during examination of the lungs. Pulmonary function tests show loss of forced vital capacity (FVC) and lung-diffusing capacity for carbon monoxide (DLCO), and high-resolution computed tomography (CT) shows a "ground glass" appearance. Pulmonary inflammation can be corroborated by bronchoalveolar lavage (BAL) testing and lung biopsy. Pulmonary function testing is recommended for monitoring patients; this monitoring should include DLCO testing every six months, especially during the first three years after the diagnosis of ILD is established. Therapy may be appropriate for patients with DLCO less than 70% or who have symptoms that show progressive decline. Little benefit has been shown with methotrexate, d-penicillamine, colchicine, azathioprine, prednisone, flucytosine (5-FC), or gamma interferon. Some studies with cyclophosphamide have shown stabilization of disease status and even improvement.

Pulmonary hypertension is a serious complication of scleroderma for which new therapies have been developed.[19] Pathophysiologic changes in pulmonary hypertension include varying degrees of vasoconstriction, arterial wall remodeling, and thrombosis in situ. Endothelial injury is probably the critical early event leading to abnormal vascular reactivity related to factors such as local release of vasoconstrictive mediator endothelin and loss of endothelium-derived vasodilators (eg, prostacyclin and nitric oxide). Functional lesions ultimately progress to arteriolar fibrosis. Patients with pulmonary hypertension often have scleroderma of long duration, limited cutaneous disease, and anticentromere antibody. They present with severe dyspnea on exertion and DLCO less than 55% or out of proportion to FVC loss (ratio >1.6). Echocardiography may show PA pressures >30 mmHg, most often higher. Cardiac catheterization may be required for further study and is the reference standard for diagnosis.

Clinical trials[22] have shown that exercise capacity is affected beneficially by three agents—epoprostenol (a prostacyclin analogue), trepostinil (a prostacyclin analogue), and bosentan (an endothelin receptor antagonist)—whose use is indicated for WHO Class III and IV patients. Bosentan is given orally, whereas the other two drugs are given by continuous intravenous infusion. Other forms of treatment are being

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studied and include inhaled prostacyclin analogues, inhaled NO, and sildenafil.

Ongoing studies of the pathophysiology of endothelial cell injury may provide new targets for disease modification in patients with scleroderma. Endothelin-1, transforming growth factor beta, connective tissue growth factor, and intracellular molecules regulating transcription (Smad proteins) all may be potential sites of intervention useful for preventing the excessive fibrosis associated with scleroderma.[24]

Although treatment for scleroderma continues to frustrate physicians and patient alike, improved understanding of the pathogenesis, natural history, and prognosis of this disease is leading to better case management. Early diagnosis, identification of patients with poor prognosis, and close monitoring of patients in the first several years is important. Morbidity in scleroderma can be reduced by appropriate use of supportive measures, including use of calcium channel blockers and proton pump inhibitors.

Expanding Role of Tumor Necrosis Factor

Aileen Dillon, MD and Ken Bulpitt, MD

Tumor necrosis factor (TNF) is a prominent proinflammatory cytokine which contributes substantially to producing inflammation in RA and the spondyloarthropathies (SpA), particularly psoriatic arthritis (PsA) and anklyosing spondylitis (AS). Three TNF inhibitors are now commercially available: etanercept (Enbrel™), infliximab (Remicade™), and adalimumab (Humira™). Building on work done in previous years, the group reviewed safety issues and attempted to compare and contrast these agents for use in patients with RA. We also reviewed use of these agents in patients with PsA and AS and discussed the possibility of developing a drug registry, classified by disease, to be used by all KP rheumatologists for patients receiving biologic agents.

 Adalimumab is a recombinant monoclonal antibody containing only human peptide sequences; infliximab is a chimeric antibody consisting of 75% human IgG1 at the constant region joined with 25% murine Ig at the antigen-binding regions. Etanercept is a recombinant fusion protein that links soluble TNF receptor (p75) to the Fc portion of human IgG1.

That an association may exist between lymphoma and TNF inhibitors is notable new safety information. According to the most recent estimate by the National Cancer Institute, the risk of lymphoma is 1 in 5000 in the general population.[25] The risk for all TNF inhibitors is estimated to be between twofold and sevenfold greater: Etanercept is at the lower end of this range, and adilimumab and infliximab are at the higher end. However, because lymphoma risk is higher in patients with RA (especially those with more severe disease) than in the general population, any potential role played by TNF inhibitors is unclear.

The risk of TNF causing reactivation of tuberculosis or similar latent infections (for example, coccidioidomycosis and histoplasmosis) exists and appears higher in patients receiving adilimumab and infliximab. PPD-positive patients therefore must be screened and treated before starting any therapeutic regimen of TNF inhibitors.

Whereas TNF agents are thought relatively safe, congestive heart failure (CHF) may be aggravated by TNF inhibitors; the current experiential recommendation based on Phase II studies is to avoid these agents entirely in patients with Class 3 or Class 4 CHF. Rare reports of liver dysfunction, demyelinating disease, and SLE-like syndromes have been described in the medical literature, and further information may be found at the US Food and Drug Administration (FDA) Web site: www.fda.gov/ohrms/dockets/ac/cder03.html#Arthritis.

Because no direct comparisons exist, only indirect comparison of the three TNF inhibitors in RA is possible. Controlled comparison is unlikely to be undertaken in the near future. Analysis aimed at determining a rational approach to selection and dosing of TNF inhibitors requires comparison of available data on the mechanism of action, kinetics, efficacy, toxicity, and cost of these drugs as well as patient acceptance of them. The mechanism of action is similar for the three agents, but the monoclonal antibodies infliximab and adalimumab have a theoretical advantage. They can bind with TNF on the cell surface. Good efficacy for each of the three TNF inhibitors has been shown in well-controlled clinical trials.[26-38] Choice of TNF agent depends on preferences of physicians and their patients.

Similarly, duration of treatment (or drug survival) after completion of blinded clinical trials as reported to the FDA suggests that comparable efficacy and toxicity is achieved by treatment with etanercept (73%),[29] adalimumab (70%),[38] and infliximab (76%)[30,32] when continued for more than two years. Treatment with etanercept continued for more than four years after the study in 52% of patients; treatment with adalimumab continued for this period in 56% of patients; data for infliximab were not available.

> **That an association may exist between lymphoma and TNF inhibitors is notable new safety information.**

Overall safety of the three TNF inhibitors was good, although (as noted earlier in this discussion) postmarketing data suggest that use of infliximab is associated with a higher incidence of mycobacterial and fungal infections as well as serious allergic reactions. The cost of treatment with a TNF inhibitor is probably comparable, although the range of cost for infliximab is large and depends on the dose required. Whether weekly or biweekly dosing with adalimumab is necessary for achieving a similar clinical effect is unknown.

The ultimate place of the most recently approved TNF inhibitor, adalimumab, and the relative strength of the three agents will require additional real-world experience. Prospective collection of data on utilization, clinical response, and toxicity of TNF inhibitors is a highly suitable task for the KP system; and this suitability is a strong argument for developing a KP rheumatic disease registry.

Data from animal and human studies suggest that TNF is pivotal in inflammation of anklyosing spondylitis (AS) and psoriatic arthritis (PsA). Small, placebo-controlled trials of etanercept and infliximab in patients with AS and PsA have shown clinically significant improvement in the drug-treated groups with regard to joint and skin activity. This improvement occurred even in patients with longstanding AS. Therapy with infliximab at a dose of 5 mg/kg—the standard dose for patients with Crohn's disease—was chosen in both diseases. Initial data for small numbers of patients with undifferentiated spondyloarthropathy have shown greater efficacy at this dose compared with the usual dose used in patients with RA (3 mg/kg). Etanercept was given at a dosage of 25 mg twice weekly. Whether either drug will prevent bony anklyosis if given to patients with early AS is unknown. Given the cost and side effects of these drugs, their role in the treatment strategy for these diseases will be determined by results of larger ongoing multicenter trials.

Chronic Disease Management and Registry

Aileen Dillon, MD

Chronic illnesses such as diabetes mellitus and RA are characterized by gradually worsening symptoms. Deterioration in functional status and overall health can be minimized by optimal care. Groups in the United States and Europe have shown that an integrated chronic care system in management of diabetes mellitus is more successful with regard to clinical outcomes, cost, quality-of-life measures, and patient and clinician satisfaction than when the previous acute, reactive model is used. The chronic care model includes an evidence-based approach to treatment, targeting all persons with the disease (population-based) and assigning high priority to patient participation (patient-centered). This approach contrasts with the typical system of intermittent short visits with a physician-driven agenda: Such a system focuses on "symptom swatting" and medication management with little emphasis on the patient's role and with little coordination or emphasis on quality improvement on the part of the health care system.

We believe that the same model should be applied throughout KP to management of a variety of musculoskeletal diseases, starting with RA. This chronic disease affects 0.9% of the population—mainly those aged from 40 to 60 years—and has considerable associated medical and societal costs.[39] Studies have shown that the incremental lifetime costs of RA are dramatically affected by age at disease onset, severity of disability at onset, and the rapidity with which the level of disability changes. These costs are direct (treatment costs, social services, private expenditure), indirect (lost productivity and earnings of patient/caregiver, lost tax revenue), and intangible (reduced quality of life).[40,41] One study[42] of cost of RA to the employer showed that the annual per capita health care cost for an employee with RA was twice that of control employees and that the cost of disability was three times the cost for controls. Evidence now shows that early recognition and aggressive management of RA is changing the slope of the disability curve in RA and is improving quality-of-life measures.

The time is right for KP to develop an approach to managing the chronic disease of RA. This approach would provide optimal care for our patients and would enable us to assess more realistically the relative strength, toxicity, and cost of drugs. We could also assess impact of disability and overall cost of this chronic disease.[43] The first stage in developing this disease management approach is to create a patient registry and tracking system. Full implementation of a chronic disease registry and approach to disease management will take a number of years; however, we are now in a position to develop a pharmacy registry for tracking patients who are receiving TNF inhibitors—a registry which will prove invaluable for assessing the relative strength, toxicity, and cost of these agents. ❖

> **The time is right for KP to develop an approach to managing the chronic disease of RA.**

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Wheat Flour from Peascods

What you get out depends on what you put in; and as the grandest mill in the world will not extract wheat flour from peascods, so pages of formulae will not get a definite result out of loose data.

— Thomas Henry Huxley, 1825-1895, English biologist and writer