Potential New Drug Targets for Osteoporosis:
Limiting Resorption, Augmenting Bone Formation

New therapies are needed to reduce the burden of osteoporosis, especially for patients with established fractures. Thanks to a clearer understanding of bone formation and resorption, novel agents that influence bone remodeling are now undergoing clinical trials. These agents may offer promise in the treatment of low bone mass.

Story on page 4.
Dear Colleague,

It is my honor to share with you the news that Cleveland Clinic’s Rheumatology Program is now ranked No. 2 in the nation in the U.S. News & World Report “Best Hospitals in America” survey. This ranking is testimony to achievements by the entire staff, as well as 16 years of visionary leadership by Dr. Gary Hoffman, during which the department became an international leader in vasculitis, systemic autoimmune diseases, arthritis care and metabolic bone diseases.

Dr. Hoffman continues to see patients in the Center for Vasculitis Care and Research that he founded. Although he has stepped down as department chair, his duties are expanding as he takes on an institutional leadership role in physician volunteerism.

Last year, the Orthopaedic & Rheumatologic Institute (ORI) was created as one of 26 Cleveland Clinic institutes that unite disciplines to optimize interdisciplinary collaboration on patient care, education and research. The institute model preserves the strengths of both the Rheumatology Program and the Orthopaedic Program – ranked No. 3 in the country by U.S. News – while creating new opportunities for synergy.

Several new collaborative clinical, academic and research programs are being developed under the ORI. An interdisciplinary arthritis center has opened to provide collaborative expert care for arthritis and other musculoskeletal conditions. Another ORI clinical initiative will utilize the electronic medical record to help identify, evaluate and treat patients with suspected osteoporotic fractures.

Multiple interdisciplinary research and educational initiatives will focus on arthritis, metabolic bone diseases, cartilage regeneration, fracture repair and bone growth, offering unparalleled opportunities for rheumatology and orthopaedic trainees.

We will continue to build upon our legacy of research in the areas of vasculitis, inflammatory arthropathies, immunology, pediatric rheumatology, general rheumatology and clinical outcomes.

It is an honor to serve as Interim Chair of a department whose staff members are deeply committed to advancing rheumatology care, research and education. You will read about some of the myriad activities in which they are involved in this issue of Rheumatology Connections.

We hope you enjoy this issue, and invite your comments and feedback.

Sincerely,

Abby Abelson, MD
Interim Chair, Department of Rheumatic and Immunologic Diseases
Vice Chair of Education, Orthopaedic & Rheumatologic Institute
Improving Patient Access, Experience

This fall, Cleveland Clinic opens the Sydell and Arnold Miller Family Pavilion, the country’s largest single-use facility for heart and vascular care, and the Glickman Tower, new home to the Glickman Urological & Kidney Institute. Both buildings will help to improve the patient experience by increasing capacity and by consolidating services, so patients can stay in one location for their care. For details, including a virtual tour, please visit meetthebuildings.com.

CME

Rheumatologists are invited to attend the following Cleveland Clinic Continuing Medical Education Symposium:

May 7 - 9, 2009
Summit on Biologics III: Biologic Therapies in Special Populations - Infections, Malignancies, Cardiovascular Disease and Other Comorbidities

Featuring a Mini-Symposium:
Managing Complex Cases in Biologic Therapies

The InterContinental Hotel and Bank of America Conference Center
Cleveland, Ohio

Online Series:
Neuroinflammatory Aspects in Rheumatology

For further information about live Cleveland Clinic Center for Continuing Education courses, call 800.238.6750 or 216.448.0770 or visit clevelandclinicmed.com; visit the website for information about online CME.

Online Services for Physicians

eCleveland Clinic Remote Consults
Request a remote second medical opinion from Cleveland Clinic rheumatologists through the secure eCleveland Clinic MyConsult Web site. Visit eclevelandclinic.org/myConsult.

Track Your Patient’s Care Online
Whether you are referring from near or far, our eCleveland Clinic service, DrConnect, allows you to track your patient’s treatment progress online, via a secure website. Visit eclevelandclinic.org or e-mail drconnect@ccf.org.
Cover Story: Novel Osteoporosis Drugs Seek to Limit Resorption, Augment Bone Formation

By Chad Deal, MD

New agents that are under study for osteoporosis target bone remodeling, a dynamic process that accelerates after menopause. Of the two classes of osteoporosis drugs, anabolic agents increase bone mass to a greater degree than antiresorptive agents. Anabolic drugs improve bone quality and increase bone strength by effecting changes in micro-architecture, including connectivity, density and geometry (changes neither revealed by DXA nor by measuring markers of bone turnover).

More anabolic agents needed

The only available anabolic agent is parathyroid hormone (rhPTH 1-34, teriparatide or Forteo®). Its use is limited to two years in the United States. The mechanism of action is still under investigation, but rhPTH likely affects multiple pathways that alter osteoblasts, bone-lining cells, osteoclasts and osteocytes.

New anabolic agents in development include a calcium-sensing receptor antagonist and antibodies that target molecules involved in the Wnt signaling pathway.

CaSR antagonist boosts PTH response

Our Center for Osteoporosis and Metabolic Bone Diseases is involved in studies of an anabolic calcium-sensing receptor (CaSR) antagonist. This G protein-coupled, seven-pass transmembrane molecule present in the parathyroid gland and kidney controls calcium homeostasis by releasing PTH. Manipulating CaSR using small-molecule allosteric modulators can affect PTH secretion.

Positive allosteric modulators are used to lower PTH secretion in patients with renal disease and hyperparathyroidism. Negative allosteric modulators are in development and block receptor function, resulting in a PTH pulse with each dose. These antagonists or calcilytics can be given orally and would not require daily injections as with teriparatide.

In order for calcilytics to become useful anabolic agents, they must stimulate the release of sufficient PTH. Anabolic action would require a short half-life and transient receptor activation to avoid prolonged PTH secretion and a catabolic state. The CaSR antagonist molecule should not exhaust the parathyroid gland, nor should it produce hyperplasia.

A proof-of-concept study with calcilytic SB-751689 (roncalceret) has shown a robust PTH response, short half-life, increases in both cortical and trabecular bone formation rate in animals, and significant increases in markers of osteoblast function (P1NP, osteocalcin and BSAP) equivalent to teriparatide. A dose-ranging clinical trial in humans is under way at Cleveland Clinic and other centers.

Wnt signaling regulates bone metabolism

Wnts are secreted proteins that regulate gene transcription of key proteins important in bone formation. Wnts activate an intracellular pathway that results in an accumulation of β-catenin.

The pathway is initiated when Wnt permits association of two membrane receptors, serum frizzled-related proteins (Fzd) and lipoprotein receptor-related protein (LRP5/6). This association
activates a protein complex consisting of axin, adenomatous polyposis coli and glycogen synthase kinase 3 or GSK3.

Without Wnt signaling, GSK3 cannot phosphorylate β-catenin, which then accumulates, translocates to the nucleus and binds to factors affecting the gene transcription central to osteoblast function.

Wnt-signaling inhibitors bind to Wnt, Fzd or LRP5/6 and decrease bone formation. Deficiencies of these inhibitors or antibodies to them increase Wnt signaling and bone formation.

**Sclerostin antibodies target bone formation**

A human disease involving high bone mass, sclerostosis, results from a homozygous mutation in the SOST gene that encodes sclerostin. Patients have a sclerostin deficiency, which allows for increased Wnt signaling. High bone mass, especially in the skull, results in cranial nerve entrapment, increased intracranial pressure and/or stroke.

Heterozygous mutations in the SOST gene produce moderate bone mass increases with fewer skeletal complications. Since sclerostin is an exclusive product of osteocytes, antibodies to sclerostin offer a way to specifically target bone formation.

A single subcutaneous dose of sclerostin given to postmenopausal women has increased P1NP, a measure of osteoblast formation, by 60 to 100 percent at 84 days. The women showed no increase in serum CTX, a measure of bone resorption, and their lumbar spine bone density increased 6 percent.

**Antiresorptive agents**

Current antiresorptive agents include the commonly prescribed bisphosphonates, as well as selective estrogen-receptor modulators, calcitonin and estrogen. Novel antiresorptive agents in development include inhibitors of cathepsin K, an osteoclast enzyme required to resorb bone matrix, and antibodies to the receptor-activator of a key cytokine in osteoclast activation.

**Cathepsin K degrades collagen**

Orally available inhibitors of cathepsin K are being evaluated in several ongoing clinical trials. This cysteine protease, selectively expressed by osteoclasts, can degrade key bone matrix proteins, including collagen. Eliminating cathepsin K in osteoclasts inhibits bone resorption.

Researchers have long recognized that bone resorption and formation are tightly coupled, so that inhibiting resorption inhibits formation. Some research suggests that cathepsin K inhibitors may have less effect on osteoclast/osteoblast interaction and bone formation than the other bisphosphonates.

Several cathepsin K inhibitors have entered clinical trials. Many have had side effects that may limit their use, including balicatib and relacatib. Odanacatib has reduced bone resorption markers in a trial of women with metastatic breast cancer.

**Denosumab mimics decoy receptor**

Trials of denosumab (the receptor-activator of nuclear factor κB ligand, or RANKL) are ongoing in our Center for Osteoporosis and Metabolic Bone Diseases and elsewhere. RANKL, a member of the tumor necrosis factor (TNF) family, is a key mediator of bone remodeling expressed by osteoblasts, synovial fibroblasts and activated T-cells. It binds to RANK, a receptor on osteoclasts, inducing their differentiation, activation and survival.

The soluble cytokine osteoprotegerin (OPG) functions as a decoy receptor by competing with RANKL for binding to RANK. Denosumab mimics OPG’s effects; the humanized monoclonal IgG2 antibody binds selectively and with high affinity to RANKL.

Our phase 2, randomized, dose-ranging trial of denosumab showed that lumbar spine density increased 4.1-8.9 percent at 24 months; BMD gains at cortical sites, such as the hip and forearm, were superior to those of alendronate; and no neutralizing antibodies developed. In ongoing phase III trials elsewhere, vertebral fracture patients receive 60-mg doses subcutaneously every six months.

As an antiresorptive agent, denosumab differs from the bisphosphonates. Bone turnover markers decline rapidly (as early as three days) and recover faster when treatment is discontinued, and denosumab does not accumulate in bone. Denosumab used in combination with PTH may augment PTH response (unlike bisphosphonates, which blunt PTH response).

Significant advances in the therapy of low bone mass appear to be on the horizon, thanks to an increased understanding of the mechanisms underlying bone formation and resorption.

Dr. Deal is Head of the Center for Osteoporosis and Metabolic Bone Diseases. Physicians may contact him at 216.444.6575 or at dealc@ccf.org.
NIH Contract Focuses on Novel Therapy for Giant Cell Arteritis and Takayasu’s Arteritis

By Carol A. Langford MD, MHS

Research activities within the Center for Vasculitis Care and Research continue to grow. Studies examining treatment with a novel agent for two forms of vasculitis are soon to open for patient enrollment.

In August 2007, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, awarded our center a contract to study the medication abatacept (CTLA4-Ig) in both giant cell arteritis and Takayasu’s arteritis.

Giant cell arteritis and Takayasu’s arteritis are vasculitic diseases that share similar clinical, histologic and immunopathogenic features. Involvement of the aorta and its main branches occurs in both diseases, causing disability, morbidity and mortality.

Critical need for new therapies

Although glucocorticoids such as prednisone provide symptomatic improvement in giant cell arteritis as well as Takayasu’s arteritis, they may be associated with significant toxicity and do not prevent disease relapses. The need to identify better treatment is critical for both diseases.

Studies of arterial tissue support that both diseases are antigen-driven, and that activated T-cells play a critical role in their pathogenesis. Abatacept is a novel agent that modulates the co-stimulation signal required for antigen-specific T-cell activation. Its actions make abatacept an appealing and innovative therapy to investigate in giant cell arteritis and Takayasu’s arteritis.

Two treatment arms

Our studies seek to examine the safety, efficacy and immunologic effects of abatacept in patients with both forms of vasculitis.

In these concurrent, randomized withdrawal trials, all participants will initially receive abatacept together with standard dosages of prednisone. At month 3, participants who are in remission will undergo a double-blinded randomization, to continue abatacept or be switched to placebo. Patients in both treatment arms will continue with a standardized prednisone taper.

Laboratory-based analyses are directly integrated into the conduct of the clinical trials to establish an immunologic correlation with the safety and efficacy that is observed.

Eligibility criteria

This study will be open to individuals with active, newly diagnosed or relapsing giant cell arteritis or Takayasu’s arteritis, who do not have features of these diseases that increase their risks of participation.

We will conduct this research in conjunction with the Vasculitis Clinical Research Consortium (VCRC), an NIH-funded collaborative network that supports research in the vasculitic diseases. VCRC centers include Boston University, Cleveland Clinic, Mayo Clinic, Johns Hopkins Medical Center and, in Canada, Mt. Sinai Hospital in Toronto and St. Joseph’s Hospital in Hamilton, Ontario.
We are examining the safety, efficacy and immunologic effects of abatacept in both forms of vasculitis.

The research is part of a portfolio of ongoing VCRC studies that includes longitudinal studies examining disease features and biomarkers, a study of positron emission tomography (PET) scanning in Takayasu’s arteritis, and a pilot trial of abatacept in Wegener’s granulomatosis.

Physicians interested in learning more about this study can contact either Dr. Langford (langfoc@ccf.org) or Katherine Tuthill, CNP (tuthillk@ccf.org). Further information about this study, including eligibility criteria, design or contact information can also be found at http://www.clinicaltrials.gov.

Dr. Langford, Director of the Center for Vasculitis Care and Research within the Department of Rheumatic and Immunologic Disease, can be reached at 216.445.6056 or at langfoc@ccf.org.

Because of its rarity in children, pediatric vasculitis may persist unrecognized for years. “Left untreated, the vasculitides can produce significant morbidity and mortality,” says Steven Spalding, MD, a pediatric rheumatologist. He and Philip Hashkes, MD, MSc, Head of the Center for Pediatric Rheumatology, see children in Cleveland Clinic’s Center for Vasculitis Care and Research.

Over the past five years, more than 80 pediatric patients have been treated in the Center. The two most common types of vasculitis affecting children are Kawasaki disease and (pictured above) Henoch-Schönlein purpura.

“Other types of vasculitis – including Takayasu’s arteritis, Wegener’s granulomatosis, microscopic polyangiitis, polyarteritis nodosa, Behçet’s disease, Churg-Strauss syndrome and CNS vasculitis – are only rarely encountered in children, even by pediatric rheumatologists,” notes Dr. Hashkes. “Such children are often referred to Cleveland Clinic, so that we can assist with their care.”

**Pediatric signs and symptoms**

Dr. Spalding notes that “manifestations of vasculitis in children typically include unexplained, persistent fevers; weight loss; malaise; and signs of gastrointestinal, pulmonary, renal, musculoskeletal or skin inflammation. However, symptoms and signs vary by disease.”

To manage these complex problems, pediatric rheumatologists work with our vasculitis experts to provide the most advanced therapies available. They also collaborate as needed with other Cleveland Clinic subspecialists, including:

- otolaryngologists specializing in the treatment of subglottic stenosis resulting from Wegener’s granulomatosis
- vascular surgeons experienced in managing stenotic or aneurysmal changes in vessels affected by vasculitis
- neurologists specializing in the diagnosis and treatment of CNS vasculitis
- radiologists with expertise in noninvasive and invasive vascular imaging techniques

**Access to clinical trials**

Children seen in the Center for Vasculitis Care and Research have access to ground-breaking research, ranging from epidemiologic studies to innovative therapeutic trials. Current studies open to children include a Pediatric Vasculitis Registry and longitudinal biomarker studies, in which clinical data are collected and blood and urine samples are studied in collaboration with Vasculitis Clinical Research Consortium members.

Referring pediatricians are notified of all evaluations and recommendations for their patient. Families are encouraged to sign up for eCleveland Clinic MyChart, a secure online health management tool supported by our electronic medical record, which gives them online access to their child’s laboratory information. “We also work closely with the Vasculitis Foundation, which provides valuable education and family support,” says Dr. Spalding.

Dr. Spalding sees children with vasculitis, joint pain, juvenile arthritis and recurrent fevers. Dr. Hashkes specializes in pediatric vasculitis as well as drug therapy for arthritis and autoinflammatory (periodic fever) syndromes. For consultations and referrals, call 216.444.5632 or 216.445.8525.
Scleroderma: Trends in Management

By Soumya Chatterjee, MD, MS, FRCP

Cleveland Clinic’s Scleroderma Program integrates optimum, evidence-based patient care with clinical and translational research exploring the complex pathogenesis and management of scleroderma. We have seen approximately 500 patients with systemic sclerosis since our program’s inception in 2005.

Our understanding of scleroderma’s complex pathogenesis, pathophysiology and pharmacotherapy has advanced considerably over the last few decades, changing quality of life and, to some extent, prognosis for patients.

Once thought of as a disease with high mortality, scleroderma is now considered to be a chronic disease with considerable diversity in presentation, rate of progression, internal organ involvement and long-term outcomes of patients. Lack of consensus remains on measuring and grading disease severity as well as differentiating potentially reversible “activity” from potentially irreversible “damage.”

Lung disease is the leading cause of death in systemic sclerosis. Our combined Rheumatology/Pulmonary Clinic is available for patients with interstitial lung disease or pulmonary hypertension. Patients are evaluated both by a rheumatologist as well as one of two pulmonary specialists in scleroderma lung disease. This ensures optimum investigation of their complications and development of the most effective management plan. We have gradually expanded the clinic’s focus to include patients with lung disease associated with other autoimmune rheumatologic disorders, such as lupus, polymyositis and rheumatoid arthritis.

**Interstitial lung disease: most common**

Non-specific interstitial pneumonitis (NSIP) is the predominant form of interstitial lung disease. Pulmonary function testing and high-resolution CT scanning of the lungs are often adequate to ascertain its presence, nature and severity.

Broncho-alveolar lavage, once considered essential in the diagnostic workup, is no longer performed routinely, as it does not help predict response to immunosuppressive therapy or long-term prognosis.

Results from the NIH Scleroderma Lung Study (SLC) were not as encouraging as one would have hoped. However, patient selection is critical; some experts believe that cyclophosphamide could have had a more significant impact on the under-represented subgroup of scleroderma patients with more severe and more progressive lung disease.

Our initial optimism about cyclophosphamide’s success in stabilizing interstitial lung disease in scleroderma has been met with disappointment. The beneficial effects on lung function and quality of life measures were no longer apparent at the end of the second year of follow-up among SLC patients after discontinuation of cyclophosphamide. Effective maintenance therapy with a less toxic long-term agent is desperately needed. Early studies indicate that mycophenolate mofetil may have some promise in this regard.

**Pulmonary hypertension: a serious complication**

A recent study found that despite optimum pharmacologic therapy, patients with scleroderma-associated pulmonary hypertension were about three times more likely to die than were patients with idiopathic pulmonary arterial hypertension. Patients can acutely decompensate and experience a rapidly downhill course despite maximal pharmacologic treatment, culminating in death while awaiting lung transplant.

We need to identify patients at risk of pulmonary hypertension, monitor them closely and institute therapy early. However, whether initiating therapy in WHO class I or II patients can slow the progression of scleroderma-associated pulmonary hypertension is unknown.
Fellowships Focus on Vasculitis
By Carol A. Langford MD, MHS

Patients with vasculitis face a number of complex medical challenges from their illness and its treatment. To help address these challenges, Cleveland Clinic’s Center for Vasculitis Care and Research has long been committed to educating physicians about the unique aspects of vasculitic disease.

In addition to educating medical students, residents and rheumatology fellows about vasculitis, this Orthopaedic & Rheumatologic Institute center offers a specific fellowship training program in vasculitis. One-year clinical or two-year investigational fellowships are available for physicians who have completed their subspecialty training.

Vasculitis fellows pursuing the investigational track will obtain a master’s degree or other postgraduate studies that provide the skills needed for a successful independent investigational career. Past Cleveland Clinic vasculitis fellows have returned to Canada, Spain, Mexico, New Hampshire, Texas, Utah and other locations to make important contributions to the care of individuals with vasculitis.

Two graduates of our vasculitis fellowship program have recently joined our faculty in the Center for Vasculitis Care and Research. Alexandra Villa-Forte, MD, MPH, completed a vasculitis fellowship here in 2004, and joined Cleveland Clinic after three years of academic practice in Brazil. Eamonn Molloy, MD, MS, a recent graduate of the Vasculitis Fellowship Program, is playing an important role in patient care and research in the Center for Vasculitis Care and Research, as well as the R.J. Fasenmyer Center for Clinical Immunology.

For further information about our one-year clinical and two-year investigational vasculitis fellowships, physicians may contact Dr. Langford, Director of the Center for Vasculitis Care and Research, at 216.445.6056 or at langfoc@ccf.org.

Addressing GI complications

Acid reflux disease and esophageal dysmotility continue to be major problems in scleroderma. Less commonly, small bowel dysmotility and pseudo-obstruction occur. These complications are very difficult to manage, especially when effective prokinetic agents such as cisapride and tegaserod have been taken off the market, and long-term use of metoclopramide and domperidone may involve risks of extrapyramidal complications. Total parenteral nutrition, associated with its own risks and complications, is often inadequate but remains the last resort in such situations.

Ameliorating skin tightness

Based on small clinical trials, we have tried methotrexate for rapidly progressive skin-tightening, severe musculoskeletal pain, joint contractures, proximal myopathy and multiple-tendon friction rubs. However, we have not been impressed with its efficacy, especially considering that skin tightness often stabilizes and may partially, spontaneously regress over the years.

Our experience with mycophenolate mofetil, supported by published studies, has been more encouraging, as it has accelerated “skin score” regression in selected patients. The potential therapeutic benefit of mycophenolate mofetil deserves further exploration in well-designed, randomized, controlled trials.

Intravenous immunoglobulin therapy has also shown promising results, providing significant pain relief, improving hand function and quality of life scores (HAQ-DI), and even softening skin in several of our patients. Though the body of literature is growing, randomized controlled trials of this agent are needed. It is expensive, and insurance approval is often hard to obtain. Moreover, side effects may be significant, and include aseptic meningitis and precipitation of oliguric acute renal failure.

Dr. Chatterjee directs the Scleroderma Program and also specializes in rheumatoid arthritis, lupus and myositis. He welcomes physician referrals and comments, and can be contacted at 216.444.9945 or at chattes@ccf.org.
In 2008, the news for patients with rheumatoid arthritis (RA) is promising due to the availability of new therapeutic agents. These agents have been demonstrated to reduce signs and symptoms of the disease, improve quality of life, retard radiographic progression and ultimately reduce the likelihood of disability and the requirement for major joint reconstruction.

Collectively, most new therapies fall into the class of biologic therapeutics, which in contrast to previous non-biologic agents, selectively target varying elements within the integrated immune response. Thus, they offer increased efficacy with acceptable rates of drug-associated toxicity.

Unfortunately for many patients with RA, the existence of numerous co-morbid conditions makes them less optimal candidates for such therapy. Chronic viral infections, in particular, pose formidable obstacles to the routine use of both non-biologic and biologic remittive drugs. Since these agents actively suppress the immune response, they can pose risks for accelerated infection-associated pathogenesis. Accordingly, rheumatologists are constantly in search of data to help them and their patients make reasonable shared and informed decisions on therapy.

**HCV: Most common dual affliction**

The most common blood-borne viral infection in the United States involves the hepatitis C virus (HCV), infecting an estimated 3.2 million individuals, according to a May 2006 report in the Annals of Internal Medicine. RA has a prevalence of nearly 1 percent and affects more than 2 million people. While accurate numbers for those dually afflicted are difficult to ascertain, there are likely tens of thousands of patients with both RA and HCV infection.

For these individuals, the therapeutic choices are far more difficult and limited, for a variety of reasons:

- The gold standard of therapy for patients with serious RA with the potential for joint damage and disability continues to be methotrexate. This agent itself is hepatotoxic, making its use in such patients highly problematic.
- Leflunomide, an alternative for many with RA, is also hepatotoxic and current guidelines advise against use of this agent in HCV-infected patients.
- While some rheumatologists favor remittive drugs of lesser potency (i.e., sulfasalazine, hydroxychloroquine), there are little data to ensure their safety in this setting. Thus, clinicians caring for such patients have been challenged for alternatives.

**TNF inhibitors’ safety**

The past several years have seen growing evidence of the safety of at least one class of biologics, namely inhibitors of tumor necrosis factor (TNF). Increasing anecdotal case reports and small retrospective and now prospective series have supported a high degree of clinical safety for the use of these agents in HCV-infected patients. A recent multicenter study from Italy, reported at the 2007 European League Against Rheumatism meeting, has clearly demonstrated both efficacy and safety in this setting.

Unfortunately, none of these studies has included serial biopsy data, which in HCV infection provide the greatest prognostic information.

In addition to these types of studies in HCV-infected RA patients, a single-center pilot study of the TNF inhibitor etanercept demonstrated superiority to placebo in enhancing the ability of standard anti-HCV therapy to both eradicate detectable virus from blood as well as normalize liver enzymes. The rationale for the study is based on the observation that HCV induces several inflammatory cytokines including TNF, which has been postulated to have a pivotal role in the disease.

**The PARTNER trial**

In an effort to definitively address whether TNF inhibitors may serve as useful adjuncts to standard antiviral therapy for HCV infection and to provide adequate safety data on their effects on liver histology, Cleveland Clinic is leading a multicenter trial on the TNF inhibitor infliximab. The Department of Rheumatic and Immunologic Diseases is collaborating on the study with the Section of Hepatology, whose Head, Nizar Zein, MD, is Principal Investigator.

The PARTNER trial (PegylAted interferon, Ribavirin and anti-TNF alpha Enhanced Response) is a randomized, blinded, controlled, multicenter efficacy and safety study of infliximab to determine whether TNF inhibition is not only safe but also efficacious in treating HCV infection.

Upon completion of this trial, rheumatologists will have a formidable body of data on the effects, and particularly the safety, of TNF inhibitors on the liver, including critical histologic effects. We hope that such data will be of critical importance to rheumatologists looking to craft long-term therapies for rheumatic disease patients requiring biologic agents.

Dr. Calabrese, is R.J. Fasenmyer Chair in Clinical Immunology and Theodore F. Classen, DO, Chair in Osteopathic Research and Education. To refer patients to Dr. Calabrese, call 216.444.5632; physicians may also reach him at calabrle@ccf.org.
Familial Mediterranean fever (FMF) is the most common genetic periodic fever syndrome, or autoinflammatory disease, resulting in recurrent attacks of fever, abdominal pain, chest pain, arthritis and rash, often from early childhood. Late complications of untreated FMF include the development of renal amyloidosis, leading to renal failure. This autosomal recessive disease is rare in the United States but is found in some ethnic groups, including Sephardic Jews, Armenians, Arabs, Italians and Turks.

In 1972, colchicine was found to be a very effective treatment for FMF, preventing amyloidosis in nearly all patients while preventing or reducing attacks in most patients. However, about 10 percent of FMF patients either do not respond to or do not tolerate colchicine, mainly due to gastrointestinal side effects. Currently, there is no alternative to colchicine.

**Genetic defect pinpointed**

About 10 years ago, the genetic defect of FMF was found to be in the MEFV gene on chromosome 16, encoding a protein called pyrin. Pyrin appears to play an important role in the regulation of production and activity of interleukin (IL)-1.

Based on this understanding and the effectiveness of anti IL-1 therapy for other closely related autoinflammatory diseases, we hypothesized that treating FMF with an anti IL-1 therapy would be effective. We recently received a grant from the FDA Orphan Disease Program to study the effect of rilonacept, a fusion protein-soluble receptor of IL-1, given as weekly subcutaneous injections to FMF patients who do not respond to or cannot tolerate colchicine.

**A grant from the FDA Orphan Disease Program allows us to study the efficacy of rilonacept in patients for whom colchicine is not an option.**
Outcomes Measures: Key to Reducing Disease Activity, Inducing Remission in Rheumatoid Arthritis

By Carmen Gota, MD

Clearly defined outcomes measures are required to attain tight control of disease activity in rheumatoid arthritis (RA). The U.S. Food and Drug Administration states that the goals of rheumatoid arthritis (RA) therapy are inducing complete remission, alleviating pain, maintaining function for essential activities, maximizing quality of life and preventing and controlling joint damage.

Current evidence indicates a need to add the following goals:
- early treatment of RA
- close follow-up of patients
- use of combination therapies
- identification and aggressive treatment of those with worse-outcome prognostic features

Complex treatment considerations

Because of its complexity, numerous clinical, structural and functional factors must guide the treatment of RA. This is in contrast to diseases such as diabetes or hypertension, which have widely accepted definitions and treatment cutoffs (glycosylated hemoglobin, targeted blood pressure levels).

Most rheumatologists rely heavily on qualitative measures such as overall clinical assessment when treating RA. Thus, some of the following validated outcomes tools for quantitative measurement are rarely used in practice:
- total swollen joint counts
- total tender joint counts
- physician and patient global assessments
- functional measures such as the health assessment questionnaire (HAQ)
- markers of inflammation
- C-reactive protein (CRP) levels
- erythrocyte sedimentation rate (ESR)

Composite measures of disease activity

To account for each variable, validated composite indices of disease activity have been used in clinical trials. Examples include the ACR score, DAS (disease activity score), SDAI (simple disease activity index) and CDAI (clinical disease activity index).

There are differences in these indices. Cutoffs for remission, and for low and high disease activity, have been established for the DAS, SDAI and CDAI, which measure disease activity at given points in time. In contrast, the ACR response measures the percentage of change in clinical status relative to baseline. Also, while an acute-phase reactant (the WSR or CRP) is used to calculate the DAS and SDAI, it is not used in the CDAI.

Alternatives to joint counts

Because counting tender and swollen joints may be challenging, additional “patient only” data collection measures have been proposed, including the patient activity scale (PAS), routine assessment of patient index data (RAPID) and global arthritis score (GAS).

Each of these measures includes patient assessment of pain, tender joint counts and functional disability indices, and appears to correlate well with validated RA outcomes tools.

Optimizing evidence-based care

Rheumatologists are challenged to incorporate evidence from outcomes-based trials when prescribing treatment for RA. The SONORA and RADIUS studies demonstrated that the rate of reaching ACR 70 scores was less than 10 percent among patients receiving standard care. In contrast, the TICORA and BeST studies found that use of composite measures to achieve tight control of RA status produced superior patient outcomes.
In the TICORA study, patients randomized to intensive therapy plus close monitoring using DAS, with a target goal of low disease activity, were compared with patients treated in standard fashion without the use of outcomes measures. Forty-one percent of those in the intensive treatment group achieved at least six months’ remission, versus 24 percent of patients receiving conventional therapy.

**Self-assessments worthwhile**

Many physicians advocate self-reported questionnaires such as the HAQ, HAQ-DI (HAQ disability index) and MDHAQ (multidimensional HAQ) as the best single measure of patient progress and outcome. These directly address the primary concerns of patients: pain, physical function, fatigue, global status and psychosocial distress. HAQ scores have been shown to predict outcomes such as treatment response, disability, cost of care, need for joint replacement and mortality.

Dr. Gota, pictured above, specializes in general rheumatology and vasculitis. Physicians may reach her at 216.444.0564 or at gotac@ccf.org.

HAQ scores can predict outcomes such as treatment response, disability, cost of care, joint replacement and mortality in RA.
Fibromyalgia syndrome affects 2 percent of the population, making up approximately 10 to 30 percent of rheumatology practices and 2 to 6 percent of primary care practices. Its pathogenesis is related to distress, disordered sleep and genetic factors, which together result in abnormal pain processing in the central nervous system, termed central sensitization.

We’ve come to recognize that fibromyalgia can be diagnosed in a variety of ways, and that a number of new agents have expanded the list of effective treatments.

The working definition
In 1990, Wolfe and colleagues, representing the American College of Rheumatology, analyzed signs and symptoms in 293 patients diagnosed by experts as having fibromyalgia. Comparing these patients to 265 controls with other pain syndromes, they found that widespread pain of at least three months’ duration and the presence of at least 11 of 18 tender points upon physical examination identified fibromyalgia with a sensitivity of 88 percent and a specificity of 81 percent. These became the ACR criteria for the classification of fibromyalgia and its working definition.

Investigators have used the presence of a large number of tender points to differentiate patients with fibromyalgia from patients with widespread pain, a more common condition affecting up to 15 percent of the population at any one time. Differentiating the conditions is important because patients with widespread pain have a better long-term prognosis than do patients with fibromyalgia.

Fatigue should be considered
Most importantly, this definition failed to include many other common symptoms of fibromyalgia, chief among them fatigue, which occurs in at least 80 percent of patients. White and others have since demonstrated that the presence and severity of fatigue differentiated patients with widespread pain, who had seven to 10 tender points, from fibromyalgia patients, who had at least 11 tender points.

To obviate the tender-point requirement and differentiate fibromyalgia from other pain syndromes, Katz, Wolfe and others developed an instrument known as the Symptom Intensity Scale (SIS), a self-administered questionnaire. Studies have documented a high diagnostic correlation with the 1990 ACR Criteria for fibromyalgia.
Expanding our treatment arsenal

Newer agents have proven useful in double-blind, placebo-controlled trials. These include gamma-hydroxybutyrate, pramipexole, and the anticonvulsants gabapentin and the newly FDA-approved pregabalin.

Non-drug treatments, including education, cognitive behavioral therapy and aerobic exercise, are equally important and efficacious. We will soon introduce a hybrid group visit/aerobic conditioning program for our fibromyalgia patients.


Dr. William Wilke specializes in drug treatment of rheumatoid arthritis, giant cell arteritis, polymyalgia rheumatica, fibromyalgia, chronic fatigue syndrome and Sjogren’s syndrome. Physicians may contact him at 216.444.5624 or at wilkew@ccf.org.

The scale offers a descriptive method for diagnosing fibromyalgia, recognizing it as a homogeneous symptom complex that includes diffuse pain and fatigue. It does not address sleep disturbance, headache, cognitive difficulties, irritable bowel and bladder, and orthostatic hypotension, all common in patients with fibromyalgia.

The magnitude of the SIS showed better statistical correlation with overall health than did the Health Assessment Questionnaire, Global Visual Analogue Scale or the Patient Activity Scale for factors such as mood, disability and accelerated mortality.

Addressing all contributing factors

The broad treatment strategy for fibromyalgia requires modification of the factors responsible for the pathologic mechanisms of central sensitization. These factors include distress, which usually takes the form of anxiety, depression and impaired mood; disordered sleep; and poor aerobic conditioning.

We identify factors for treatment using the SIS for diagnosis and severity, the Brief Patient Health Questionnaire-9 for depression and anxiety, the Mood Disorders Questionnaire (MDQ) to identify bipolar disorder, and the Epworth Sleepiness Scale to identify patients with primary sleep disorders.
Staff

Rheumatology Locations

Main Campus
9500 Euclid Ave./A50
Cleveland, OH 44195
216.444.5632

Beachwood Family Health and Surgery Center
26900 Cedar Road
Beachwood, OH 44122
216.839.3840

Independence Family Health Center
5001 Rockside Road
Crown Center II
Independence, OH 44131
216.986.4000

Solon Family Health Center
29800 Bainbridge Road
Solon, OH 44139
440.519.3003

Strongsville Family Health and Surgery Center
16761 SouthPark Center
Strongsville, OH 44136
440.878.2500

Westlake Family Health Center
30033 Clemens Road
Westlake, OH 44145
440.899.5555

Willoughby Hills Family Health Center
2570 SOM Center Road
Willoughby Hills, OH 44094
440.943.2500

Abby Abelson, MD
Interim Chair, Department of Rheumatic and Immunologic Diseases
Vice Chair of Education, Orthopaedic & Rheumatologic Institute
Specialty Interest(s): Osteoporosis in men and women, metabolic bone disease, Paget’s disease, steroid-induced osteoporosis, premenopausal low bone mass, transplant-related osteoporosis and low bone mass, rheumatoid arthritis, psoriatic arthritis, seronegative spondyloarthropathy

MAIN CAMPUS RHEUMATOLOGY/IMMUNOLOGY
Referrals: 216.444.5632 or 800.553.5056

General Rheumatology
Matthew Bunyard, MD
Director of Clinical Operations
Specialty Interest(s): Rheumatoid arthritis, spondyloarthropathies, psoriatic arthritis, gout

Soumya Chatterjee, MD, MS, FRCP
Specialty Interest(s): Scleroderma, rheumatoid arthritis, lupus, myositis

Carmen Gota, MD
Specialty Interest(s): Rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, psoriatic arthritis, ankylosing spondylitis, vasculitis, general rheumatology

Rula Hajj-Ali, MD
Specialty Interest(s): Systemic inflammatory diseases, uveitis, vasculitis, central nervous system vasculitis

Elaine Husni, MD, MPH
Vice Chair, Department of Rheumatic and Immunologic Diseases
Director, Arthritis and Musculoskeletal Treatment Center
Specialty Interest(s): Rheumatoid arthritis, osteoarthritis, psoriatic arthritis, use of complementary and alternative medicine for arthritis, health outcomes research
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<tr>
<th>Anna Koo, MD</th>
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<tr>
<td>Head, Section of Therapeutic Plasmapheresis</td>
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<td>Specialty Interest(s): Therapeutic apheresis, general rheumatology</td>
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<tr>
<th>Brian Mandell, MD, PhD</th>
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<tr>
<td>Professor and Vice Chairman, Department of Academic Medicine, Cleveland Clinic Lerner College of Medicine</td>
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<tr>
<td>Specialty Interest(s): Vasculitis, gout, systemic lupus, myositis, multi-system involvement in autoimmune disease</td>
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<th>Raymond Scheetz, MD</th>
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<tbody>
<tr>
<td>Specialty Interest(s): Metabolic joint disease, rheumatoid arthritis, lupus, relapsing polychondritis, myositis</td>
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<td>Specialty Interest(s): Drug treatment for rheumatoid arthritis, polymyalgia rheumatica, fibromyalgia, Sjogren’s syndrome</td>
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<tr>
<td>Leonard Calabrese, DO</td>
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<tr>
<td>R.J. Fasenmyer Chair in Clinical Immunology</td>
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<tr>
<td>Theodore F. Classen, DO, Chair in Osteopathic Research and Education</td>
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<tr>
<td>Specialty Interest(s): HIV/AIDS, vasculitis, hepatitis C</td>
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<th>Eamonn Molloy, MD, MS</th>
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<tr>
<td>Specialty Interest(s): Adult immunodeficiency, rheumatoid arthritis, vasculitis</td>
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<th>Osteoporosis and Metabolic Bone Diseases</th>
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<tr>
<td>Chad Deal, MD</td>
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<tr>
<td>Head, Center for Osteoporosis and Metabolic Bone Diseases</td>
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<tr>
<td>Specialty Interest(s): Osteoporosis, metabolic bone disease, steroid osteoporosis, connective tissue disease</td>
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<th>Bruce Long, MD</th>
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<tr>
<td>Specialty Interest(s): Osteoporosis and bone disorders, Vitamin D, autoimmune disorders, pharmacology</td>
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<th>Angelo Licata, MD, PhD</th>
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<tr>
<td>Clinical Trials Director</td>
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<td>Specialty Interest(s): Osteoporosis and metabolic bone diseases</td>
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<th>Pediatric Rheumatology</th>
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<td>Philip Hashkes, MD, MSc</td>
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<tr>
<td>Head, Center for Pediatric Rheumatology</td>
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<tr>
<td>Specialty Interest(s): Pediatric rheumatology, drug therapy for arthritis, periodic fever syndromes, pediatric vasculitis</td>
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<th>Steven J. Spalding, MD</th>
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<tr>
<td>Specialty Interest(s): Pediatric vasculitis, recurrent fever syndromes, juvenile arthritis</td>
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Rheumatologist Awarded a Second Endowed Chair

Leonard Calabrese, DO, holder of the R. J. Fasenmyer Chair in Clinical Immunology, has recently been awarded the Theodore F. Classen, DO, Chair in Osteopathic Research and Education. As Classen Chair, he will further research and graduate education at South Pointe Hospital as well as Cleveland Clinic. He is the first Cleveland Clinic physician to hold multiple endowed chairs.

Rheumatology Connections, published by Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases, provides information about state-of-the-art diagnostic and management techniques as well as current research.

Please direct any correspondence to:

Abby Abelson, MD
Interim Chair, Rheumatic and Immunologic Diseases
Cleveland Clinic/A50
9500 Euclid Avenue
Cleveland, Ohio 44195
Phone: 216.444.3876
Email: abelsona@ccf.org

Managing Editor: Cora M. Liderbach
Art Director: Irwin Krieger
Photographers: Tom Merce, Willie McAllister

Rheumatology Connections is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered, and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

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Specialty Interest(s): Pediatric vasculitis, recurrent fever syndromes, juvenile arthritis

Alexandra Villa-Forte, MD, MPH  
Specialty Interest(s): Vasculitis, lupus

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Alexandra Villa-Forte, MD, MPH  
Specialty Interest(s): Vasculitis, lupus

REGIONAL RHEUMATOLOGY

Cleveland Clinic  
Beachwood/ 216.839.3840  
Howard Epstein, MD  
Specialty Interest(s): Lupus, rheumatoid arthritis, osteoarthritis, tendonitis, gout, polymyositis, ankylosing spondylitis

Cleveland Clinic  
Independence/216.986.4000  
Alla Model, MD  
Specialty Interest(s): General rheumatology, rheumatoid arthritis, osteoporosis, women’s health

Cleveland Clinic  
Solon/440.519.3003  
Chad Deal, MD  
Head, Center for Osteoporosis and Metabolic Bone Diseases  
Specialty Interest(s): Osteoporosis, metabolic bone disease, steroid osteoporosis, connective tissue disease

Rajul M. Desai, MD, MPH  
Specialty Interest(s): General rheumatology, scleroderma and related disorders

Rochelle Rosian, MD  
Specialty Interest(s): Rheumatology, general internal medicine

Cleveland Clinic Strongsville/440.878.2500  
Elizabeth File, MD  
Specialty Interest(s): General rheumatology, osteoporosis, metabolic bone disease

Cleveland Clinic Westlake/440.899.5555  
Judith Manzon, MD  
Specialty Interest(s): General rheumatology, rheumatoid arthritis, osteoarthritis

Susan Mathai, MD  
Specialty Interest(s): General rheumatology, arthritis, lupus, gout, myositis

Cleveland Clinic Willoughby Hills/440.943.2500  
Janice Granieri, MD  
Specialty Interest(s): General rheumatology, including lupus, rheumatoid arthritis, osteoporosis, Sjogren’s syndrome, osteoarthritis, soft-tissue rheumatic conditions

Jeffrey Wisnieski, MD  
Specialty Interest(s): General rheumatology evaluation and management, infusion therapy for osteoporosis, rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, Crohn’s disease, ulcerative colitis

For our most current directory of Cleveland Clinic rheumatologists and their practice locations, please visit clevelandclinic.org/staff.
The new Arthritis and Musculoskeletal Treatment Center is leading efforts to integrate patient care, clinical research and teaching within the Cleveland Clinic Orthopaedic & Rheumatologic Institute. The center serves as the focal point at Cleveland Clinic for the expert diagnosis and treatment of patients with all types of arthritis and musculoskeletal diseases. Some of the conditions we see include:

- rheumatoid arthritis
- psoriatic arthritis
- osteoarthritis
- tendonitis
- bursitis
- soft-tissue injuries
- knee pain
- hip pain
- simple fractures

Appointments and visits in the state-of-the-art facility are streamlined for patients, who can enjoy access to novel therapies and skilled, compassionate care from physicians and arthritis care providers familiar with their needs.

Joining forces to improve care
An important part of our mission is collaborative orthopaedic and rheumatologic care for individuals with arthritis and musculoskeletal disorders. Our faculty of office-based orthopaedic surgeons, rheumatologists, physical and occupational therapists, and musculoskeletal radiologists works closely with nutritionists, specially trained nurses and patient educators. This multidisciplinary team will also focus on the development and application of new diagnostics and therapeutics.

Sharing knowledge
Education is another part of the center’s mission as our faculty train future investigators and healthcare professionals, and heighten public awareness of arthritis and musculoskeletal diseases.

For information or to refer a patient to the Arthritis and Musculoskeletal Treatment Center, please call 216.445.3330.