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Dear Colleague,

I am delighted to share with you this latest issue of *Rheumatology Connections*, which spotlights some of the most notable developments in research and clinical practice taking place in Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases.

One of this issue’s themes is the benefit that multidisciplinary collaboration brings to the patient experience. Such collaboration is the centerpiece of Dr. Soumya Chatterjee’s report (p. 10) of a complex patient with antisynthetase syndrome whose diagnosis and management required the pooled expertise of our combined rheumatology/pulmonary clinic. Teamwork with our pulmonary medicine colleagues is likewise a focus of Dr. Carol Langford’s compelling review (p. 4) of four patients whose cavitary lung lesions may or may not have been the result of active granulomatosis with polyangiitis (GPA) (Wegener’s).

Collaboration across disciplines is also evident in Dr. Elaine Husni’s report (p. 13) on her ongoing trial of viscosupplementation to optimize physical therapy for knee osteoarthritis, a study in which she is partnering with colleagues from orthopaedics and sports health. And collaboration on the clinical front is highlighted in Dr. Matthew Bunyard’s profile (p. 11) of his activities in expanding the musculoskeletal ultrasound expertise in our Arthritis Center in conjunction with a physician from Cleveland Clinic’s Department of Rehabilitation Medicine.

These and other contributions to the issue also underscore the diversity of our specialty and our department’s wide-ranging clinical and research activities. Dr. Gary Hoffman launches the issue with an elegant discussion (p. 3) of his research exploring whether giant cell arteritis (GCA) and Takayasu’s arteritis are a continuum of the same disease. Dr. Bruce Long shares a richly practical overview (p. 6) of how our Center for Osteoporosis and Metabolic Bone Disease works to optimize bone health in transplant recipients at Cleveland Clinic. And Dr. Chad Deal profiles our work to enhance our electronic medical record’s ability to consistently follow our patients and provide validated data for clinical research with our innovative iVHR, or integrated visual health record (p. 8).

It is my honor to share the work of my colleagues with you in this issue, which underscores what an exciting time it is to be a rheumatologist. I hope you share that excitement, and I welcome your questions, comments and input on our programs and activities.

Sincerely,

Abby Abelson, MD
Chair, Rheumatic and Immunologic Diseases

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Cleveland Clinic’s Rheumatology Program is ranked among the top 3 in the nation in *U.S. News & World Report*’s “America’s Best Hospitals” survey.
Emerging evidence suggests that giant cell arteritis (GCA) and Takayasu’s arteritis (TAK) may be a continuum of the same illness. This article reviews their commonalities and differences and shares insights on this question from ongoing Cleveland Clinic research.

**Giant Cell Arteritis**

GCA is the most common form of vasculitis among adults older than age 50. It is most often recognized in white individuals, especially those living in northern latitudes. Incidence rates among people older than 50 years vary from 30 to 70 cases per 100,000 in Scandinavia to less than 10 per 100,000 in southern Europe and about 1 to 2 per million in Asia. GCA is highly uncommon among blacks (0.4/100,000/year). The median age in most series is about 70 to 75. There is a clear gender bias, with women affected about three to four times more often than are men.

**Takayasu’s Arteritis**

TAK is similar to GCA in many ways, yet different in others. The most obvious difference is age. The median age at TAK onset is 25 to 30. TAK has a similar but more striking gender bias, with females affected at least eight times more often than are males. While much of the TAK literature has emphasized a predilection for Asians, recent reports that reflect diverse racial and ethnic populations (e.g., in Italy, France, South Africa, Mexico, South America and the United States) have raised questions about the accuracy of this perceived predominance among Asians.

Demographic features of patients and disease manifestations between cohorts can vary considerably. In TAK cohorts in Japan, Korea, the United States, France and Italy, females account for 80 percent or more of patients, while in India females make up just over 60 percent of those affected. In Japan almost all patients are Asian; in the U.S. and Italy patients are predominantly white; and in Africa they are almost entirely black.

**Comparing Clinical Profiles**

Can one effectively argue that these diseases are indeed a continuum of the same illness? Most agree that the age boundaries for what is called either GCA or TAK are arbitrary. Many investigators ignore this parameter.

Both GCA and TAK involve the aorta and its primary branch vessels, with the most frequent lesions being within the thoracic aorta and its arch vessels. Imaging studies have revealed marked overlap in disease topography (Figures 1 and 2). Postmortem studies in GCA have shown histological evidence of active disease in vessels of the same caliber and distribution as in TAK, although stenoses and aneurysms are far less common in life in GCA. Both GCA and TAK are very responsive to corticosteroid therapy, and both have high rates of relapse, leading many authorities to believe that neither of these diseases is self-limiting.

**Skewed Phenotypes of a Single Disease?**

In our own studies comparing diseases, the same standard interview tool, examination and vascular imaging protocol were applied to all patients. While similarities were common, a greater frequency of certain findings was noted in GCA, including jaw claudication, visual loss or aberration, and scalp tenderness. Conversely, pulselessness, blood pressure asymmetry and bruits were more common in TAK.

These findings have led us to suggest that these may not be separate diseases but rather skewed phenotypes of a single disease, influenced by genetic background, age-related structural changes, immunologic senescence and environmental triggers. Definitive proof of that hypothesis is the focus of our ongoing research.

*Dr. Hoffman is a member of the Department of Rheumatic and Immunologic Diseases and the Center for Vasculitis Care and Research. He is Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He can be reached at 216.445.6996 or hoffmag@ccf.org.*
Confounding Cavities

By Carol A. Langford, MD, MHS

Cavitating lung nodules are defined radiographically as a lucency within the lung tissue that may or may not contain a fluid level and that is surrounded by a wall of varied thickness. Pulmonary cavities occur commonly in granulomatosis with polyangiitis (GPA) (Wegener’s). However, while a lung cavity may develop as a result of active disease in a patient with GPA, other causes must also be considered, as exemplified by the following cases from our institution.

Case 1
A 55-year-old man with GPA on maintenance mycophenolate mofetil presented with palpable purpura and sinonasal symptoms that included increased epistaxis and nasal crusting. Despite a lack of chest symptoms, computed tomography (CT) was performed and revealed cavitary lung disease (Figure 1). Following a bronchoscopy that was negative for infection, induction therapy with prednisone and methotrexate was started, and the patient had complete resolution of the cavity on follow-up imaging.

Case 2
A 22-year-old man with GPA on maintenance methotrexate developed streaky hemoptysis and was found to have worsening cavitary lung lesions. After a bronchoscopy was negative for infection, induction therapy with prednisone and cyclophosphamide was started. After initial improvement, the patient was transitioned to azathioprine, after which the pulmonary cavities grew (Figure 2). Bronchoscopy now revealed Aspergillus fumigatus. After treatment with antifungal therapy, the cavitary lesions improved. The patient subsequently developed a relapse of GPA and has done well on rituximab combined with voriconazole.

Case 3
A 66-year-old man had a history of GPA that originally presented with sinus disease, alveolar hemorrhage, pauci-immune crescentic glomerulonephritis and a positive myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA). While on maintenance azathioprine, he developed a harsh productive cough with a new cavitary lung lesion without evidence of active disease involving other organs (Figure 3). A sputum culture grew Mycobacterium avium complex (MAC), and the patient was started on antimicrobials. Despite this treatment, the lesion worsened. Bronchoscopy was negative for MAC or other infection with an unremarkable cytologic examination. A thoracoscopic biopsy revealed a poorly differentiated non-small-cell lung carcinoma.
Case 4

A 36-year-old woman was diagnosed with GPA after presenting with massive pulmonary cavities and subglottic stenosis (Figure 4). Confirmatory histology was obtained from subglottic and transbronchial biopsies, and she had positive proteinase 3 ANCA. She was treated with prednisone and cyclophosphamide with initial improvement. After eight weeks she developed increased cough and fever. While some cavities had improved, others had enlarged and developed satellite lesions (Figure 5). Bronchoscopy was performed twice and did not reveal infection. Surgical biopsy was considered but carried a high risk due to the size of the cavities. After discussion with pulmonary and infectious disease consultants, the patient received broad empiric treatment for bacterial and fungal organisms. After four weeks of antimicrobial therapy during which her lesions stabilized but did not improve, she was treated with rituximab. Her CT findings gradually improved (Figure 6 shows the same area of lung parenchyma as in Figure 5), allowing reduction in prednisone and discontinuation of the antimicrobials.

Discussion

Cavitary lung lesions carry a broad differential diagnosis that includes the following in addition to vasculitis: neoplasm, embolism with infarction, pulmonary sequestration, bullae/cysts with fluid, bronchiectasis and a wide spectrum of infections ranging from aerobic and anaerobic bacteria to mycobacteria and fungi. Even in patients who have a firmly established diagnosis of GPA, cavities may not always be the result of active disease. It is also possible, particularly in an immunosuppressed patient with GPA, for two causes to be present in which a cavity formed by active disease becomes superinfected.

As seen in the cases profiled here, cavitary lung disease in GPA can present with cough, hemoptysis, dyspnea, pleuritic chest pain or even no symptoms, as in Case 1. The development of a new cavity should prompt a careful assessment for active disease in other organ sites. Even when this is found, however, evaluation should be performed to rule out infection prior to aggressive immunosuppression. If no infection is found and the patient is treated for GPA, cavities must be monitored radiographically to confirm that they respond to therapy. A cavity that worsens with immunosuppression should heighten concern for a superimposed process. In some instances, bronchoscopy may reveal an organism, as in Case 2, or a surgical biopsy may be required, as in Case 3.

There are currently no factors short of microbiologic and histologic analysis that can determine whether a cavity in a patient with GPA may be due to another cause. Characteristics of the cavity such as wall thickness, intracavitary fluid/material, fever, acute-phase reactants or ANCA are not helpful in this regard.

Pulmonary cavities in patients with GPA can be very treatment-responsive, as in Case 1. When their course is complex, detection and treatment of the contributing factors can bring about a reduction in cavitary size and clinical improvement.

These cases highlight how multidisciplinary collaboration at Cleveland Clinic — among rheumatologists, pulmonologists, radiologists, thoracic surgeons and infectious disease experts — yields benefits for the assessment and management of GPA patients who have complex cavitary pulmonary disease.

Dr. Langford is Director of the Center for Vasculitis Care and Research as well as Vice Chair for Research for the Department of Rheumatic and Immunologic Diseases. She can be reached at 216.445.6056 or langfoc@ccf.org.
Optimizing Bone Health in Transplant Patients

By Bruce Long, MD

If you have a busy rheumatology practice, don’t be surprised if one of your next patients is an organ transplant recipient or candidate asking for advice about a related complication such as osteoporosis. According to the U.S. Department of Health and Human Services, 79 Americans receive organ transplants every day. More than 400 organ transplants are performed yearly at Cleveland Clinic. For patients with end-stage organ failure, transplantation is now a well-accepted option for a second chance at life.

Changes in bone health in transplant recipients may not present as dramatically as a cyclosporine-related gout attack, but they are still serious, can develop rapidly and may lead to osteoporosis with resulting fractures, debility and death. Interventions to optimize bone health in organ transplant recipients enhance these patients’ survival and quality of life.

Many Reasons for Increased Bone Risk
The reasons for low bone mass in transplant recipients include factors present before transplant, such as those associated with the underlying disease, inflammation, treatments and chronic illness, as well as post-transplant factors, most notably anti-rejection medications.

Persons ill enough to need an organ transplant often already have significant bone disease (see box on page 7 for examples). In addition, transplant candidates are generally too sick for vigorous physical activity, so they miss out on exercises to promote balance and bone strength. Of course, the traditional osteoporosis risk factors — age, family history, hormonal status, nutrition, and other secondary diseases and medications — may further contribute to low bone mass. Prior osteoporosis could even affect the transplant procedure. The kyphosis or loss of rib-to-pelvis space from multiple vertebral compression fractures can, if severe enough, prevent the allograft from fitting in the available space.

The most commonly used anti-rejection medicines that adversely affect bone are prednisone, tacrolimus and cyclosporine. Based on experimental models, mycophenolate mofetil, azathioprine and sirolimus are not thought to cause bone loss.

Glucocorticosteroids adversely impact bone in several ways. They stimulate osteoclasts, inhibit osteoblasts, increase apoptosis of osteoblasts and osteocytes, decrease gonadotropins, reduce calcium intestinal absorption and enhance renal calcium excretion. Glucocorticosteroids’ effect on bone loss is most pronounced in the first few months of use.

The contribution of tacrolimus or cyclosporine to bone loss in humans is less clear, as any effect is confounded by the fact that these agents are often given with prednisone. Studies have been largely confined to experimental animals. Both tacrolimus and cyclosporine are calcineurin inhibitors whose effects are mediated by T lymphocytes. In rat models, there is rapid cancellous bone loss after exposure to these drugs.
Cleveland Clinic’s Approach
At our Center for Osteoporosis and Metabolic Bone Disease, we like to see patients before their transplant and as needed thereafter to optimize their bone health. This includes a visit shortly after the transplant to make sure they are on a good bone health program, because bone mass can decline rapidly in the first year after transplant.

We begin with a history and physical exam followed by bone mineral density (BMD) measurement of the spine and hip by dual-energy X-ray absorptiometry (DXA) (Figure 1). Key points of the history include assessment of risk factors for osteoporosis and falls — based on a review of medications, a detailed dietary calcium evaluation and assessment for underlying conditions associated with metabolic bone diseases — and consideration of other risk factors or past events that would influence choice of anti-resorptive or anabolic agents.

During the exam, we especially evaluate height, posture, spinal configuration, balance, strength, and signs of previous fractures or of underlying metabolic conditions that may affect bone. The latter include overactive thyroid, hypogonadism, connective tissue disorders and inflammatory diseases. Additional studies are influenced by the underlying disease state and risk factors but usually involve a blood count and chemistry panel to assess calcium and alkaline phosphatase levels; renal, liver and thyroid function; and levels of phosphorus, parathyroid hormone, vitamin D, serum markers of bone formation and urine markers of bone degradation. We discuss bone physiology and how the patient’s disease and risk factors may contribute to changes in bone status, as well as the transplant’s likely effect on bone.

The individual’s bone health therapy depends on the needs identified from this assessment. Most patients need calcium and vitamin D supplements, although dietary calcium intake must be accounted for to avoid prescribing excessive amounts. We usually recommend a weight-bearing exercise program and, if needed, therapies to improve strength and balance. If the BMD measurement reveals osteoporosis, or if the patient has a history of fragility fractures, is taking a significant glucocorticosteroid dose or has other significant risks, we add an appropriate anti-resorptive or anabolic medication after discussing its use and potential side effects with the patient.

Our priority for transplant recipients is to maintain the quality of life for these patients who have been given a second chance. Because of the threat that osteoporosis can pose, the early interventions we offer to optimize bone health make our center an integral part of these patients’ care team.

Dr. Long, a staff physician in the Center for Osteoporosis and Metabolic Bone Disease, has an interest in bone disorders of organ transplant patients. He can be reached at 216.444.3864.

Common causes of existing bone disease in transplant candidates
- Patients with severe chronic obstructive pulmonary disease (COPD) may have bone changes due not only to COPD’s systemic inflammation but also to tobacco, vitamin D deficiency and glucocorticosteroids.
- Cystic fibrosis patients have additional risk factors related to malabsorption and hypogonadism.
- Renal transplant patients often have renal osteodystrophy with hyperparathyroidism.
- Patients with alcoholic liver cirrhosis may have low bone density from the actions of alcohol, malnutrition, inadequate vitamin D conversion and hypogonadism.
- Patients with primary biliary cirrhosis may retain toxins that affect osteoblast function.
- Heart transplant candidates with severe cardiomyopathies often are on loop diuretics and have decreased renal function, vitamin D deficiency and secondary hyperparathyroidism, all of which are associated with bone loss.

Bone mass can decline rapidly in the first year after transplant, so a visit shortly after transplantation is recommended to make sure patients are on a good bone health program.
Every physician who works with the electronic medical record (EMR) knows that many of its features facilitate patient care. However, for organizing and evaluating clinical information, it may not work exactly the way you want. The EMR should enable quick and efficient organization of patient data in a format that allows easy and rapid evaluation of disease status and patient outcomes. An ideal EMR system would allow healthcare providers to assemble the complex data from all parts of the medical record, integrate patient-reported data and display the information in a format that allows rapid visual assessment of patient status. The result would be more time spent with each patient making medical decisions and less time spent on electronic documentation. That translates to improved patient care.

To move closer to that ideal, Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases is in the process of developing an integrated visual health record (iVHR) that combines patient-collected and physician-collected data with the functionality of the EpicCare EMR (Epic). The system assembles information from patients, the EMR and physicians and visually displays this information during the patient visit while trending data from past encounters.

The development of iVHR was made possible by an innovative program that allows real-time interaction between a Web service and Epic and is an integral part of a Cleveland Clinic spin-off company also known as iVHR. Our development of iVHR followed conversations and consultations with multiple other centers that are working to make their EMR a more efficient and effective tool in the clinical setting, including Dr. Eric Newman and his colleagues at the Geisenger Clinic.

**How iVHR Works**

The patient-supplied data are entered into iVHR via validated questionnaires completed by the patient on a touch-screen tablet device prior to the appointment. This allows a comprehensive review of patient status, eliminates manual data entry and allows caregivers to review the data before entering the exam room. Self-reported health status, quality-of-life measures, assessments of functional status and a complete review of systems can be entirely or almost entirely collected while the patient is in the waiting room. iVHR automatically scores patient-validated functional outcomes and quality-of-life measures, making the data available to the physician at the time of the visit and storing it for future use.

A visual display or “dashboard” is created from the patient questionnaires, presenting lab data from Epic in real time and information from the clinic note, as well as displaying key elements critical for evaluating important patient data. Clinic notes are structured using “discrete elements” designed to capture and display parameters that are important for assessing patient status and quality indicators.
Disease-Specific Questionnaires
Each patient will answer a core set of questions, but the system allows for tailored disease-specific questions that allow patients with, for example, rheumatoid arthritis, vasculitis or osteoporosis to answer targeted questions that are important and unique to their disease process. This disease-specific functionality can make it possible for providers to assess patient response to therapy.

iVHR will allow patients who have Internet access to complete their questionnaires before their appointment date using MyChart, Cleveland Clinic’s interactive personal health record, via a secure Web connection. This will reduce time spent in the waiting room and improve efficiency.

The standardized electronic data collection developed for iVHR will allow storage, retrieval and reporting of patient data for outcomes and quality measures. This system will make the EMR work for healthcare providers by shifting time spent on documentation to decision-making and by streamlining and improving care delivery. We are confident it will make the EMR work for patients as well by leading them to be more informed about their healthcare and by improving patient outcomes.

Dr. Deal is Director of the Center for Osteoporosis and Metabolic Bone Disease. He also serves as Vice Chair for Quality and Outcomes in the Department of Rheumatic and Immunologic Diseases. Physicians may contact him at 216.444.6575 or dealc@ccf.org.
Case Study:
A Patient with Proximal Myopathy, Cough and Progressive Shortness of Breath on Exertion

By Soumya Chatterjee, MD, MS, FRCP, FACP, FACR

Presentation
A 66-year-old man was initially seen in our rheumatology clinic with a five-month history of polyarthralgia associated with swollen fingers, wrists and knees as well as significant early-morning stiffness. He also developed progressive proximal myopathy. He had no fever, chills, headaches, dysphagia or sicca symptoms. In a few months, he developed progressive shortness of breath on exertion and a nonproductive cough.

Evaluation
He had a positive ANA (5.7 OD ratio [normal, < 1.5]) and a positive Jo-1 antibody (antibody to histidyl transfer RNA synthetase). His creatine kinase was 700 U/L (normal, 30-220). EMG was consistent with a necrotizing myopathy. On pulmonary function testing, his forced vital capacity was 80 percent of predicted and his carbon monoxide diffusing capacity was 67 percent of predicted. Thoracic high-resolution CT scan revealed evidence of interstitial lung disease (ILD) characterized by bilateral patchy ground-glass opacities suggestive of active alveolitis, most extensive at the lung bases (Figure 1). A few months later, the skin of the tips and radial margins of his fingers started thickening and cracking, matching the classic description of “mechanic’s hands.”

Diagnosis
The patient was seen in our combined rheumatology/pulmonary clinic and bronchoscopy was arranged. Bronchoalveolar lavage indicated alveolitis with pathologic changes on biopsy consistent with organizing pneumonia. All cultures were negative. The constellation of manifestations, including inflammatory muscle disease, ILD, mechanic’s hands and inflammatory polyarthritis, along with positive antibodies to histidyl transfer RNA synthetase (Jo-1 antibody), confirmed the diagnosis of antisynthetase syndrome.

Management
The patient was started on daily oral cyclophosphamide along with high-dose oral prednisone. The dose of cyclophosphamide was gradually increased with close monitoring of his complete blood count. There was substantial improvement in proximal muscle strength, and his creatine kinase normalized (66 U/L) in a few months. However, the cyclophosphamide dose had to be further increased because repeat bronchoscopy still showed active alveolitis. Subsequently, his ILD improved and his exertional dyspnea, pulmonary function test results and thoracic high-resolution CT scan all showed significant improvement. Because his condition was in remission, cyclophosphamide was discontinued after 12 months and he was started on a maintenance immunosuppressive regimen of oral methotrexate 15 mg weekly along with prednisone.

Comment
This case is a good example of high-complexity medical decision-making. It should be recognized that important and often lifesaving management decisions about rare and complex conditions such as this frequently have to be based on expert opinions alone, as well-designed randomized controlled trials are often not available. It is imperative that cases like this be managed jointly by a rheumatologist and a pulmonologist.
Our combined rheumatology/pulmonary clinic makes such close collaboration possible. In this clinic, decisions about the investigation and management of complicated cases like this can be made in conjunction by two different subspecialists who can combine their respective perspectives. Patients appreciate getting collaborative opinions about their care from specialists with distinct areas of expertise who are experienced in managing different aspects of their disease. Moreover, rheumatology trainees benefit from the unique opportunities to learn about the methods involved in such complex decision-making and from the abundant opportunities for fellowship research projects.

Dr. Chatterjee runs Cleveland Clinic’s rheumatology/pulmonary clinic with staff pulmonologist Joseph Parambil, MD, who has a special interest in autoimmune rheumatic disease-associated interstitial lung disease and pulmonary hypertension. This clinic integrates evidence-based care with clinical and translational research on the complex pathogenesis and management of rheumatic diseases affecting the lung. Dr. Chatterjee can be contacted at 216.444.9945 or chattes@ccf.org.

Figure 1. Thoracic high-resolution CT scan in a 66-year-old man with interstitial lung disease and fibrosis associated with antisynthetase (anti-Jo-1) syndrome. Note the bilateral patchy ground-glass opacities suggestive of active alveolitis, most extensive at the lung bases, along with bilateral subpleural reticular infiltrates and interlobular septal thickening.

Figure 1. Thoracic high-resolution CT scan in a 66-year-old man with interstitial lung disease and fibrosis associated with antisynthetase (anti-Jo-1) syndrome. Note the bilateral patchy ground-glass opacities suggestive of active alveolitis, most extensive at the lung bases, along with bilateral subpleural reticular infiltrates and interlobular septal thickening.

Musculoskeletal Ultrasound: Expanding Its Use as Its Indications Grow

By Matthew P. Bunyard, MD, FACR

Cleveland Clinic is one of a limited number of academic rheumatology programs nationwide to participate in the American College of Rheumatology’s (ACR) recent “Train the Trainer” pilot program in musculoskeletal ultrasound (MSUS). Our participation has enabled us to bolster the MSUS offerings in our Arthritis Center and enhance collaborative care within Cleveland Clinic’s Orthopaedic & Rheumatologic Institute.

Benefits of Ultrasound in Rheumatology

MSUS has become an established imaging technique for many articular and periarticular musculoskeletal conditions. Ultrasound is arguably the imaging modality of choice for tendon, bursa, synovium and joint effusion. It can be a valuable complementary clinical tool for enhancing musculoskeletal practitioners’ diagnostic abilities, procedural skills and management decisions. As in obstetrics, urology and cardiology, ultrasound in the context of musculoskeletal disease has the benefit of being a real-time and natural extension of the physical examination.

Other advantages include its portability, noninvasiveness and avoidance of radiation exposure, as well as the fact that it is multiplanar, repeatable and relatively inexpensive (especially compared with MRI).
Figure 1. Musculoskeletal ultrasound (MSUS) findings in a 54-year-old man with joint pain in the hand and possible inflammatory arthropathy. He was seronegative and radiographs were normal, but MSUS examination of his left second metacarpophalangeal joint revealed an erosion of bone at the dorsal surface of the second metacarpal head (arrows). The erosion was confirmed on orthogonal views.

Multiple studies have documented that MSUS-guided injections in joint and soft tissue structures compare favorably with other injection-guidance methods in terms of both accuracy and outcomes. Additional studies in patients with rheumatoid arthritis reveal that MSUS can demonstrate subtle synovitis not confirmed on physical exam and bony erosions not visualized on plain radiography (Figure 1).

The ‘Train the Trainer’ Impetus
Over the last decade, Europe has led the way in the use of MSUS by radiologists and nonradiologists alike. In the United States, there is a growing interest among private practice and academic musculoskeletal medicine clinicians (rheumatologists, orthopaedists, physiatrists and sports medicine specialists) to integrate MSUS into their own practices.

Recognizing that many academic rheumatology programs lack staff trained in MSUS, the ACR piloted its Train the Trainer project in 2011 with the goal of ensuring that participating locations have an identified MSUS expert who can then train his or her department’s fellows and other colleagues in MSUS use. The project has been administered in concert with the Ultrasound School of North American Rheumatologists (USSONAR), a training program run by physician faculty who are leaders in rheumatology-based MSUS.

I had the privilege of being selected by the ACR as one of 30 inaugural Train the Trainer “student educators.” The curriculum is largely Web-based and consists of online reading and quizzes. Written and video resources are also available. Case scans submitted by the student educators are reviewed and graded online by the faculty. The centerpiece is a three-day MSUS course with live model and cadaver practice, and a final exam caps off the nine-month-long training. Completion of the curriculum is a significant time commitment for any clinician.

With the completion of this formal MSUS training, I have joined my colleague, Michael Schaefer, MD, a physiatrist who practices in our Arthritis Center, in offering MSUS services and serving as an MSUS educator for our colleagues and fellows. Under the collaborative model of Cleveland Clinic’s Orthopaedic & Rheumatologic Institute, our Arthritis Center draws on the multidisciplinary expertise of three rheumatologists, a physiatrist and two nonoperative orthopaedists. In addition to MSUS-guided injections, we offer diagnostic MSUS services, and I am now expanding the use of MSUS beyond our Arthritis Center into our Rheumatology Clinic.

Looking Ahead
Our current use of MSUS focuses on improving and expediting diagnoses, enhancing disease monitoring and improving injection accuracy. The general scope of use is likely to expand, especially as additional advanced biologic therapies are developed for musculoskeletal conditions, as MSUS might have a role in ensuring their optimal delivery to target locations.

For now, the greatest limitation to MSUS use is provider skill level, especially in diagnostic assessment. The absence of official certification criteria is also an impediment, although the ACR’s Train the Trainer initiative is an important step forward. We are eager to disseminate the use of this valuable clinical tool more broadly among our staff and fellows and ultimately to assess its effect on patient outcomes.

Dr. Bunyard is Director of Clinical Operations for the Department of Rheumatic and Immunologic Diseases and is one of the Arthritis Center rheumatologists. He can be reached at 216.445.3460.
Optimizing Physical Therapy for Knee OA
With and Without Viscosupplementation

By M. Elaine Husni, MD, MPH

Despite an abundance of studies on the various treatment modalities for osteoarthritis (OA) of the knee, there is little consensus on how best to implement these therapies and in what order. To help address this question, I have teamed with Cleveland Clinic colleagues in sports medicine, rehabilitation and orthopaedics to study the efficacy of viscosupplementation in patients with knee OA requiring standardized physical therapy. This article reviews the rationale for our multidisciplinary investigation and what we hope to learn.

The Challenge of Promoting Pain-Free Exercise
Physicians can choose from a multitude of OA treatment options: medications (acetaminophen, NSAIDs, narcotics); therapy (physical, occupational); braces, splints or other medical devices; intra-articular injections (cortisone and viscosupplementation); and surgical intervention (arthroplasty, osteotomy).

First-line treatment for patients with OA is exercise rehabilitation, self-management and weight reduction, if applicable. Regular exercise, particularly if focused on the target joint, may be of great benefit in providing transient relief of OA pain and improved function. Rehabilitation (treatments that increase flexibility, range of motion, endurance and quadriceps/hamstring strength) may help to increase functional ability and improve quality of life in persons with OA. However, the magnitude and progression of the therapy regimen can be limited by the patient’s pain, as can patient adherence to therapy.

Persistent knee pain in persons with OA is the single biggest barrier to exercise, and it reduces the patient’s ability to participate in aggressive strength training in physical therapy programs. If pain can be managed, the efficacy of physical therapy interventions aimed at improving function and quadriceps strength may increase. Adequate pain relief may be essential for adherence to and proper execution of physical therapy; specifically, increasing functional outcomes may be critical to postponing the end stages of OA and the need for total joint replacement.

Debate Surrounds Efficacy of Viscosupplementation
Viscosupplementation is a treatment for OA pain relief that involves injection of a hyaluronic acid preparation into the knee joint. Hyaluronic acid is a naturally occurring substance found in the synovial fluid. This technique was approved by the FDA in 1997 and was used in Europe and Asia for several years before that.

Many clinical studies have demonstrated that viscosupplementation (hyaluronic injections) can reduce pain and improve function for up to six months in patients with mild to moderate knee OA. However, critics note that the studies have been limited by poor effect size, small sample size or lack of generalizability. There is also a lack of consensus on whether viscosupplementation is more or equally effective than cortisone injections.

Synvisc-One® (hylan G-F 20), approved by the FDA in February 2009, is an elastoviscous high-molecular-weight fluid containing hylan polymers. These polymers are derivatives of hyaluronic or sodium hyaluronate produced from chicken combs. Synvisc-One is administered as a single 6-mL intra-articular injection. It has been associated with reducing knee OA pain for up to 26 weeks, potentially resulting in fewer patient visits due to knee OA and lower overall treatment costs.

The biologic rationale for the therapeutic use of synthetic hyaluronic acid in knee OA was its potential to increase the viscosity of synovial fluid. Numerous clinical trials reported multiple benefits in knee OA pain and function, compared with placebo. This raised questions about the magnitude of the therapeutic effects of hyaluronic acid products.

Prospective Study of Viscosupplementation
Plus Physical Therapy
In light of these questions, we have joined with colleagues from Cleveland Clinic’s Department of Orthopaedic Surgery and Center for Sports Health to undertake a prospective study to assess whether adjunctive use of Synvisc-One will improve outcomes such as pain and function, measured by the Knee injury and Osteoarthritis Outcome Score (KOOS), in patients with primary knee OA requiring standardized physical therapy. Our goal is to determine whether Synvisc-One augments physical therapy adherence and performance, and thereby results in improved outcomes (including function and pain), compared with standardized physical therapy alone.

We will use a prospective, randomized, double-blind (one injector/one blinded observer) study design with a control group that receives sham needle injections. The study will be conducted at multiple locations across Cleveland Clinic (Cleveland and Florida). After meeting inclusion criteria, patients with primary knee OA pain will be randomly assigned to an intra-articular injection of Synvisc-One or a sham needle insertion in addition to standardized PT. We look forward to sharing results as the study proceeds.

Dr. Husni is Vice Chair of the Arthritis and Musculoskeletal Center and Director of Clinical Outcomes Research for the Department of Rheumatic and Immunologic Diseases. She is the principal investigator of the study described here and has a strong research interest in musculoskeletal issues. She can be reached at 216.445.1853 or husnie@ccf.org.
Cleveland Clinic rheumatology fellows are traveling the world this year — from Chicago to Berlin — to present research projects of their own and to gain critical exposure to the latest research advances in our field.

Research is central to Cleveland Clinic’s rheumatology fellowship program, as we are committed to helping our trainees become critical thinkers in research methodology. In light of the limited number of training programs that prepare physicians for independent research careers, we have focused our fellowship program on fostering physician-scientists who will be prepared to help develop and evaluate the rheumatologic remedies of tomorrow.

Rheumatology Fellows Research Review Committee
A centerpiece of this focus is our recently developed Rheumatology Fellows Research Review Committee. Although much training still takes place informally between individual mentors and mentees, this committee provides a more formal process for mentoring — and one with an explicit research orientation and implementation plan.

The committee meets every three to four months specifically to review the fellows’ research projects. It is led by Elaine Husni, MD, MPH, and includes five other members of the Department of Rheumatic and Immunologic Diseases staff: Department Chair Abby Abelson, MD; Soumya Chatterjee, MD; Chad Deal, MD; Gary Hoffman, MD, MS; and Carol Langford, MD, MHS.

These senior staff members provide feedback to the fellows and mentor them on the clarity of their hypotheses, their proposals’ feasibility, their potential impact on the field, and budget and compliance issues. Research proposals require advance approval by the committee, and fellows are expected to carry out an original research idea rather than piggybacking on a research project with a senior staff member. Committee sessions are organized both to help first-year fellows with initiating a successful project and to assist second-year fellows in ensuring implementation and follow-through to abstract or manuscript submission.

“The Rheumatology Fellows Research Review Committee has been instrumental in providing valuable advice and guidance throughout my research projects,” says Chang Lin, MD, a current fellow. “It helped me in producing quality research that has been presented at national rheumatology meetings.”

Since the committee’s inception, both the number (Figure 1) and the quality of abstract presentations and article publications by our fellows have increased.

Relevant Regardless of Background
Because physicians can enter the fellowship from any of several stages of their professional lives — straight from medical residency, after being in clinical practice, or after some advanced training such as a PhD or MPH program — the program aims to make research relevant regardless of the fellow’s background.

“Our approach helps ensure that we can meet the need for physician-scientists who are armed with excellent clinical skills and a meaningful research experience,” explains Dr. Husni, Director of Clinical Outcomes Research in the Department of Rheumatic and Immunologic Diseases. “It is critical to have physicians in training interacting with all personnel involved with research from the earliest stages, including answering to reviewers, distilling hypotheses, planning careful data collection and analyses, and ultimately submitting a manuscript.”

Figure 1. Trends in article publications and abstract presentations by Cleveland Clinic rheumatology fellows.

*Partial data, as the 2010-2012 fellowship is still in process
## Featured Clinical Research

The studies below are highlights from more than 60 ongoing clinical research studies within the Department of Rheumatic and Immunologic Diseases.

<table>
<thead>
<tr>
<th>Title</th>
<th>Site Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis Clinical Research Consortium (VCRC): Longitudinal Protocols and Genetic Repository One-Time DNA Protocol for Takayasu's Arteritis, Giant Cell Arteritis, Churg-Strauss Syndrome, Polyarteritis Nodosa, Granulomatosis with Polyangiitis (Wegener's) and Microscopic Polyangiitis</td>
<td>Carol Langford, MD</td>
</tr>
<tr>
<td>Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION)</td>
<td>Elaine Husni, MD</td>
</tr>
<tr>
<td>COMPASS 1-3: Cardio-metabolic Outcome Measures in Psoriatic Arthritis Study</td>
<td>Elaine Husni, MD</td>
</tr>
<tr>
<td>Defining Mechanisms of Atherosclerosis in Autoimmune Diseases</td>
<td>Rula Hajj-Ali, MD</td>
</tr>
<tr>
<td>Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Tocilizumab in Active Systemic Juvenile Idiopathic Arthritis</td>
<td>Steven Spalding, MD</td>
</tr>
<tr>
<td>VCRC Concurrent Pilot Studies in Giant Cell Arteritis and Takayasu's Arteritis to Examine Abatacept in Large Vessel Vasculitis (AGATA)</td>
<td>Carol Langford, MD</td>
</tr>
<tr>
<td>Randomized Placebo Phase Study of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis (RAPPORT)</td>
<td>Steven Spalding, MD</td>
</tr>
<tr>
<td>Use of Febuxostat in Allopurinol-Allergic Patients</td>
<td>Brian Mandell, MD, PhD</td>
</tr>
<tr>
<td>Study of Fibromyalgia Outcomes</td>
<td>Carmen Gota, MD</td>
</tr>
<tr>
<td>Follow-Up in the Trial of Early Aggressive Therapy in Juvenile Idiopathic Arthritis (TREAT in JIA)</td>
<td>Steven Spalding, MD</td>
</tr>
<tr>
<td>Unique Vulnerabilities of the Thoracic Aorta Autoimmune Large Vessel Vasculitis</td>
<td>Gary Hoffman, MD</td>
</tr>
<tr>
<td>Relapse Rate with Long-Term Maintenance Therapy for Granulomatosis with Polyangiitis (Wegener's)</td>
<td>Alexandra Villa-Forte, MD</td>
</tr>
<tr>
<td>A Cost-Effectiveness Analysis of CBC Monitoring in Patients on Cyclophosphamide for Granulomatosis with Polyangiitis (Wegener's)</td>
<td>Atul Khasnis, MD</td>
</tr>
<tr>
<td>Detection of an Infectious Retrovirus in Blood Cells of Patients with Fibromyalgia</td>
<td>Carmen Gota, MD</td>
</tr>
<tr>
<td>Adult-Onset Blau-Like Autoinflammatory Disease</td>
<td>Qingping Yao, MD, PhD</td>
</tr>
<tr>
<td>Plasma Exchange and Glucocorticoid Dosing in the Treatment of ANCA-Associated Vasculitis (PEXIVAS)</td>
<td>Carol Langford, MD</td>
</tr>
<tr>
<td>International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS)</td>
<td>Chad Deal, MD</td>
</tr>
<tr>
<td>ACR/EULAR Study to Develop Classification and Diagnostic Criteria for Primary Systemic Vasculitis</td>
<td>Leonard Calabrese, DO</td>
</tr>
<tr>
<td>Osteoporosis Treatment Initiation in Treatment-Naive Patients with a T-Score &lt; –2.5</td>
<td>Chad Deal, MD</td>
</tr>
<tr>
<td>A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Tocilizumab vs. Placebo in Patients with Systemic Sclerosis</td>
<td>Soumya Chatterjee, MD</td>
</tr>
<tr>
<td>Prospective, Randomized, Placebo-Controlled, Double-Blind Study of Macitentan in Patients with Ischemic Digital Ulcers Associated with Systemic Sclerosis</td>
<td>Soumya Chatterjee, MD</td>
</tr>
<tr>
<td>Outcomes of Patients with Reversible Cerebral Vasocostriction Syndrome (RCVS)</td>
<td>Rula Hajj-Ali, MD</td>
</tr>
<tr>
<td>Serial Assessment of the Immunologic Profile in Patients with Granulomatosis with Polyangiitis (Wegener's)</td>
<td>Atul Khasnis, MD</td>
</tr>
<tr>
<td>Study to Evaluate PF-04236921 in Systemic Lupus Erythematosus</td>
<td>Mehnrnaz Hojati, MD</td>
</tr>
<tr>
<td>Study of Primary Angiitis of the Central Nervous System (PACNS)</td>
<td>Rula Hajj-Ali, MD</td>
</tr>
<tr>
<td>A Randomized, Double-Blind Study to Evaluate Pomalidomide (CC-4047) in Subjects with Diffuse Cutaneous Systemic Sclerosis with Interstitial Lung Disease</td>
<td>Soumya Chatterjee, MD</td>
</tr>
<tr>
<td>Investigating the Efficacy of Synvisc-One as Adjunctive Therapy for Patients with Knee OA Requiring Physical Therapy</td>
<td>Elaine Husni, MD</td>
</tr>
</tbody>
</table>