Dear Colleague,

It is an honor to share this 2009 issue of Cleveland Clinic Rheumatology Connections with you. The Department of Rheumatic and Immunologic Diseases has been ranked No. 2 in the U.S. News & World Report “Best Hospitals in America” survey. I am proud to serve as Interim Chair of a department whose legacy in research, patient care and education continues to expand rheumatology frontiers.

This year has been one of impressive accomplishments by many of our distinguished staff. In this issue, we share with you some of the wide-ranging research initiatives in many of our clinical centers. Each area of investigation has a potential impact on our understanding of the pathogenesis and treatment of rheumatic diseases.

• **Arthritis and Musculoskeletal Treatment Center** – Collaboration between Cleveland Clinic rheumatologists and cardiologists has uncovered key factors that may trigger premature cardiovascular risk, observed in patients with inflammatory conditions such as rheumatoid arthritis, systemic immune-mediated diseases and vasculitis. The potential risks of NSAIDs and COX-2 Inhibitor use are being evaluated in the PRECISION trial. Novel modalities to evaluate atherosclerotic plaque are also being investigated by rheumatology investigators, along with cardiologists and radiologists.

• **Center for Osteoporosis and Metabolic Bone Diseases** – Several studies in this center examine novel agents as well as new combinations of existing agents. Investigators are studying zoledronate after a course of teriparatide; denosumab efficacy; and the effect of combination therapy with raloxifene and teriparatide on back pain in osteoporosis. The center is also active in the clinical care of patients with transplant-related bone conditions.

• **Center for Vasculitis Care and Research** – The experienced staff in this center are involved in a diverse portfolio of research, including the use of abatacept in Wegener’s granulomatosis, giant cell arteritis and Takayasu’s arteritis, and mortality in giant cell arteritis. The role of microparticles and their relationship to the pathogenesis of atherosclerosis in Wegener’s is an example of our translational endeavors. Remarkable work in the field of single-organ vasculitis has also shed light on immune-mediated pathogenesis.

• **R.J. Fasenmyer Center for Clinical Immunology** – While maintaining a prominent role in continuing medical education involving immunology and therapeutics in rheumatic diseases, this center has also been active in research. Studies have focused on progressive multifocal leukoencephalopathy in patients taking immune-modulating medications and on patients with common variable immunodeficiency.

• **Center for Pediatric Rheumatology** – Among the myriad ongoing studies by our pediatric rheumatology investigators are a demonstration of the positive effect of recent juvenile arthritis therapies by the observed decline in joint replacement surgery incidence as patients age. An innovative study on mortality in pediatric rheumatic diseases from the world’s largest registry has also shed light on prognosis.

Since all of our staff are actively dedicated to their clinical rheumatology practices, their investigations have a direct impact on patient care. Thus, in this issue you will also find practical clinical pearls, such as ways to distinguish CNS vasculitis from reversible cerebral vasoconstriction syndrome.

I am proud to work with colleagues whose passion for research is matched by their commitment to clinical care; to educating their peers, trainees and students; and to sharing their skills and talents, as evidenced by the articles within these pages. We hope that you enjoy Rheumatology Connections, and invite your comments and feedback.

Sincerely,

Abby Abelson, MD
Interim Chair, Rheumatic and Immunologic Diseases

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One Physician, Two Chairs

As the first Cleveland Clinic physician to hold two endowed chairs, Leonard Calabrese, DO, understands the importance of philanthropy in supporting medical research and education.

Dr. Calabrese, of the Department of Rheumatic and Immunologic Diseases, has held the R.J. Fasenmyer Chair in Clinical Immunology since 1999; in 2008, he became the first to hold the Theodore F. Classen, DO, Chair in Osteopathic Research and Education.

“The two chairs are hand-in-glove,” Dr. Calabrese says. “As medical technology has advanced in the past 20 years, we have increased the distance between patient and physician. In osteopathic medicine, we say that caring must always inform competence.”

The Fasenmyer Chair supported his exploration of initiatives in HIV, hepatitis C and autoimmune diseases. “A decade ago, I was seeing patients full-time,” he recalls. “I had tons of research ideas, but little outlet to exercise them. The Fasenmyer Chair allowed me to engage in research and education in the context of care.”

The Classen Chair will enhance those opportunities by supporting research and graduate education in osteopathic medicine at South Pointe Hospital, a Cleveland Clinic hospital, and at Cleveland Clinic.

“At South Pointe Hospital, we are bringing in some of the finest Cleveland Clinic teachers from various areas of medicine,” says Dr. Calabrese.

He hopes to make one research project under way – involving osteopathic manipulative medicine and fibromyalgia – a national research project.

“We’re also conducting a long-term study into empathy in healthcare. Everybody in this country wants to have a relationship with their physicians,” says Dr. Calabrese. “They want to be heard. They want to know that their doctor can stand in their shoes, even just for a moment.”

To reach Dr. Calabrese, physicians may call 216.444.5258 or email calabrl@ccf.org.
Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed pain reliever in the United States. Pain management in patients with osteoarthritis or rheumatoid arthritis often requires long-term use of these medications.

Recent safety concerns about the cardiovascular toxicity of one NSAID, rofecoxib (Vioxx®), led to its removal from the market worldwide. The relative cardiovascular safety of remaining NSAIDs, such as naproxen (Naprosyn® or Aleve®), ibuprofen (Motrin®) and the remaining COX-2 inhibitor, celecoxib (Celebrex®), remains uncertain.

Recent research has highlighted the association of increased cardiovascular events in patients with inflammatory arthritis. Cleveland Clinic cardiologists, rheumatologists and other specialists are collaborating on a multinational, multicenter study to address these concerns. Further collaborative research will help develop methods to decrease this risk in our patients with systemic rheumatic disease.

The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial will evaluate the cardiovascular safety of celecoxib, ibuprofen and naproxen. Approximately 20,000 patients with symptomatic osteoarthritis or rheumatoid arthritis at high risk for, or with, established cardiovascular disease will be randomized in the double-blind, triple-dummy study.

The primary study endpoint of PRECISION will be the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. The trial will continue until 762 primary events have occurred, with at least 18 months follow-up. Patients will also be evaluated for gastrointestinal side effects and nephrotoxicity, and each agent’s efficacy in managing arthritis pain will be assessed.

Several factors make the PRECISION trial novel compared to similar trials done previously, including: the noninferiority trial design for both intent-to-treat (ITT) and modified ITT populations (requiring a 97.5 percent upper confidence interval of the hazard ratio <1.12); provision of a proton-pump inhibitor for all study subjects; and inclusion of both concomitant aspirin users and non-users.

Dr. Husni, Vice Chair, Arthritis and Musculoskeletal Treatment Center and Director, Clinical Outcomes Research, is site principal investigator for PRECISION and a key member of the multidisciplinary team overseeing the trial. Physicians may reach her at 216.445.1853 or at husnie@ccf.org.

“The PRECISION trial seeks to provide definitive information for patients who need to know the safest approach for relieving arthritis pain. Prior trials of pain relievers have not focused on these patients, who are at high risk for cardiovascular disease. We are committed to conducting this trial using the best scientific methods to answer a critically important public health question.”

Steven Nissen, MD, Principal Investigator, PRECISION; Chairman, Cleveland Clinic Department of Cardiovascular Medicine; Director, Joseph J. Jacobs Center for Thrombosis and Vascular Biology
The NIH Roadmap initiative has stimulated much cross-pollination in academic research. Traditionally, most clinical research was “assigned” to one broad scientific area, with little interdepartmental teamwork.

With advancing medical technology, improved collaboration is critical. The institute model used at Cleveland Clinic facilitates interdisciplinary as well as cross-disciplinary research.

Researchers from the Orthopaedic & Rheumatologic Institute and the Heart & Vascular Institute are collaborating on research stimulated by evidence of a higher prevalence of cardiovascular disease in patients with systemic autoimmune diseases. Patients with rheumatoid arthritis (RA) are at higher risk of cardiovascular morbidity and mortality. The reason for this may be a combination of the following: higher inflammatory milieu, an increase in novel and traditional cardiovascular risk factors, direct effects on the vasculature and endothelium, and the potential influence of arthritis medications.

Traditionally, rheumatologists and cardiologists rarely reached out to one another. We have benefited from the input of our cardiologist colleagues on study design, research methodologies and outcomes measures, as the following studies illustrate:

**COX-2 inhibitors and plaque**

This collaborative study with Interventional Cardiology and rheumatology fellow Atul Khasnis, MD, involved a systematic analysis of trials employing serial intravascular ultrasound (IVUS) to study plaque progression in angiographic coronary artery disease.

The FDA recently added a “black box warning” to both prescription and over-the-counter NSAIDs and COX-2 inhibitors about potential cardiovascular risks. The exact mechanism underlying increased risks is an area of intense clinical investigation. This trial was undertaken to compare the effects of COX-2 inhibitors versus traditional NSAIDs alone among 464 patients treated with a COX-2 inhibitor and 473 patients treated with NSAIDs alone in the REVERSAL, CAMELOT, ACTIVATE, ASTEROID and ILLUSTRATE trials.

Clinical and laboratory characteristics were comparable at baseline and follow-up.

COX-2 inhibitor use was not associated with a greater percent atheroma volume (PAV, 38.1±9.6 versus 38.1±9.2%, p=0.10) or total atheroma volume (TAV, 189.9±84.6 versus 186.5±80.6 mm³, p=0.11) at baseline. Changes in PAV (+0.31±0.43 versus +0.38±0.42%, p=0.78) and TAV (−3.9±3.4 versus −5.3±3.4 mm³, p=0.20) were not significantly different in the two groups (COX-2 inhibitors and traditional NSAIDs).

We concluded that use of COX-2 inhibitors did not modify the rate of atheroma progression or associated arterial remodeling when compared with NSAID use in coronary artery disease. This suggests that the mechanism underlying a potential increase in cardiovascular events is likely attributable to other factors such as thrombosis.

**Anti-TNF therapy and lipids**

A second collaborative study, with Preventive Cardiology, addressed whether anti-tumor necrosis factor (anti-TNF) therapy modified the lipid profile in patients with systemic rheumatic diseases.

We collected data on lipid profiles and C-reactive protein (CRP) levels from the PreCIS (Preventive Cardiology Information System) Database in 265 patients with diseases such as RA, systemic lupus erythematosus (SLE), vasculitis or ankylosing spondylitis (AS).

Ninety-five patients were treated with anti-TNF therapy, and 170 patients were not. Mean patient age was 52.6 +/- 14.9 years; 28.7 percent were male. Cardiovascular risk factors (BMI, hypertension, current smoking, diabetes, etc.) did not differ statistically between groups.

We measured total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG) and CRP levels at baseline and at three-month follow-up.

Mean (SD) concentrations of HDL cholesterol (57 versus 59, p=0.38) and LDL cholesterol (106 versus 108, p=0.87) were similar in the treated and untreated groups, as were average CRP concentrations (5.02+/−10.8 versus 5.38+/−9.7, p=0.09).

However, triglyceride levels differed significantly in the anti-TNF-treated versus the non-treated groups (119 versus 149, p=0.05). We concluded that anti-TNF therapy may create a more favorable triglyceride profile among patients with systemic rheumatic diseases, thus decreasing cardiovascular risks. Larger studies will need to be performed to better quantify this association.

Physicians may reach Dr. Husni or request references for this article at 216.445.1853 or husnie@ccf.org.

1 Use of Cyclo-Oxygenase-2 Inhibitors is not Associated with Accelerated Progression of Coronary Atherosclerosis. A. Khasnis, M.E. Husni, L. Cho (Rheumatology); SJ Nichols, M. Shao, EM Tuzcu, S. Nissen (Interventional Cardiology)

2 The Effect of TNF Alpha Treatment on Lipid Profiles of Patients with Systemic Rheumatic Disease. ME Husni, B. Hoar, LH Calabrese (Rheumatology); SHazen, L Cho, B Hoar (Preventive Cardiology)
Arthritis and Musculoskeletal Treatment Center: Integrated Diagnostic and Treatment Services
By M. Elaine Husni, MD, MPH

The Orthopaedic & Rheumatologic Institute’s Arthritis and Musculoskeletal Treatment Center is the first multidisciplinary clinic to combine the expertise of different disciplines with an institute model for timely, coordinated assessment and treatment of joint pain and related musculoskeletal conditions.

Our goal is to provide your patients with optimal care, to return them to their usual level of activity as soon as possible.

Joint pain may have many different causes, including trauma and congenital disorders, and may be associated with more than 100 types of arthritis and related diseases. Because more than one type of specialist can treat these problems, patients with joint symptoms may find it difficult to be directed promptly to the right provider.

The physicians in our center have a specific interest in disorders causing joint pain and work efficiently as a multidisciplinary team to provide early diagnosis and prompt treatment for patients. Our Arthritis and Musculoskeletal Treatment Center is staffed by rheumatologists, orthopaedic surgeons, musculoskeletal radiologists, physical and occupational therapists, brace technicians and musculoskeletal patient educators.

Our physicians obtain a detailed history and physical, and discuss the patient’s joint symptoms to determine the potential cause. For some patients, further imaging or therapy will be recommended within our center. For other patients, timely referral to other specialists who focus on a particular disorder allows for more targeted treatment.

To refer patients to Cleveland Clinic’s Arthritis and Musculoskeletal Treatment Center, please call 216.445.3330 or 800.223.2273, ext. 53330. Physicians may reach Dr. Husni, Vice Chair, Arthritis and Musculoskeletal Treatment Center and Director, Clinical Outcomes Research, at 216.445.1853 or husnie@ccf.org.

Osteoporosis Treatment: Clinical Trials Key to Advancing State of the Art
By Chad Deal, MD

The National Osteoporosis Foundation estimates that more than 10 million U.S. women over age 50 have osteoporosis, and 34 million have low bone mass that may progress to osteoporosis. Adequate calcium and vitamin D intake are the foundation of therapy for low bone mass, but additional drug therapy is needed when fracture risk is significant.
Current guidelines recommend treatment for postmenopausal women and men over 50 when lumbar spine or hip T-scores are less than -2.5. Treatment is also indicated for patients with osteopenia whose T-scores fall between -1.0 and -2.5 when additional factors increase fracture risk. In the United States, an absolute fracture risk model, FRAX, has been helpful in evaluating risk and making decisions on treatment initiation.

**Balancing fracture reduction with safety**

In clinical trials, new osteoporosis therapies must balance vertebral and non-vertebral fracture reduction with an acceptable safety profile.

Current osteoporosis drugs are classified as either antiresorptive (decreasing resorption by osteoclasts) or anabolic (stimulating bone formation by osteoblasts).

Antiresorptive agents include the bisphosphonates (alendronate, risedronate, ibandronate, zoledronate); estrogen; an estrogen agonist/antagonist (raloxifene); and calcitonin. The only anabolic agent is teriparatide (TPTD), a recombinant preparation of parathyroid hormone (PTH).

While these drugs effectively reduce fractures, they all have some limitations. TPTD must be given as a daily injection and is approved for no more than two years of use. Oral bisphosphonates can cause GI side effects. A major clinical trial linked the intravenous bisphosphonate zoledronate with atrial fibrillation. Antiresorptive agents eventually decrease bone formation over time. In rare cases, long-term antiresorptive therapy has been associated with a low turnover state that may cause fractures.

**Comparing approaches to osteopenia**

The Center for Osteoporosis and Metabolic Bone Diseases has participated in several clinical trials evaluating new therapies and combinations of established therapies for low bone mass:

**Combining raloxifene with TPTD.** In this trial, raloxifene did not blunt the effect of TPTD on bone density and bone markers as seen in earlier trials of alendronate plus TPTD. This is an important benefit for women who may want to continue raloxifene for its demonstrated reduction in breast cancer. In fact, patients on raloxifene and TPTD had greater bone density gains and less hypercalcemia than those on TPTD alone.

**Targeting back pain as the study endpoint.** TPTD has reduced back pain in clinical trials, but no trial has compared its effect on back pain to that of other therapies. We are now participating in a multicenter study evaluating back pain in patients treated with teriparatide versus risedronate.

**Following TPTD treatment with zoledronate.** Patients who finish a course of TPTD need to continue therapy with an antiresorptive agent. Alendronate has been shown to further increase bone mass after one year of TPTD treatment. We are conducting a single-center, investigator-initiated trial using zoledronate. Interim results demonstrate that it maintains and increases bone mass in more than 90 percent of patients after treatment with TPTD.

**Investigating alternative anabolic agents.** Alternatives to teriparatide, which must be given as a daily injection, are in development. We evaluated a novel anabolic agent that interacts with the calcium-sensing receptor in a multicenter trial. Each oral dose of this receptor antagonist triggers the release of PTH from the parathyroid gland. Although initial results did not meet the expected study endpoint, efforts to develop an oral agent with this mechanism of action continue.

**Helping an antiresorptive agent reach the FDA.** Denosumab has been submitted to the FDA for approval for the treatment of postmenopausal osteoporosis (FDA response date: October 2009). This fully human antibody against RANKL, a critical cytokine in osteoclast maturation and survival, is injected subcutaneously every six months. In its registration trial (FREEDOM), denosumab significantly reduced spine, hip and non-vertebral fractures in postmenopausal women. We participated in the multicenter DECIDE trial, which found that bone mass gains were significantly greater at all skeletal sites among patients treated with denosumab versus alendronate.

These clinical trials allow us to advance the state of the art in osteoporosis care. They are critical as we continue to strive for improved treatments.

Dr. Deal is Head of the Center for Osteoporosis and Metabolic Bone Diseases. To discuss whether a patient may be eligible for one of the center’s clinical trials or to obtain further details, physicians may contact Dr. Deal at 216.444.6575 or at dealc@ccf.org.
Patients with systemic vasculitides face a number of medical challenges that do not end with the illness and its treatment. Among them are premature atherosclerosis as a cause of morbidity and mortality, and fibromyalgia, depression and sleep apnea as factors that can impact quality of life. Our desire to improve all aspects of health for vasculitis patients has driven us to study these important issues.

**Studying premature atherosclerosis in WG**

Advances in treatment have led to better survival in patients with Wegener’s granulomatosis (WG). However, premature atherosclerosis has emerged as a significant morbidity, independent of traditional cardiovascular risk factors. The link between WG and atherosclerosis is not well-characterized. However, the association raises the possibility that persistently active vasculitis, or non-specific inflammation, plays a role in early atherosclerosis.

Through funding support from the American Heart Association, we are working to better understand the pathogenesis of atherosclerosis in WG by examining the role of microparticles in these patients.

**Microparticles as prognostic markers**

Microparticles are membrane fragments that bud off from normal cells, including leukocytes, platelets and vascular endothelial cells, during activation or apoptosis. Substantial evidence suggests that microparticles are potential prognostic markers for thrombosis and atherosclerotic vascular disease. In addition, elevations in circulating microparticles are associated with cardiovascular risk and appear to indicate a poor clinical outcome.

In collaboration with Roy Silverstein, MD, Chairman of Cell Biology in the Lerner Research Institute, we hope to assess the role of microparticles and their interaction with platelets through the scavenger receptor CD36 to shed light on the pathogenesis of atherosclerosis in WG. This study may also serve as a model to further explore the role of inflammation in atherosclerosis, both in inflammatory and non-inflammatory conditions.

**Pilot study focusing on quality of life**

In systemic vasculitis, there is great need to allow not only physician assessments but also patient-centered outcome measures to guide treatment decisions. This need has served as an impetus for assessing pain, fatigue and mental health in these patients.

We are currently conducting a pilot study to examine the frequency of fibromyalgia, depression and sleep apnea in patients with systemic vasculitis using four validated instruments:

- London Fibromyalgia Epidemiologic Study Screening Questionnaire
- Symptom Intensity Scale

In addition, we are capturing quality of life scoring using the Short Form 36 questionnaire.

Such studies are important, as the frequency of fibromyalgia, depression and sleep apnea has not been established in patients with vasculitis. These patients could develop such conditions as a result of being diagnosed with a life-threatening disease; because of the disease itself; due to medications used to treat the disease; or from a combination of these factors.

Through this pilot study, we are striving to improve the care of patients with systemic vasculitis by addressing their quality of life.

Dr. Hajj-Ali, principal investigator for both studies in the Center for Vasculitis Care and Research, specializes in vasculitis, uveitis and central nervous system vasculitis. Physicians may reach her at 216.444.9643 or at hajjalr@ccf.org.
Focal single-organ vasculitis (SOV), affecting the abdominal and genitourinary organs, breast, aorta or other sites, is both unusual and the simplest part of the spectrum of vasculitis. Focal SOV is usually an unexpected finding in resected tissues from patients presenting with inflammatory or non-inflammatory abnormalities, such as mass lesions.

When the preoperative suspected diagnosis is malignancy, relief often follows the good news that such was not the case. However, confusion may result when isolated vasculitis is found in the biopsy or resected tissue.

**Excellent outlook**

Only occasionally does such a localized process evolve into systemic disease. The prognosis of focal SOV tends to be excellent. Treatment is usually limited to resection of the focal lesion or organ (e.g., testis, gallbladder, uterus) if that is feasible. Systemic immunosuppressive therapy is usually not required.

The diagnosis of focal SOV is always presumptive and requires exclusion of systemic illness at the time of diagnosis, as well as throughout the period of continued care.

In addition to these important clinical points that guide the diagnosis and treatment of SOV, such observations raise questions that may hold the key to a better understanding of vasculitis and autoimmunity in general. The field of autoimmunity has progressed because of studies of circulating and tissue-bound immune-reactive cells, cytokines and antibodies.

**Possible clues to etiology**

What has brought those cells to the site of injury remains a mystery for most forms of vasculitis. Might the etiology of at least certain forms of vasculitis be related to generation of neoantigens in the native vessel, making that vessel the target of a pathogenic immune response? This would not be dissimilar to mutations that produce neoantigens in malignant cells, resulting in tissue-specific immune responses.

A testable hypothesis derived from these observations would be that spontaneous mutations in substrate play a role in the etiology of vasculitis and other autoimmune diseases. Territories that share homologous antigens could then become targeted through mechanisms of molecular mimicry, possibly explaining the etiology of multi-system disease.

Dr. Hoffman, Harold C. Schott Chair of Rheumatic and Immunologic Diseases, and Director, Physician Volunteer Programs, specializes in vasculitis. Physicians may reach him at 216.445.6996 or at hoffmag@ccf.org.
To address the important issue of morbidity and mortality associated with giant cell arteritis (GCA), a recent study was performed at the Cleveland Clinic Center for Vasculitis Care and Research.

The study examined rates of in-hospital mortality associated with GCA as compared with non-GCA controls. It also determined the contribution of cardiovascular outcomes (myocardial infarction, cerebrovascular disease and aortic aneurysm) to the mortality associated with GCA.

Largest study of its kind
The study utilized data from the 2004 Nationwide Inpatient Sample, a 20 percent sample of all discharges from U.S. acute care hospitals. Records coded for GCA (n = 4,566) were matched with 18,264 controls, making this the largest study of outcomes in GCA to date.

Logistic regression was used to calculate odds ratios for GCA compared to controls for in-hospital mortality and for each of the cardiovascular outcomes. Odds for the mortality associated with each cardiovascular outcome were also calculated.

In-hospital mortality lower
We found that GCA was associated with significantly reduced odds of in-hospital mortality as compared with controls upon univariate analysis.

GCA was associated with significantly increased odds of cerebrovascular disease and thoracic aortic aneurysm as compared with controls, which is consistent with the known predilection of GCA to cause arteritis in these vascular territories.

Reduced odds for MI surprising
However, GCA was associated with reduced odds of myocardial infarction as compared with controls. In addition, the odds of mortality associated with cerebrovascular disease were reduced for GCA compared with controls.

Despite controlling for these factors, GCA was associated with significantly reduced odds of in-hospital mortality upon multivariate analysis. This suggests that additional factors may contribute to the observed reduction of in-hospital mortality in GCA patients.

Ongoing studies at the Cleveland Clinic Center for Vasculitis Care and Research are available to patients with GCA to further expand our understanding of this disease.

Dr. Molloy, of the Center for Vasculitis Care and Research and the R.J. Fasenmyer Center for Clinical Immunology, specializes in vasculitis, adult immunodeficiency, rheumatoid arthritis and systemic autoimmune diseases. Physicians may reach him at 216.444.8834 or molloye@ccf.org.

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CI = confidence interval. *Adjusted for demographic and clinical variables, including age, sex, race, income, insurance payer, length of stay, diabetes mellitus, hypertension, myocardial infarction, cerebrovascular disease, aortic aneurysm and AHRQ comorbidity measures.
Wegener’s Granulomatosis: Strategies for Improving Outcomes

By Alexandra Villa-Forte, MD, MPH

Wegener’s granulomatosis (WG) is a complex systemic inflammatory disease that frequently affects the upper and lower respiratory tracts and kidneys. For more than 40 years since its description in 1931, WG had been associated with a poor prognosis and a high rate of mortality.

The prognosis of WG dramatically changed with the introduction of glucocorticoid and cyclophosphamide therapy in the 1970s by Fauci and Wolff.

**Critical findings emerge**

Over time, three important observations were made. First, despite the high rate of remission and survival, relapse was frequent in WG. Second, prolonged or repeated therapy with cyclophosphamide resulted in substantial morbidity. Third, a subgroup of patients with WG had milder disease. These observations led to the investigation of therapies with similar effectiveness but less toxicity.

**Safer approaches pursued**

In 2007, the Cleveland Clinic Center for Vasculitis Care and Research published its 12-year experience applying two therapeutic strategies to the care of WG:

1. treatment of mild-to-moderate WG with methotrexate, a less toxic agent, in place of cyclophosphamide and
2. induction of remission with cyclophosphamide for severe disease, and switching therapy in three to six months to a safer agent to maintain remission.

Our results showed that use of methotrexate in place of cyclophosphamide to treat mild-to-moderate disease produced a comparable rate of remission. Thus, it is possible to completely avoid the use of cyclophosphamide in a selected subgroup of patients with WG. It is also possible to limit cyclophosphamide’s use to three to six months in patients with severe disease.

We find that these strategies have led to a great reduction in treatment-associated morbidity and mortality without decreasing effectiveness.

**Multispecialty monitoring key**

A key aspect of caring for patients with WG is ongoing and frequent monitoring for relapse as well as morbidity associated with treatment or the disease itself. A multidisciplinary approach is essential to providing optimal care for this complex disease. At Cleveland Clinic, multiple specialists experienced with rare diseases work together to deliver the best possible care for patients with WG.

Dr. Villa-Forte specializes in vasculitis; physicians may reach her at 216.445.9437 or at villaa@ccf.org.

Vasculitis Patients Sought for Trials of Novel Treatments

By Carol A. Langford MD, MHS

Clinical trials are an important part of research conducted within the Center for Vasculitis Care and Research. Our current trials focus on the exploration of novel treatment options for giant cell arteritis (GCA), Takayasu’s arteritis (TAK), and Wegener’s granulomatosis (WG). All of these trials are actively enrolling new participants; inquiries about patient eligibility are welcomed.

**NIH funding for abatacept studies**

In 2007, we were awarded a contract from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health to study the safety, efficacy and immunologic effects of the medication abatacept (CTLA4-Ig) in patients with active GCA or TAK.

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

In our other clinical trial, abatacept is being studied in patients who have mild, relapsing WG. All participants enrolled in this open-label trial will receive abatacept.

**Study consortium wide-ranging**

These clinical trials are part of a portfolio of ongoing studies being conducted in conjunction with the Vasculitis Clinical Research Consortium (VCRC).

This NIH-funded collaborative network supports research in the vasculitic diseases and includes 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.

Other VCRC projects include longitudinal studies to examine biomarkers and a study of positron emission tomography in TAK.

Physicians interested in learning more about any of these studies can contact either Dr. Langford, Director of the Center for Vasculitis Care and Research, at langfoc@ccf.org, or Katherine Tuthill, CNP, at tuthilikk@ccf.org.

Further information about these studies, including eligibility criteria, design or contact information, can also be found at www.clinicaltrials.gov.
Common Variable Immunodeficiency Predisposes to Autoimmune Disease

By Eamonn Molloy, MD, MS

Patients with common variable immunodeficiency (CVID) face a number of challenges. First of all, they face a delay in diagnosis, typically between five and 10 years. This likely pertains to the heterogeneous nature of CVID, as well as to a pervasive lack of awareness of adult-onset immunodeficiencies among physicians.

CVID patients also may endure a variety of complications, in addition to an increased risk of infections. Recurrent infections, especially of the upper and lower respiratory tract, are the clinical hallmark of CVID.

Range of autoimmune manifestations

However, CVID has many facets, including a predisposition to autoimmune diseases, systemic granulomatous inflammation, lymphoproliferative disease and other malignancies. Thus, CVID displays the full spectrum of disorders attributable to dysregulation of the immune system.

Autoimmune manifestations of CVID may include:
- idiopathic thrombocytopenic purpura
- autoimmune hemolytic anemia
- systemic autoimmune diseases, including inflammatory arthritis and vasculitis

Overtreatment a risk of misdiagnosis

Finally, if the potential association of these secondary disorders with CVID is unrecognized, patients diagnosed may be inappropriately treated with aggressive immunosuppressive therapy. Unless used judiciously, immunosuppressive therapy may have serious repercussions for patients with CVID. Patients who are not receiving concomitant immunoglobulin replacement therapy are particularly at risk.

Research initiated at the R.J. Fasenmyer Center for Clinical Immunology at Cleveland Clinic aims to characterize the clinical and immunologic correlates of the autoimmune manifestations of CVID. We are conducting this research in collaboration with colleagues from the Department of Allergy and Immunology, and the Lerner Research Institute.

Efforts are also under way to enhance our ability to predict which patients may be at particular risk of developing autoimmune complications of CVID.

Dr. Molloy, of the R.J. Fasenmyer Center for Clinical Immunology, specializes in adult immunodeficiency, vasculitis, rheumatoid arthritis and systemic autoimmune diseases. Physicians may reach him at 216.444.8834 or molloye@ccf.org.
Progressive multifocal leukoencephalopathy (PML) is a rare, frequently fatal, infectious complication caused by reactivation of the JC polyomavirus in immunocompromised patients.

PML has been reported in patients with chronic inflammatory rheumatic diseases. Such cases have traditionally been ascribed to the immunosuppressive medications administered to these patients. However, research recently performed at the Cleveland Clinic R.J. Fasenmyer Center for Clinical Immunology challenges this assumption.

Our research was stimulated by a case seen on hospital rounds involving an unfortunate young woman with systemic lupus erythematosus (SLE) who succumbed to PML despite receiving only minimal immunosuppressive therapy for SLE.

Upon reviewing the literature, a picture began to emerge: a significant over-representation of SLE as the underlying diagnosis among patients with rheumatic diseases who subsequently developed PML. Many of these patients had also been treated with minimal immunosuppressive therapy for SLE.

This data suggests that the risk of PML in patients with SLE was not entirely attributable to profound iatrogenic immunosuppression, and was instead related to other factors — potentially including SLE itself.

Corroborating risk in SLE

Because literature reviews are subject to publication bias, a second study was undertaken to corroborate this data. For this study, data were obtained from the U.S. Nationwide Inpatient Sample database, a 20 percent sample of all hospital discharges weighted to represent the entire U.S. inpatient population.

Data were obtained for the years 1996 to 2005, inclusive. After excluding established risk factors for PML, such as HIV/AIDS, cancer and organ transplantation, the rate of PML per 100,000 cases was 10-fold higher in SLE, as compared with rheumatoid arthritis.

This data supports the hypothesis that SLE is associated with a specific predisposition to PML. Recent reports of PML among patients treated with promising biologic agents — including natalizumab, rituximab and efalizumab — serve to emphasize the importance of increasing awareness of PML among physicians who treat patients with rheumatic diseases and of clearly understanding the risk attributable to these diseases themselves.

Maintaining high index of suspicion

It is likely that PML is underdiagnosed in patients with rheumatic diseases because PML may not be considered when patients succumb to presumed neuroinflammatory manifestations of their disease. Therefore, a high index of suspicion must be maintained in patients with chronic rheumatic diseases who develop unexplained neurologic deficits.

Further research is required to understand the pathophysiology of PML as it relates to SLE and other rheumatic diseases.

Dr. Molloy, of the R.J. Fasenmyer Center for Clinical Immunology, specializes in vasculitis, adult immunodeficiency, rheumatoid arthritis and systemic autoimmune diseases. Physicians may reach him at 216.444.8834 or molloye@ccf.org.
Pediatric rheumatologists diagnose and manage more than 170 conditions, both inflammatory and non-inflammatory, affecting approximately 3/1,000 children. We tend to regard most of these conditions as chronic, and to study outcomes in terms of remission versus active disease; organ and radiologic damage; and function and quality of life. But few studies have investigated mortality outcomes.

**Higher mortality reported**

Studies to date have found an increased rate of mortality in juvenile rheumatoid arthritis (JRA), childhood systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDMS), various vasculitides and systemic sclerosis.

JRA studies from the 1960s and 1970s demonstrated a mortality rate of 1 to 4.6 percent that decreased in the 1980s and early 1990s to about 1 percent, but represents a standardized mortality rate of 3.3 when compared to the general population. The main causes of mortality reported were amyloidosis (in Europe), macrophage activation syndrome and infection.

In SLE, reported survival rates ranged from 83 to 95 percent at five years, 76 to 95 percent at 10 years, and 50 to 76 percent at 15 years, with renal failure and infections being the main causes of death.

The most recent JDMS study reported a mortality rate of approximately 1.5 to 2.5 percent over three to five years, mainly from respiratory insufficiency or gastrointestinal perforation.

The five-year mortality rates reported for systemic sclerosis, Henoch-Schönlein purpura, Kawasaki disease and polyarteritis nodosa are 5 to 10 percent, less than 1 percent, 0.04 to 0.17 percent and 55 percent, respectively.

**Limitations of prior studies**

However, most of these studies involved relatively small cohorts; reported mortality only for specific diseases; had a follow-up of less than 10 years; and were based on data prior to the 1990s, prior to the development of new therapies for pediatric rheumatologic diseases.

In addition, most of the larger studies were based on physician surveys and questionnaires, with no strategies to verify accuracy of the responses.

In studies involving national cohorts, diagnoses were usually not assigned by pediatric rheumatologists. No data is available on mortality rates for many rare rheumatic diseases (primary vasculitis, autoinflammatory diseases) and non-inflammatory rheumatic conditions, including pain syndromes (fibromyalgia).

In addition, causes of death were usually not adequately verified, and no systematic attempt was made to look for potential risk factors/predictors of mortality early in the disease course.

**New study based on pediatric rheumatology registry**

Therefore, we have performed a systematic study funded by the Northeast Ohio Chapter of the Arthritis Foundation on mortality outcomes for all pediatric rheumatologic conditions. We used the Indianapolis Pediatric Rheumatology Disease Registry, run by Dr. Suzanne Bowyer. It is the world’s largest registry of patients with these conditions, with nearly 50,000 patients registered.

Our specific aims were to estimate the mortality rate for patients with pediatric rheumatic conditions, to describe the causes of death, and to test hypotheses on possible risk factors for mortality early in the disease course. We hope to publish results shortly and believe that the main message will be encouraging for those who treat pediatric rheumatologic conditions, as well as patients and families.

To refer patients to Dr. Hashkes or to colleague Steven Spalding, MD, in Cleveland Clinic’s Section of Pediatric Rheumatology, please call 216.445.8525 or 216.445.1099.
Joint Replacement Surgery Rates Decline in Juvenile Rheumatoid Arthritis

By Philip J. Hashkes, MD, MSc

Juvenile idiopathic arthritis, previously known as juvenile rheumatoid arthritis (JRA), is the most common rheumatic disease of childhood, having a prevalence of about 1:1000. Recent data show that most children never achieve long-term remission. Between 50 to 70 percent of patients with polyarticular or systemic-onset JRA, and 40 to 50 percent of patients with pauciarticular JRA, continue to have active disease in adulthood.

One of the deleterious outcomes of JRA is the need for joint replacement surgery, usually in young adulthood. In the literature, the percentage of JRA patients requiring major surgery, including joint replacement, ranges from 7 to 50 percent.

Treatments have improved
Treatment for JRA has changed markedly in the last 15 years, with the introduction of intra-articular steroid injections in the mid-1980s, methotrexate in the early 1990s and biologic disease-modifying agents including etanercept, adalimumab, abatacept, infliximab and anakinra in the last decade.

While the impact of these new therapies is clear with regard to reducing short-term disease activity, their impact on long-term outcomes has been less studied.

Study challenges
As a measure of the effectiveness of the new treatments for JRA, we sought to examine changes in the rates of large-joint replacements at Cleveland Clinic from 1990 to 2007 in patients with the diagnosis of JRA. This type of study normally presents difficulties because:

• Joint replacement surgery is usually performed after the patient has stopped growing, usually in adulthood, and is no longer followed by a pediatric rheumatologist.

• Most pediatric rheumatologists practice in self-standing children’s hospitals, so their patients are transferred elsewhere when they become adults.

• Even for patients still followed by a pediatric rheumatologist, joint replacement surgery is almost always performed by an adult orthopedist in another hospital. (Only on rare occasions is joint replacement surgery performed in children before the completion of growth).

Outcomes tracked more easily
Cleveland Clinic is unique in that it is one of the only medical centers in the country offering a continuum of care between pediatric and adult rheumatologists, and pediatric and adult orthopedists, in the same institute.

Thus, data on joint replacements rates in adult JRA patients could be obtained from the same place where they were treated as children, allowing us to search our database over the past 17 years for changes in this important long-term outcome of JRA.

In initial results presented as an abstract at the 2008 American College of Rheumatology annual meeting (Arthritis Rheum 2008;58 suppl:S713-4), we demonstrated a significant decrease in the rate of joint replacement surgery between 1990 and 2007. We are currently examining, by case-control study, the factors potentially involved in this decreased rate – particularly the effects of modern therapy.

To refer patients to Dr. Hashkes or to colleague Steven Spalding, MD, in Cleveland Clinic’s Section of Pediatric Rheumatology, please call 216.445.8525 or 216.445.1099.
In 2007 and 2008, Cleveland Clinic leadership, particularly Education Institute Chairman James Stoller, MD, MS, and Chief of Staff Joseph Hahn, MD, convened focus groups of physicians. They discovered a grassroots movement among staff (senior physicians and leaders) who were already engaged in service for the medically indigent and the children of Northeast Ohio. Furthermore, they discovered that many other staff wished to become involved. The result was the creation of the Staff Volunteer Programs in the Spring of 2008 and my appointment as the programs’ Director.

A significant response

The next step was to 1) assess the magnitude of staff involvement in the community, 2) determine the nature of our community involvement and 3) stimulate volunteerism among staff.

Surveys of staff annual performance reviews, a separate e-questionnaire and a mailing to staff who retired in the past five years identified many who were currently engaged in medically related volunteerism.

These individuals were interviewed, a compendium of volunteer activities was generated, task forces were formed, and leaders were appointed to better define activities of potential high priority.

Task Force scope is broad

Areas of commitment and leadership are:

1. Community Outreach – Pamela Holmes, Executive Director, Community Relations
2. Schools – Rosalind Strickland, Director, Civic Education Initiatives
3. International Developing Countries – Brian Smith, Director, Strategic Project Development
4. Free Clinics – Gary Hoffman, MD, Rheumatic and Immunologic Diseases, Office of Professional Staff Affairs
5. Cleveland Clinic Lerner College of Medicine – Kathleen Franco, MD, Associate Dean, Admissions & Student Affairs
6. Stopping Violence in our City – Ellen Rome, MD, MPH, Associate Chief of Staff, and Kate Nagel, Government Relations

Task Force goals include identifying strategies that will allow more staff opportunities for service. We know that staff volunteers can add great value based on their past experience, insight and energy. Through participation, they can enhance opportunities to be agents of change in creating a better city and world.

Dr. Gary Hoffman, Director, Staff Volunteer Programs, holds the Harold C. Schott Chair in Rheumatic and Immunologic Diseases. To refer patients to Dr. Hoffman in the Center for Vasculitis Care and Research, or to discuss our Staff Volunteer Programs with him, please call 216.445.6996 or email hoffmag@ccf.org.
The R.J. Fasenmyer Center for Clinical Immunology Education and Research has provided high-quality CME programs to clinicians and allied health professionals in the field of Clinical Immunology since 2005. Committed to high-quality, low-cost education, the center has an emphasis on chronic viral diseases and vasculitis.

Courses have covered diverse subjects such as HIV disease, biologic therapies and allergy. More than 47,000 learners have benefited from our portfolio of live courses, web-based programs (including live and archived webcasts and podcasts), and print and online monographs.

The center is directed by Leonard H. Calabrese, DO, the R.J. Fasenmyer Chair in Clinical Immunology, as well as the Theodore F. Classen, DO, Chair in Osteopathic Research and Education. It also promotes excellence in patient care and innovative research in clinical immunology, and works with volunteer and community-based institutions to promote public education and awareness in the field.

Enduring CME on Cleveland Clinic CME Website

Through the Cleveland Clinic Center for Continuing Education, we offer the following programs:

Biologic Therapies for Autoimmune and Inflammatory Disease States
- Autoimmune & Inflammatory Disorders – A Changing Concept: The R.J. Fasenmyer Annual Lecture -ship in Clinical Immunology
- New Targets in Multiple Diseases
- Biologic Therapeutic Classes and Agents: Shared Mechanisms of Action Across Disease States
- State of the Art: Biologic Toxicity Epidemiology, Clinical Spectrum, Diagnosis and Prevention
- Psoriasis and Arthritis
- Rheumatoid Arthritis, Juvenile Arthritis, Ankylosing Spondylitis
- Biologics and Gastroenterology
- Biologic Therapies and the Allied Health Professional
- Role of Biologic Therapies in Patients with Refractory Disease
- Immunocompetence and Biologic Therapies: Assessing Risks and Preventing Complications from Infections

Neuroinflamatory Aspects in Rheumatology
- Vasculitis of the CNS
- PML: An Infectious Complication of the CNS in Immunosuppressed Patients
- Headache in Patients with Rheumatic Disease
- Neuropsychiatric SLE

Current and Emerging Trials, Mechanisms and New Agents in B-Cell Directed Therapies

Hepatic Effects of Biologic Agents: Current and Future Issues in the Treatment of Rheumatoid Arthritis

B-Cell Literature Review

Rheumatoid Arthritis Virtual Grand Rounds

Rheumatoid Arthritis eJournal Club

Cleveland Clinic CME

For continuing medical education in all fields, visit the Cleveland Clinic Center for Continuing Education at clevelandclinicmeded.com. Live CME and a variety of web-based learning opportunities are offered, and physicians can manage their CME credits using the myCME Web Portal, available 24/7.

Coming Up: 2010

Bone Innovation Summit

This Orthopaedic & Rheumatologic Institute symposium, slated for May 12-14, 2010, continues the legacy of the Cleveland Clinic Musculoskeletal Innovation Summits, bringing together clinicians, scientists, industry, foundations and government leaders to explore:
- Clinical biology of bone health and bone regeneration
- Latest advances in the diagnosis and treatment of bone disease and fracture prevention
- The forefront of tissue engineering and bone repair, with a focus on care for military injuries and severe trauma
- Best practice models and public policy related to assessment and management of clinical outcomes and quality in bone health

This popular event will span two and a half days and will be held at the InterContinental Hotel and Bank of America Conference Center on the Cleveland Clinic campus. For more information, please contact Carolyn Jirousek at 216.445.2028 or 800.223.2273, ext. 52028, or at jirousc@ccf.org.
Selected journal articles published in 2008 by Cleveland Clinic staff rheumatologists:


General Referrals to Cleveland Clinic
24/7 hospital transfers or physician consults
800.553.5056

Referrals to Department of Rheumatic and Immunologic Diseases
216.445.0096 or 800.223.2273, ext. 50096

Arthritis and Musculoskeletal Treatment Center
Referrals/Appointments
216.445.0096 or 800.223.2273, ext. 50096
On the Web at clevelandclinic.org/arthritis and clevelandclinic.org/ortho

Services for Physicians

Physician Directory
View all Cleveland Clinic staff online at clevelandclinic.org/staff.

Physician Liaison
Referring physicians have a direct and personal link to Cleveland Clinic with our Physician Liaison. For help with any interaction involving Cleveland Clinic, contact Physician Liaison Kate Kenny at clevelandclinic.org/ContactKate.

Critical Care Transport Worldwide
Cleveland Clinic’s critical care transport team serves critically ill and highly complex patients across the globe. The transport fleet comprises mobile ICU vehicles, helicopters and fixed-wing aircraft. The transport teams are staffed by physicians, critical care nurse practitioners, critical care nurses, paramedics and ancillary staff, and are customized to meet the needs of the patient. Critical care transport is available for children and adults.

To arrange a transfer for STEMI (ST elevated myocardial infarction), acute stroke, ICH (intracerebral hemorrhage), SAH (subarachnoid hemorrhage) or aortic syndromes, call 877.279.CODE (2633).

For all other critical care transfers, call 216.444.8302 or 800.553.5056.

Track Your Patient’s Care Online
Whether you are referring from near or far, DrConnect offers secure access to your patient’s treatment progress at Cleveland Clinic. To establish a DrConnect account, visit clevelandclinic.org/drconnect or email drconnect@ccf.org.

Online Medical Second Opinions
Request a secure online medical second opinion from Cleveland Clinic specialists. Visit clevelandclinic.org/myconsult for more information.

Outcomes Data Available
The latest Outcomes book from the Cleveland Clinic Orthopaedic & Rheumatologic Institute is available. Our Outcomes books contain clinical outcomes data and information on volumes, innovations, research and publications. To view Outcomes books for many Cleveland Clinic institutes, visit clevelandclinic.org/quality.

Cleveland Clinic’s Rheumatology Program is again ranked No. 2 in the nation by U.S. News & World Report.
These cerebral angiograms of a patient with reversible cerebral vasoconstriction syndrome (RCVS) clearly show multiple areas of stenosis and dilatation in multiple vessels (arrows, top), followed by their resolution (bottom). Reversibility of cerebral angiographic abnormalities is an essential finding in RCVS.

RCVS comprises a group of diverse conditions, all characterized by reversible multifocal narrowing of the cerebral arteries and heralded by sudden, severe “thunderclap” headaches. Associated neurologic deficits may or may not be present. RCVS includes:

- benign angiopathy of the central nervous system (BACNS)
- Call-Fleming syndrome
- postpartum angiopathy
- migrainous vasospasm
- drug-induced “arteritis”

RCVS is a major mimicker of pathologically documented central nervous system vasculitis and should be distinguished from it given the therapeutic and prognostic implications.

Disturbance in the control of cerebral vascular tone is believed to be the critical element in the pathophysiology of RCVS. The alteration in vascular tone may be spontaneous or evoked by various exogenous or endogenous factors. There is no evidence of vasculitic changes in the brain tissue in RCVS.

It is essential for clinicians evaluating patients for CNS vasculitis to be aware of RCVS and to distinguish it from pathologically documented CNS vasculitis. Treatment of RCVS does not require immunosuppressive medications, as is the case with pathologically documented CNS vasculitis.

Dr. Hajj-Ali, member of the Center for Vasculitis Care and Research, specializes in CNS vasculitis along with colleague Leonard Calabrese, DO, R.J. Fasenmyer Chair in Clinical Immunology. Physicians may reach Dr. Hajj-Ali at 216.444.9643 or at hajjalr@ccf.org and Dr. Calabrese at 216.444.5632 or calabrl@ccf.org.