Rheumatology Connections

An Update for Physicians | Fall 2013

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Dear Colleagues,

I’m pleased to share this issue of Cleveland Clinic’s *Rheumatology Connections* with you. The articles here demonstrate the exciting synergy that results from collaboration among the members of the Department of Rheumatic and Immunologic Diseases and with their colleagues beyond the department.

These fruitful “connections” are evident throughout the issue:

- Dr. Elaine Husni profiles our biobank enterprise, which is generating exciting opportunities for biomarker research into the etiology of cardiovascular disease in psoriatic arthritis, immune regulation in granulomatosis with polyangiitis (GPA; Wegener’s), and biomarker analysis in reversible cerebral vasoconstriction syndrome and lupus (page 3).
- Dr. Carol Langford and Dr. Gary Hoffman’s collaboration with trainees has furthered our understanding of the efficacy of maintenance therapy after rituximab treatment for GPA (page 4).
- The collaborative work of Dr. Atul Khasnis has shed light on immunologic perturbations in patients with GPA (page 6).
- Emerging discoveries about the role of microparticles in the etiology of atherosclerosis in patients with GPA have been made possible by the work of Dr. Rula Hajj-Ali and colleagues (page 8).
- The efforts of many specialists from across Cleveland Clinic have expanded opportunities in patient care, research and education through our multidisciplinary Lupus Clinic (page 12).
- Under the direction of Dr. Carmen Gota, Cleveland Clinic’s interdisciplinary Fibromyalgia Clinic has created new treatment paradigms for the management of a therapeutically challenging condition (page 14).
- The fifth Biologic Therapies Summit, held earlier this year under the direction of Dr. Leonard Calabrese, was a success thanks to the collaboration of many staff in the department as well as rheumatologists and specialists from around the world (page 16).

It is the synergy from collaboration that has yielded these diverse and dynamic projects in scientific discovery, patient care, clinical research and education. That collaboration makes me feel honored to work with my 32 rheumatology colleagues at Cleveland Clinic. I hope you enjoy reading about their work. Please contact me with your questions or comments.

Happy Holidays!

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How Can Biobanking Advance Rheumatology Practice?
The Rationale and Early Payoffs of Comprehensive Efforts at Cleveland Clinic
By M. Elaine Husni, MD, MPH

Biobanking is an increasingly integral part of Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases. As scientific research places further emphasis on improving individualized care, or personalized medicine, the science of biobanking can provide clues and insights to improve patient outcomes. After briefly outlining the essentials and benefits of biobanking, this article profiles the several active biobanks managed by our department.

All About Matching Specimens with Clinical Data
Biobanks, or biorepositories, store biological specimens, such as blood, plasma and urine, and combine them with corresponding clinical data from the individuals who supplied the specimens. This biorepository of data links valuable, highly specific, de-identified health information to individual biosamples. Through this combination of specimens and comprehensive clinical information, biobanks provide a structured and novel way to match clinical data with biological samples.

Beyond this core utility, biobanks also serve as exceptional network-building tools, allowing researchers with shared interests to connect and collaborate in disease investigation.

Good Governance Is Paramount
The success of biobanks requires planning and organization, as storage procedures and longitudinal data collection can be complex and demand scrupulous attention to ethical principles and scientific integrity. At Cleveland Clinic, a biobank governing committee is responsible for reviewing the scientific, legal and ethical components of a proposed biobank study while ensuring adherence to IRB policies and procedures for protection of human research subjects.

Because the Department of Rheumatic and Immunologic Diseases includes numerous researchers involved in the collection and storage of human biospecimens in a variety of rheumatic diseases, our group holds quarterly biobank meetings to establish guidelines and best practices for managing our biobanks’ daily operations. We also have two biobank coordinators, Lori Strozniak and Kelly Goodrich, who help implement biobank research protocols and interact with research participants to obtain informed consent and handle recruitment, enrollment and follow-up.

Promoting Early Detection of Cardiovascular Disease in PsA
Elaine Husni, MD, MPH, and colleagues are using biobank resources to recruit participants with psoriatic arthritis (PsA) who consent to provide blood and urine samples and longitudinal clinical data. PsA is a heterogeneous disorder associated with inflammatory arthritis and skin psoriasis. Many, but not all, patients with PsA are at increased risk for cardiovascular disease, so detecting those who are may promote earlier treatment and improved outcomes.

The PsA registry is our largest biorepository, securely storing more than 1,000 biosamples and data on nearly 200 patients. It is focused on correlating clinical data with serum biomarkers of cardiovascular inflammation, subclinical measures and disease activity.

Probing Immune Dysfunction in GPA (Wegener’s)
Atul Khasnis, MD, MS, has teamed with colleagues at Case Western Reserve University to investigate granulomatosis with polyangiitis (GPA; Wegener’s), an unusual multisystem disease characterized by inflammation of small and medium-size blood vessels in various organs that can lead to ischemia, hemorrhage and organ failure.

Central to his efforts is biobanking — specifically, collecting and examining serum biosamples with the aim of better understanding dysfunction of the immune system in GPA. With the advent of biologically targeted therapies such as rituximab, which is FDA-approved for the treatment of GPA, there is a greater need to understand the impact of such treatments on the immune system in this and similar complex illnesses. See the full article on Dr. Khasnis’ work in this area on page 6.

Providing More Clues in CNS Disorders
Rula Hajj-Ali, MD, and her team are studying reversible cerebral vasoconstriction syndrome (RCVS) and central nervous system (CNS) vasculitis. RCVS comprises a group of diverse conditions

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Rituximab-Induced Remission in Granulomatosis with Polyangiitis: To Add or Not to Add a Conventional Maintenance Agent? Retrospective Data from 110 Patients

By Lama Azar, MD; Jason Springer, MD; Carol A. Langford, MD, MHS; and Gary S. Hoffman, MD, MS, MACR

Rituximab (RTX) is an effective remission-inducing agent in granulomatosis with polyangiitis (GPA; Wegener’s). It is uncertain whether RTX is best used with or without a conventional agent for remission maintenance. To explore this question, Cleveland Clinic’s Center for Vasculitis Care and Research conducted a single-center retrospective study to assess the efficacy and safety of RTX induction therapy in patients in whom RTX was used alone vs. in combination with a conventional maintenance agent.

Study Design at a Glance
We retrospectively analyzed data on all patients with GPA treated by our center with at least one course of RTX (four weekly doses of 375 mg/m² IV, or two fixed doses of 1,000 mg IV two weeks apart) until November 2011. Remission was defined as a Birmingham Vasculitis Activity Score (modified for Wegener’s) of 0.

Results
In all, 110 patients (median age, 50 years; 51 percent women) were included (Figure 1). In 91 percent, the indication for the first RTX infusion was relapsing or persistent disease. Median follow-up was 23 months (interquartile range [IQR], 10-50).

Complete remission was achieved in 97 percent of patients. Relapses occurred in 47 percent, and the median time to relapse was 13 months (IQR, 7-20.5). Within a subset of 16 patients who were relapse-free at two years after one RTX course, remissions endured for two to six years in eight patients.

Relapse-free survival was significantly higher in patients receiving a conventional maintenance agent (azathioprine [AZA], methotrexate [MTX]) or, if AZA or MTX were not tolerated, mycophenolate mofetil [MMF]) in conjunction with RTX and glucocorticoids (n = 49) than

Improving Outcomes in Patients with Lupus
Mehrnaz Hojjati, MD, and colleagues are directing Cleveland Clinic’s lupus registry. A great deal of what we have learned about lupus over the past decade has originated from large patient databases and registries.

Early recognition and diagnosis of RCVS can save patients the risks of unnecessary immunosuppression.

We are now building a repository of clinical data, radiologic findings and biological samples from patients with RCVS and CNS vasculitis. By investigating biomarkers to help diagnose RCVS and develop therapeutic targets, we hope to better distinguish RCVS from other cerebral arteriopathies, both inflammatory and noninflammatory.

A Bright Future for Biobanks
The future of biobanking is full of promise and possibilities. The networking opportunities and resources that biobanks provide are priceless, and they open the door for collaborations with colleagues near and far.

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in those not receiving a maintenance agent \((n = 43)\) \((P = .04)\) (Figure 2). The hazard ratio for relapse was 0.54 (95% confidence interval, 0.30-0.99) in those receiving a second agent for remission maintenance.

Serious adverse events did not differ between the two groups.

**Implications Until Prospective Trials Are Performed**

Addition of a conventional maintenance agent to RTX and glucocorticoids reduced the incidence of GPA relapse without resulting in a higher incidence of adverse events. Prospective trials comparing conventional immunosuppressive maintenance agents with repeated scheduled RTX doses are needed. Until those data are available, our findings support the addition of a conventional maintenance agent (AZA or MTX), in the absence of contraindications or intolerance, to reduce the risk of GPA relapse.

*This research was originally presented by Dr. Azar at the 2012 American College of Rheumatology Annual Meeting.*

Dr. Azar completed a rheumatology fellowship in the Department of Rheumatic and Immunologic Diseases in 2013.

Dr. Springer completed a vasculitis fellowship in the Department of Rheumatic and Immunologic Diseases in 2013.

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Dr. Hoffman is the founder of the Center for Vasculitis Care and Research and a staff member in the Department of Rheumatic and Immunologic Diseases. He is also Professor of Medicine, Cleveland Clinic Lerner College of Medicine. He can be reached at hoffmag@ccf.org or 216.445.6996.
In Search of Biomarkers:

Collaboration to Study Immunologic Perturbations in Granulomatosis with Polyangiitis Looks to Ultimately Guide Therapy

By Atul Khasnis, MD, MS

Cleveland Clinic’s Center for Vasculitis Care and Research each year manages more than 500 patients with granulomatosis with polyangiitis (GPA; Wegener’s). This patient volume confers a responsibility to study GPA while also positioning us well to do so. Our efforts in this area include a distinctive ongoing collaboration with Case Western Reserve University (CWRU), profiled below, to prospectively study immunologic perturbations in GPA.

Unmet Needs in Our Understanding of GPA

GPA is an uncommon but potentially life-threatening disease characterized by granulomatous inflammation and, typically, medium and small vessel vasculitis. Affected patients experience serious morbidity from effects of the disease itself and the immunosuppressive medications used to treat it. Patients and their physicians share a strong need to better understand this unusual and uncommon disease.

The immunologic underpinnings of GPA are incompletely understood. Anti-neutrophil cytoplasmic antibodies (ANCAs) are observed in GPA, but their role in pathogenesis is controversial. Gaining immunologic insights into GPA will enable better understanding of the mechanisms of disease onset and sustenance and the triggers of relapse. It will also help identify potential therapeutic targets. All of this will allow for better disease management and patient care.

Identification of reliable biomarkers of disease activity is a longstanding need in GPA. Comparing immunologic parameters during active disease and remission — an important focus of our research collaboration — may yield insights into such potential biomarkers.

The Research Project at a Glance

Our collaboration with CWRU is a prospective observational study funded through Cleveland Clinic’s R.J. Fasenmyer Center for Clinical Immunology. Patients in the study are managed by their own rheumatologists while the research team periodically collects clinical data (captured in an electronic database) paired with blood samples for immunologic studies on a longitudinal basis. The blood samples are sent to the clinical research unit laboratory at Cleveland Clinic, where they are processed for immunologic cells, serum and plasma. These samples are then frozen and stored until they undergo immunologic analyses by two seasoned immunology labs at CWRU.

Our interest lies in examining the immune systems of patients with GPA in detail, so we are analyzing T cells, B cells (Figure 1), monocytes and dendritic cells for phenotype, activation, exhaustion and cycling by flow cytometry. In the future, based on preliminary data, we plan to perform functional studies on these cell subsets in the hope of advancing our understanding of their role in disease pathogenesis. We plan to extend these immunologic studies to neutrophils as well, as neutrophils likely play an important role in GPA pathogenesis. One unanswered question is whether immunologic disturbances observed in peripheral blood accurately reflect immunologic perturbations in inflamed tissues. While we are now performing these studies on peripheral blood, we hope to perform relevant studies on tissue samples obtained for clinically indicated reasons in the future.

Three Primary Research Goals

The project’s three main goals are:

• To study differences in patients’ immune systems during active GPA disease and remission. This will allow us to better understand mechanisms that drive systemic inflammation in GPA. We also plan to search for B-cell subsets that may be responsible for ANCA production. By comparing the immunologic profiles of active disease and remission in GPA, we hope to identify clinically useful immunologic biomarkers of disease activity that can be validated in a patient population of appropriate sample size. Determining disease activity has implications for changing immunosuppression, which is fraught with risk of medication toxicity. Thus the identification of biomarkers promises to facilitate therapeutic decision-making.

• To elucidate the effects of rituximab on the immune systems of patients with GPA. Rituximab (RTX), an anti-CD20 monoclonal antibody (biologic agent), has been approved by the FDA for treatment of GPA. Its main mechanism is thought to be elimination of B-cell subsets that bear CD20 on their surface. Since B cells are part of the immune system (a network), it is plausible that deleting B cells may have qualitative and quantitative impact on other immune cells. We are attempting to evaluate the effects of RTX beyond B-cell depletion, such as effects on the immunologic profiles of other immune cells during B-cell depletion and reconstitution. We are comparing patients who receive RTX with those who have received nonbiologic immunosuppression, with the aim of understanding any unique immunologic aspects of RTX-mediated immunosuppression in GPA.

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• To identify predictors of relapse in GPA. GPA is a relapsing disease, and the cause of relapse is unknown. Ongoing relapses can lead to accrual of organ damage, resulting in increased morbidity and significant impact on quality of life. Since we plan to enroll patients during remission and follow them longitudinally, we will have an opportunity to identify any consistent immunologic changes predating a flare (i.e., “immunologic signatures”) that could be used to guide therapeutic decisions once validated in an appropriately sized patient population.

Benefits in External Validity and Ongoing Collaboration

This project offers a unique opportunity to understand the pathogenesis of GPA. Because this is an observational study and none of its clinical management decisions are influenced by the research protocol, it provides a high level of external validity (i.e., real-world applicability). It also represents an ongoing collaboration between two major academic institutions, Cleveland Clinic and CWRU, that is likely to meaningfully advance our understanding of GPA.

The project’s other key investigators are Leonard Calabrese, DO, and Carol Langford, MD, MHS, of Cleveland Clinic and Michael Lederman, MD, and Donald Anthony, MD, PhD, of CWRU.

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Figure 1. B-cell gating strategy for assessment of B-cell subset frequencies in patients with granulomatosis with polyangiitis (GPA; Wegener’s).
Granulomatosis with polyangiitis (GPA; Wegener’s) is characterized by necrotizing granulomatous inflammation and vasculitis of the small and medium-size blood vessels. Although survival of patients with GPA has improved with immunosuppressive therapy, atherosclerosis has emerged as a significant GPA-associated morbidity that is independent of traditional cardiovascular risk factors. Coronary artery disease, stroke and peripheral occlusive disease occur more frequently in patients with GPA than in healthy controls. The link between GPA and atherosclerosis is not well characterized at a mechanistic level, but it raises the possibility that persistently active vasculitis, or nonspecific inflammation, plays a role in early atherosclerosis.

Microparticles as Markers of Cardiovascular Risk

An increasing body of evidence suggests that, in the course of systemic inflammation, cell-derived microparticles may be prognostic markers for thrombosis, atherosclerotic vascular disease and systemic inflammation. Microparticles are membrane-bound vesicles that bud off normal cells, including leukocytes, platelets and vascular endothelial cells, during activation or apoptosis (Figure 1).

Elevated levels of circulating microparticles have been shown to be associated with cardiovascular risk and are indicative of a poor clinical outcome. Circulating microparticle counts are increased in patients with cardiovascular risk factors. Moreover, microparticle counts are an independent marker of subclinical carotid atherosclerosis in asymptomatic subjects and may be more valuable for mortality prognosis than usual biological markers of myocardial infarction are. In addition, several studies point to microparticles as effectors of vascular wall inflammation.

Microparticles may contain pro-inflammatory mediators, such as IL-1, and can interact directly with activated vascular endothelial cells, triggering monocyte arrest in inflamed and atherosclerotic endothelium. Furthermore, microparticles can interact directly with platelets through the CD36 receptor (Figure 2). This raises the prospect of a novel mechanism for platelet-dependent monocyte recruitment in inflammation and atherosclerosis.

The Link with Rheumatic Diseases

In rheumatic conditions such as rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitides and specifically GPA, microparticle counts can potentially serve as important markers of disease activity.
In keeping with its overall mission, Cleveland Clinic’s Center for Vasculitis Care and Research is studying the relationship between inflammatory disease in GPA and the development of atherosclerosis, with the aim of better understanding the pathogenesis of atherosclerosis in GPA. Our research findings have suggested that (1) the recurrent inflammatory burst that occurs during each relapse in patients with GPA may have a direct role in the pathogenesis of atherosclerosis, and (2) levels of circulating microparticles are elevated during relapse and correlate with platelet reactivity.1

Our Latest Findings — and Implications

We recently further assessed the role of microparticles and their interaction with platelets and vascular endothelial cells in the pathogenesis of atherosclerosis in GPA.2 Microparticles isolated from plasma of GPA patients were added at various ratios to human dermal microvascular endothelial cells (huDMVEC) and incubated for timed periods. Cells were then detached, washed, resuspended in buffer and analyzed by immunofluorescence flow cytometry with anti-ICAM-1 IgG to detect endothelial cell activation. An isotope-matched control IgG was used as control. In addition, fluorescently tagged normal human platelets were incubated with GPA patient-derived microparticles (at a microparticle-to-platelet ratio of 10-to-1), and platelet activation was detected by flow cytometry with PAC-1, an antibody to the activated form of the α2bβ3 integrin.

This study found that:
• Microparticles induce ICAM expression on huDMVECs.
• Platelet surface expression of activated α2bβ3 integrin was significantly enhanced when platelets from healthy donors were pre-incubated with patient-derived microparticles.

These findings demonstrate that microparticles isolated from the plasma of GPA patients can activate platelets and vascular endothelial cells. This suggests a possible role for microparticles as an interface between inflammation and atherothrombosis in GPA — a possibility that we look forward to evaluating in future investigations.

References


Dr. Hajj-Ali is a staff physician in the Center for Vasculitis Care and Research, Department of Rheumatic and Immunologic Diseases, with a special interest in systemic vasculitides and central nervous system vasculitis. She can be reached at hajjalr@ccf.org or 216.444.9643.

On hospital rounds, I was recently asked, “If you could have only one test in a patient with small vessel vasculitis, what would it be?” Some were surprised by my answer: a urinalysis.

To my mind, few tests have the ability to provide information that can detect and potentially prevent the presence of organ- and life-threatening disease the way a urinalysis can. Moreover, the urinalysis is a test that has meaning not only at diagnosis but throughout the patient’s course.

Glomerulonephritis is an important vasculitic manifestation that is typically asymptomatic. In granulomatosis with polyangiitis (Wegener’s) (GPA) and microscopic polyangiitis (MPA), glomerulonephritis can be rapid and severe, requiring dialysis, which has a profound effect on patient quality of life and outcome. Glomerulonephritis can also occur in other forms of vasculitis, including eosinophilic granulomatosis with polyangiitis (Churg-Strauss), IgA vasculitis (Henoch-Schönlein) and cryoglobulinemic vasculitis.

Urinalysis and Serum Creatinine

One may ask, if the concern is the kidneys, why wouldn’t my one test be a serum creatinine? There is no question that serum creatinine is important, as it provides a measure of renal function. However, since an elevated creatinine means that more than 50 percent of renal function has potentially been lost, the goal is to detect glomerulonephritis before a creatinine rise occurs, which the urinalysis is able to do. In glomerulonephritis, the earliest finding is microscopic hematuria with dysmorphic red blood cells, followed...
and/or accompanied by red blood cell casts (Figure 1). Abnormal urinalysis findings, when followed by prompt evaluation and intervention, provide an opportunity to minimize renal injury and damage that can lead to permanent loss of kidney function.

Utility Continues Beyond Diagnosis

The urinalysis remains important even after a diagnosis of GPA or MPA has been made. Studies have shown that although glomerulonephritis is present in 20 percent of patients at diagnosis, 80 percent will go on to have renal disease at some point during their disease course (Hoffman GS, et al. Ann Intern Med. 1992;116(6):488-498). This means that ongoing vigilance for emerging glomerulonephritis is critical. Such vigilance can be ensured by including a urinalysis in the routine monitoring lab tests for patients with vasculitic diseases in which glomerulonephritis can occur. Another strategy we have used is to teach patients to perform urine dipstick self-testing in between their routine monitoring labs.

One confounding issue is that after a patient has had glomerulonephritis, the urine will not always clear completely. It is not uncommon for proteinuria to persist as a result of damage that is not reflective of active disease. Hematuria and even red blood cell casts have also been found to persist in selected patients (Magrey MN, et al. Medicine. 2009;88(6):315-321). The interpretation of such findings must factor in the creatinine measurement, the presence of other disease features and whether there has been a change from previous observations. If it remains unclear whether the findings are indicative of active glomerulonephritis, a renal biopsy may be required.

Although not new or fancy, the urinalysis exemplifies the impact a single biomarker can have in medicine.

Detecting Urothelial Toxicity from Cyclophosphamide

Urinalysis also plays a valuable role in monitoring for urothelial toxicity in cyclophosphamide-treated patients. During treatment, cyclophosphamide can cause bladder injury as a result of urothelial toxicity from the metabolite acrolein. Patients receiving daily cyclophosphamide should take it all at once in the morning and then drink a large amount of fluid throughout the day to minimize urothelial exposure to toxic metabolites, and intermittent cyclophosphamide should be given with hydration and consideration for 2-mercaptoethane sulfonate sodium (MESNA). New microscopic hematuria in a patient receiving cyclophosphamide should raise suspicion for urothelial toxicity. Bladder injury can manifest severely as hemorrhagic cystitis and also represents a risk factor for later development of transitional cell carcinoma. While limiting cyclophosphamide exposure to three to six months through use of staged regimens appears to have reduced the risk of bladder cancer, the agent still poses potential toxicities.


The Urinalysis as a Biomarker

In rheumatology, biomarker discovery is an important avenue of investigation, and our Center for Vasculitis Care and Research is actively engaged in biomarker research here and through the Vasculitis Clinical Research Consortium. Although not new or fancy, the urinalysis exemplifies the impact a single biomarker can have in medicine. As we appropriately expand our range of biomarkers, we must remember the important role that the humble yet powerful urinalysis has in the care of our patients.

Dr. Langford is Director of the Center for Vasculitis Care and Research as well as Vice Chair for Research, Department of Rheumatic and Immunologic Diseases. She can be reached at langfoc@ccf.org or 216.445.6056.
Osteoporosis Outcomes Snapshots

By Chad Deal, MD

To promote transparency and continuous improvement, Cleveland Clinic has been publishing annual Outcomes books for more than a dozen of its institutes since 2007. The 2012 Outcomes book for the Orthopaedic & Rheumatologic Institute shares data on diverse clinical measures across the Department of Rheumatic and Immunologic Diseases. Below is a sampling of the book’s data for our Center for Osteoporosis and Metabolic Bone Disease.

For more outcomes from our department, visit clevelandclinic.org/outcomes.

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71%, 78%, 82%

Percentage of patients with low bone mass and high fracture risk by FRAX® who were started on an osteoporosis medication within 90, 180 and 365 days, respectively, of their DXA bone scan*

*Among 816 patients during 2009-2012 not on treatment at the time of the DXA scan. Osteoporosis medications included bisphosphonates, denosumab, raloxifene and teniparatide.

Why it matters: Guidelines recommend pharmacotherapy for patients with low bone mass (T score < –2.5) at the hip or lumbar spine or with a 10-year absolute fracture risk (as calculated by FRAX) > 20 percent for major osteoporotic fracture or > 3 percent for hip fracture.

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74%

Percentage of patients on glucocorticoids with > 20% 10-year risk for major osteoporotic fracture (by FRAX) who were treated with an osteoporosis medication within one year of DXA*

*From data among 1,476 patients receiving glucocorticoids for more than 90 days during 2010-2012 who were assessed by absolute fracture risk categories for major osteoporotic fracture.

Why it matters: National Osteoporosis Foundation guidelines for glucocorticoid-induced osteoporosis recommend therapy if a patient’s 10-year absolute risk for major osteoporotic fractures (by FRAX) is greater than 20 percent.

Related outcome: 72 percent of patients on glucocorticoids with a 10-year risk for major osteoporotic fractures between 10 and 20 percent were treated with an osteoporosis med within one year, satisfying the stricter American College of Rheumatology guideline recommendations.

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>99%

Percentage of patients treated with zoledronic acid who had vitamin D testing within 90 days before infusion*

*Among 1,411 patients during 2010-2012.

Why it matters: Zoledronic acid (Reclast®) infusion for osteoporosis may be associated with hypocalcemia after infusion. Patients with hypovitaminosis D are at high risk for hypocalcemia. A vitamin D level is deemed standard of care in patients prior to infusion.

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80%

Percentage of denosumab recipients who received a second dose of the medication at 180 ± 60 days after the first dose*

*Among 59 patients during 2010-2012.

Why it matters: Denosumab is indicated for patients with low bone mass at high risk for fracture. Once therapy is started, guidelines recommend treatment at six-month intervals; delays in treatment result in loss of effect.

Related outcome: A third dose of denosumab was given to 92 percent of patients within 180 ± 60 days of the second dose.

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Dr. Deal is Director of the Center for Osteoporosis and Metabolic Bone Disease as well as Vice Chair for Quality and Outcomes in the Department of Rheumatic and Immunologic Diseases. He can be reached at dealc@ccf.org or 216.444.6575.
Making a Difference for Patients with a Multidisciplinary Lupus Clinic

By Howard R. Smith, MD, and Mehrnaz Hojjati, MD

Case Presentation

A 48-year-old man presented to his primary care physician reporting the following symptoms over the prior month: fatigue, low-grade fevers, 15-pound weight loss, new-onset shortness of breath, numbness/tingling over the left foot, and polyarthralgia involving the metacarpophalangeal and proximal interphalangeal joints, wrists, shoulders and knees. His history was notable for hypertension and tobacco chewing for 20 years, and his family history was notable for lupus (systemic lupus erythematosus; SLE) in an aunt. Preliminary lab evaluation by his primary care physician showed an elevated ESR (87 mm/hr) and positive anti-nuclear antibody (ANA) findings (1:640 titer) (Figure 1).

He was referred to Cleveland Clinic’s Center for Vasculitis Care and Research, where further testing revealed elevated anti-dsDNA antibodies, leukopenia and thrombocytopenia, a low C3 level, proteinuria, and anti-cardiolipin IgM antibodies. Serology for anti-neutrophil cytoplasmic antibodies, cryoglobulins, hepatitis and HIV was negative, as was serum protein electrophoresis. Chest CT revealed pulmonary emboli (Figure 2), and EMG showed moderate sensory axonal neuropathy with a mononeuritis multiplex pattern.

Anticoagulation was initiated, along with methylprednisolone, and the patient had same-day appointments at Cleveland Clinic to see a rheumatologist with lupus expertise at the Lupus Clinic, a nephrologist for a renal biopsy, and a neurologist and an infectious disease specialist to rule out lupus mimics. Lupus nephritis and lupus vasculitis were confirmed on further evaluation and renal biopsy. A coordinated course of therapy was initiated that included pulse corticosteroids and additional immunosuppressive therapy with monthly IV cyclophosphamide.

The Case for a Streamlined Multidisciplinary Approach

The above vignette represents the complexity of symptoms with which some SLE patients present, underscoring the importance of a multidisciplinary approach to address all medical aspects of these patients’ cases and fully optimize their care. This case exemplifies the type of patient evaluated and managed at Cleveland Clinic’s new multidisciplinary Lupus Clinic, which was established by the Department of Rheumatic and Immunologic Diseases to integrate the management of patients with SLE and provide comprehensive, leading-edge care.

Same-day access to other specialists with expertise in SLE involving other organs is a cornerstone of the Lupus Clinic.

Figure 1. Anti-nuclear antibody indirect immunofluorescence staining showing a nucleolar pattern.

For patients with complex SLE cases, the Lupus Clinic provides access to the department’s team of rheumatologists specializing in SLE along with streamlined access to subspecialists in other disciplines, including nephrologists, dermatologists, neurologists and preventive cardiologists (see sidebar for additional case example). The clinic offers both consultative services and long-term management, including treatments directed at all of SLE’s diverse facets, such as arthritis, dermatitis, nephritis and cerebritis.

Same-day access to other specialist providers with expertise in SLE involving other organs, such as the kidneys and the skin, is a cornerstone of the Lupus Clinic. It serves to ensure both maximum convenience for patients and care that addresses all aspects of their condition, whether it be SLE or related connective tissue diseases such as overlap syndromes.

Going Beyond the Diagnosis

The Lupus Clinic provides care that goes beyond the diagnosis, focusing on routine follow-up appointments that are tailored to patients’ needs and disease complexity. For instance, patients who are at higher risk for frequent disease flares or end-organ involvement
(e.g., renal complications, which are often clinically asymptomatic) are monitored via simple urine and blood tests at routine follow-up visits. Lupus patients evaluated in the clinic are also offered screening for modifiable cardiovascular risk factors, through Cleveland Clinic’s state-of-the-art Preventive Cardiology Program, as well as lifestyle modification counseling and therapeutic guidance based on their risk stratification.

Additionally, the Lupus Clinic offers interested patients the opportunity to enroll in Cleveland Clinic’s lupus registry, which is directed by Mehrnaz Hojjati, MD, in the Department of Rheumatic and Immunologic Diseases (see details in biobanking article on pages 3-4). The clinic likewise gives patients easy access to investigational clinical trials in SLE and other challenging autoimmune diseases, facilitated by on-site clinical research coordinators. As the Lupus Clinic’s cumulative patient base grows, we look forward to sharing research insights that emerge from these trials.

Drs. Smith and Hojjati are staff physicians in the Department of Rheumatic and Immunologic Diseases whose specialty interests include lupus. Dr. Smith can be reached at smithh4@ccf.org or 216.444.4555. Dr. Hojjati can be reached at hojjatm@ccf.org or 216.444.5624.

A Case Study in Collaboration

A 29-year-old woman presented to her primary care physician reporting six weeks of swelling of the fingers and knees, facial rash, and stabbing pain in the chest with breathing. Examination confirmed pleurisy and edema (Figure 3), and lab results revealed anemia, leukopenia and positive ANA findings.

She was referred to Cleveland Clinic’s Lupus Clinic for further evaluation and treatment. At the Lupus Clinic, she was diagnosed with SLE and found to also have pericarditis and proteinuria. She was started on oral steroid therapy and further evaluated by subspecialists in cardiology, nephrology and dermatology. Additional testing was conducted, including a kidney biopsy.

Her physicians conferred with the referring physician, and a coordinated course of therapy was proposed. It was decided to initiate treatment with the IV immunosuppressants cyclophosphamide and methylprednisolone followed by oral hydroxychloroquine, prednisone and mycophenolate mofetil. The patient received detailed education about her disease and the proposed treatment. After her questions and concerns were addressed, treatment started. She fared well, with rapid resolution of the arthritis, rash and pericarditis. Her kidney function improved, and six months later she had only mild proteinuria and mild renal insufficiency.
The Fibromyalgia Clinic: Why a Specialized Multidisciplinary Approach Makes Sense for Fibromyalgia and Chronic Fatigue Syndrome

By Carmen Gota, MD, and Sara Davin, PsyD

About 4 percent of the general population is estimated to suffer from fibromyalgia, which is probably an underestimate of the condition’s actual prevalence.

In tertiary rheumatology practices, approximately 20 to 30 percent of patients seen are diagnosed with fibromyalgia.

A Quintessentially Clinical Diagnosis

The diagnosis of fibromyalgia is clinical. It is based on the combination of chronic widespread pain, fatigue and nonrestorative sleep as well as many other somatic complaints, such as headaches, memory and concentration impairment, irritable bowel symptoms, urinary frequency and dizziness. Individuals with fibromyalgia typically report pain that is worsened at night, with sitting and after exercise. Most patients also report symptoms of depression, anxiety and other mood problems. To illustrate just how widespread the aforementioned symptoms are in this population, Table 1 lists their prevalence among the first 305 patients in Cleveland Clinic’s Fibromyalgia Clinic cohort.

The maladaptive chronic stress response that leads to fibromyalgia results from a combination of factors, including genetic predisposition, personality traits, environment, traumatic events and emotional problems. These factors trigger and contribute to the persistence of stress and thus of fibromyalgia symptoms. Although the clinical presentation is the same, the specific causal pathways of fibromyalgia differ among individual patients. Thus, each patient may be conceptualized as having a unique fibromyalgia “fingerprint.”

Pharmacotherapy: Important but Not Adequate

Three drugs have been approved for the management of fibromyalgia: pregabalin and the serotonin-norepinephrine reuptake inhibitors milnacipran and duloxetine. In randomized controlled studies, half the patients treated report an improvement in pain of approximately 30 percent. Responders report an average 2-point decrease in pain on an 11-point visual analog scale. However, research shows that for patients with fibromyalgia to feel significantly improved, at least a 50 percent improvement in pain is needed. Notably, other symptoms besides pain, such as fatigue, sleep and mood, need to be addressed and improve as well.

Pharmacotherapy remains an important component of fibromyalgia treatment, but it is insufficient as an isolated intervention, in view of the condition’s multifactorial and unique etiology, as outlined above. A multidisciplinary approach is necessary.

Interdisciplinary Offerings to Address Broad Patient Needs

Because of these challenges, Cleveland Clinic’s Orthopaedic & Rheumatologic Institute and its Neurological Center for Pain collaborated to develop a specialized fibromyalgia clinic in early 2012. The goal of the Fibromyalgia Clinic is to offer multidisciplinary care to patients with fibromyalgia and chronic fatigue syndrome, as well as to help advance knowledge about these difficult conditions through research and education.

Each fibromyalgia patient may be conceptualized as having a unique fibromyalgia “fingerprint.”

Each patient is evaluated by specialists in rheumatology, psychology and physical therapy to obtain a comprehensive evaluation regarding symptoms, deconditioning, stressors, depression, mood, sleep disorders and maladaptive behaviors in response to pain and fatigue. After this initial evaluation, patients are invited to participate in our two distinctive treatment offerings:

• One-Day Intensive Fibromyalgia Program. In the summer of 2013, the Fibromyalgia Clinic launched the One-Day Intensive Fibromyalgia Program, designed for all patients with fibromyalgia. The program immerses participants in a day of education related to fibromyalgia, addressing the maladaptive stress responses that lead to fibromyalgia and reviewing the effectiveness of available interventions. Patients are provided with essential tools, approaches and coping skills for self-management of fibromyalgia. Interactive sessions are led by staff from our program’s three disciplines — rheumatology, physical therapy and psychology — and participants are given educational materials and resources to use at home.

• Fibromyalgia Management Program. The Fibromyalgia Management Program is a coordinated, multidisciplinary treatment plan that includes participation in a cognitive-behavioral therapy group. Targets for modification are maladaptive thoughts, beliefs and attitudes toward pain, and skills-building in healthy behaviors is emphasized. Physical therapists work with patients...
to develop a home exercise program tailored to each patient’s baseline abilities, and they recommend outpatient physical therapy and follow-up visits to monitor progress. Patients return regularly (approximately every three months) for medication and medical management in the clinic, when treatment progress is further assessed.

Our fibromyalgia registry has so far enlisted more than 700 patients. We plan to use the registry’s extensive data to identify patient subsets and create pathways to reduce the cost of care and improve outcomes.

### New and Evolving Initiatives

The Fibromyalgia Clinic staff believes strongly in the value of education and advocacy for the fibromyalgia population. Our team is developing a newsletter for patients to provide education and updates on scientific research and new developments related to fibromyalgia. We are also developing portable, electronic methods of education and intervention for patients established in the Fibromyalgia Clinic. Finally, we are conducting extensive data collection through our fibromyalgia registry, which so far has enlisted more than 700 patients. Our major interests for research using these data include identifying patient subsets and creating pathways to reduce the cost of care and improve outcomes.

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Dr. Davin is Associate Director of the Fibromyalgia Clinic and a psychologist in the Neurological Center for Pain in Cleveland Clinic’s Neurological Institute. She can be reached at davins@ccf.org or 216.445.3977.

**Table 1. Prevalence of Common Fibromyalgia Symptoms in the First 305 Patients in the Fibromyalgia Clinic Cohort**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>98.7%</td>
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<tr>
<td>Widespread pain for three months or more</td>
<td>97.1%</td>
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<tr>
<td>Current depression (PHQ-9 score &gt; 10)</td>
<td>88.6%</td>
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<tr>
<td>Unrefreshing sleep</td>
<td>85.8%</td>
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<tr>
<td>Headaches</td>
<td>82.5%</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>79.5%</td>
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<tr>
<td>Memory difficulty</td>
<td>75.5%</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>67.5%</td>
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<tr>
<td>Constipation alternating with diarrhea</td>
<td>61.8%</td>
</tr>
<tr>
<td>Current severe or moderate-to-severe depression (PHQ-9 score ≥ 15)</td>
<td>45.8%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>41.8%</td>
</tr>
</tbody>
</table>

PHQ-9 = Patient Health Questionnaire-9

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Biologic Therapies Summit and Vasculitis Symposium
Build Audience and Expertise for 2015 and Beyond

What’s both domestic and international, live and online, and five times a bigger draw than when it started a decade ago?

If you guessed the Biologic Therapies Summit from Cleveland Clinic’s R.J. Fasenmyer Center for Clinical Immunology, you guessed right. In May, the center offered the biennial summit for the fifth time, in conjunction with the 22nd Annual Cleveland Review of Rheumatic Diseases. The theme of this year’s three-day CME-certified course was “Lessons Learned from the First Decade, Focusing on New Targets and Agents.”

“The summit has grown from a small meeting of about 100 people to drawing more than 500 over the years, with attendees this year from more than 30 states and nine countries,” says the summit’s program director, Leonard Calabrese, DO, Director of the R.J. Fasenmyer Center for Clinical Immunology in the Department of Rheumatic and Immunologic Diseases. Many attendees have been to all five summits, he adds.

“We offer three days of intense teaching in what many say is the finest clinical meeting in rheumatology they have ever attended,” says Dr. Calabrese. “Some of the world’s leading authorities in biologics participate, including rheumatologists, gastroenterologists, dermatologists and neurologists. Everyone shares information on the use of biologics in their respective fields.”

This year’s faculty was evenly split between Cleveland Clinic experts and their colleagues from around the nation and the world, including speakers from Greece and Ireland. After kicking off the summit with a review of recent basic science breakthroughs in biologics and the potential clinical implications, they shifted to in-depth sessions on approved agents, new agents, predicting toxicity, clinical controversies and new indications.

**Reaching Beyond Ohio — and Beyond Real Time**

Though the summit is held in Cleveland, its reach extends far beyond, as tens of thousands of medical professionals worldwide have viewed some or all of it online (see box), where it’s available on demand as a series of CME-certified webcasts ranging from 15 to 60 minutes in length. The webcasts will remain posted for free CME credit until the Biologic Therapies VI Summit, planned for 2015.

This year’s Biologic Therapies V Summit also was available for real-time viewing, and Dr. Calabrese hopes to offer more-targeted worldwide simulcasts in 2015 and beyond. Possible examples include simulcasts focusing on the reactivation of hepatitis B in China or the reactivation of tuberculosis in the Middle East.

**Vasculitis Merits a Dedicated Precourse Symposium**

One sign of the success of the Biologic Therapies Summit is the interest in the daylong symposium on vasculitis that has immediately preceded the past two summits, in 2011 and 2013. Nearly 300 attendees from diverse medical and surgical specialties participated in this year’s symposium, entitled “Large Vessel Vasculitis, Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome), and Other Unique Vasculitides.” This focus complemented the emphasis on small vessel vasculitis of the 2011 symposium, entitled “New Directions in Small Vessel Vasculitis: ANCA, Target Organs, Treatment, and Beyond.”
Missed the Courses?

No problem. Free CME-certified webcasts of Biologic Therapies V Summit sessions are available now in convenient segments (some as short as 15 minutes) at ccfcme.org/RheumCME. And free CME-certified online monographs based on the summit and the precourse symposium on large vessel vasculitis are coming soon to the same website.

These activities have been approved for AMA PRA Category 1 credit™.

“The Biologic Therapies Summit offers three days of intense teaching in what many say is the finest clinical meeting in rheumatology they have ever attended.”

— Program Director Leonard Calabrese, DO
Cleveland Clinic Plays Exclusive Role in Updating 
Musculoskeletal Volume of The Netter Collection

Cleveland Clinic’s Orthopaedic & Rheumatologic Institute partnered with the publisher of The Netter Collection of Medical Illustrations to comprehensively update the series’ recently published three-part Musculoskeletal System volume. The collaboration represents the first time a medical center has provided exclusive clinical content guidance for a volume of this iconic collection of anatomic illustrations that has educated generations of medical students.

The effort helps complete the second edition of the nine-volume collection, marking the first revision since its mid-20th-century introduction by revered physician and medical illustrator Frank H. Netter, MD.

Co-editors of the second edition’s Musculoskeletal System volume are Joseph P. Iannotti, MD, PhD, Chair of Cleveland Clinic’s Orthopaedic & Rheumatologic Institute, and Richard D. Parker, MD, Chair of the Department of Orthopaedic Surgery. They enlisted the assistance of 50 Cleveland Clinic staff, mostly from the Orthopaedic & Rheumatologic Institute.

“Our publishing partner, Elsevier, wanted to ensure that the updated volume retained the appeal The Netter Collection has always had,” says Dr. Parker. “So we shared a mutual commitment to the same precision, clarity and proficiency in presenting complex concepts simply.”

Specific Role for Rheumatology

Among the experts enlisted was Chad Deal, MD, Vice Chair for Quality and Outcomes in the Department of Rheumatic and Immunologic Diseases. Dr. Deal served as section editor for the comprehensive sections on rheumatic diseases and metabolic diseases in Part III of the volume (Biology and Systemic Diseases), drawing on the expertise of more than a dozen Department of Rheumatic and Immunologic Diseases colleagues and of Ronald Midura, PhD, of the Department of Biomedical Engineering.

Their charge was to update and refresh the volume’s text, add modern imaging where appropriate, organize the content in keeping with modern practice and medical instruction, and guide illustration updates where needed. The latter were carried out by a team of medical illustrators working in the Netter style (Dr. Netter died in 1991).

The Pleasures of Revisiting an Old Friend

“Every medical student and resident across many decades now remembers the Netter publications and how valuable they have been as an aid to understanding anatomy and basic science,” notes Dr. Deal. “It was a pleasure to work with the Netter team to update and expand the rheumatology content for this publication.”

“The medical illustrations in The Netter Collection are second to none,” adds fellow contributor Abby Abelson, MD, Chair of the Department of Rheumatic and Immunologic Diseases. “We were honored to partner on this valued resource, making it a part of the educational legacy of the Orthopaedic & Rheumatologic Institute and Cleveland Clinic.”

The Netter Collection’s second edition is available in electronic and print formats with the hallmark covers that led the collection to be affectionately known as the “Green Books.” The Musculoskeletal System volume (volume 6) consists of three parts — Upper Limb (Part I), Spine and Lower Limb (Part II) and Biology and Systemic Diseases (Part III) — released between late 2012 and early 2013.

“Every medical student and resident across many decades remembers the Netter publications and how valuable they have been as an aid to understanding anatomy and basic science.”

— Chad Deal, MD, section editor for the rheumatic and metabolic diseases portions of The Netter Collection’s revised Musculoskeletal System volume
## Featured Clinical Research

Below are highlights among the dozens of clinical research studies within the Department of Rheumatic and Immunologic Diseases. For details on a given study, contact the principal investigator (see clevelandclinic.org for a directory with contact information).

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<td>Leonard Calabrese, DO</td>
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<td>Phase 1, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Tolerability of MEDI-551 in Scleroderma</td>
<td>Soumya Chatterjee, MD</td>
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<td>Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Tocilizumab vs. Placebo in Patients with Systemic Sclerosis</td>
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<td>Lymphoproliferative Disorders in Patients with Primary Immunodeficiency</td>
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<td>Carmen Gota, MD</td>
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<td>Carmen Gota, MD</td>
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<td>Defining Mechanisms of Atherosclerosis in Autoimmune Diseases</td>
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<td>Long-Term Outcomes of Patients with Reversible Cerebral Vasocostriction Syndrome (RCVS)</td>
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<td>The INTERNational Study of Primary Angitis of the CEntral Nervous System (INTERSPACE)</td>
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<td>Development of a Web-Based Data Management System for the Study of Primary Angitis of the Central Nervous System</td>
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<td>Systemic Lupus Erythematosus Biobank Study</td>
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<td>Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION)</td>
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<td>COMPasS Study: Cardiometabolic Outcome Measures in Psoriatic Arthritis Study</td>
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<td>Ethnographic Research Study: Osteoarthritis and Obesity Pilot Project</td>
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<td>Serial Assessment of the Immunologic Profile in Patients with Granulomatosis with Polyangiitis (Wegener’s)</td>
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<td>Vasculitis Clinical Research Consortium (VCRC): Longitudinal Protocols and Genetic Repository One-Time DNA for Takayasu’s Arteritis, Giant Cell Arteritis, Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss), Polyarteritis Nodosa, Granulomatosis with Polyangiitis (Wegener’s) and Microscopic Polyangiitis</td>
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<td>International, Open-Label, Randomized Controlled Trial Comparing Rituximab with Azathioprine as Maintenance Therapy in Relapsing ANCA-Associated Vasculitis (RITAZAREM)</td>
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<td>International Collaborative Study of Susac Syndrome</td>
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<td>Adult-Onset Periodic Disease Associated with NOD2/CARD15 Gene Mutation</td>
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<td>Qingping Yao, MD, PhD</td>
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