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ADVANCES IN RHEUMATOLOGY

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The rheumatology program at NewYork-Presbyterian Hospital is comprised of faculty affiliated with Weill Cornell Medicine and Hospital for Special Surgery, and Columbia University College of Physicians and Surgeons. The program provides state-of-the-art care to patients with the broad range of inflammatory and autoimmune diseases, pursues groundbreaking research at both the laboratory level and through clinical studies, and offers comprehensive training to medical residents and fellows.

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL RHEUMATOLOGY 2016-17

NewYork-Presbyterian Rheumatology ranks #2 in the nation.

Vasculitis: Rethinking Therapeutic and Diagnostic Approaches

Novel Applications of Standard Therapies

With new drug development specifically targeting vasculitis being limited, **Robert F. Spiera, MD,** Director of the Vasculitis and Scleroderma Program at Hospital for Special Surgery, rheumatologist **Lindsay L. Lally, MD,** and their colleagues turned to investigating existing therapies based on mechanism of action that would seem relevant to some of the less common diseases found under the vasculitis umbrella.

Dr. Robert F. Spiera

Polymyalgia Rheumatica

"Polymyalgia rheumatica is a condition that affects about 1 percent of people over the age of 50 at some point in their lives," says Dr. Spiera. "The good news is that it's easily treatable, the bad news is that it is generally treated with a long course of steroids. Treatment with steroids, even at low doses in an elderly population, comes at an enormous cost in terms of morbidity, increasing, for example, the potential for skin fragility, diabetes, osteoporosis, muscle weakness, cataracts, and cognitive dysfunction."

(continued on page 2)

Identifying the Potential for Infections in Lupus

As a clinician researcher in the Lupus Center in the Division of Rheumatology at NewYork-Presbyterian/ Columbia University Medical Center, **Teja M. Kapoor, MD**, spends a good deal of her time on the trail of opportunistic infections that can develop in patients with systemic lupus erythematosus (SLE).

"Lupus is a very complex disease," says Dr. Kapoor, who previously completed a fellowship in rheumatology at Columbia and joined the faculty last July. "It tends to affect young women who are in the prime of their lives. Along with coping with this lifelong disease, they are also prone to developing infections, sometimes from the medications used to treat lupus."

Powerful immunosuppressants typically prescribed for SLE increase the risk for infections, a major cause of morbidity and mortality. One of the best-studied opportunistic infections is *Pneumocystis carinii* pneumonia (PCP); however, the prevalence of PCP in SLE is not clearly defined. "Rheumatologists have differing opinions about using PCP prophylaxis, and the medication that is most commonly used may cause trouble for our lupus patients," says Dr. Kapoor. She and her Columbia colleagues set out to analyze the prevalence of the infection, with a focus on validating the PCP and SLE diagnoses using an electronic medical record database.

Working with a team at Columbia University's Clinical Data Warehouse, the researchers analyzed electronic medical record data of patients treated at Columbia from 2000 to 2014 using ICD-9 diagnostic codes. "We then created a cohort of 2,013 patients identified as true SLE based on methods we validated," says Dr. Kapoor.

"The strength of having an electronic medical record-based database, rather than an administrative database, is it gives us access to the actual medical

(continued on page 3)

Vasculitis: Rethinking Therapeutic and Diagnostic Approaches *(continued from page 1)*

Dr. Lindsay L. Lally

Seeking to find a less toxic therapy for patients with polymyalgia rheumatic (PMR), Drs. Spiera and Lally turned their attention to interleukin-6, a component of important pathophysiological pathways in PMR. In a small proof-of-concept study, they evaluated tocilizumab, a drug designed to specifically block this pro-inflammatory cytokine, to determine its potential use to treat PMR.

The researchers enrolled 10 patients with newly diagnosed polymyalgia rheumatica who had received less than one month of treatment with corticosteroids. Patients were administered tocilizumab once a month by intravenous infusion in addition to corticosteroids, but were tapered off the steroids much more quickly than is done in routine clinical practice. "Within four months of trial entry, the nine patients that completed the trial were no longer on steroids, and all of them remained in relapse-free remission at 12 months, which was maintained at the 15-month follow-up," says Dr. Spiera.

The pilot study, which was the first prospective study targeting the interleukin-6 molecule in newly diagnosed patients with PMR, suggests that tocilizumab could be a relevant drug with a robust steroid-sparing benefit in the treatment of PMR and serve as a platform for launching a larger trial that would better define the role of this drug in this disease.

Granulomatosis with Polyangiitis

In 2010, results of an NIH-funded clinical trial evaluating rituximab versus cyclophosphamide for severe ANCA-associated vasculitis were published in *The New England Journal of Medicine.* Dr. Spiera served as an investigator and author on the study, which showed that rituximab therapy was as effective as cyclophosphamide in inducing remission in patients, and was superior to cyclophosphamide in those with relapsing disease. "Rituximab has since made major inroads in the treatment of ANCA-associated vasculitis with regard to treating major organ complications," says Dr. Spiera. "These patients previously could go into kidney failure or suffer respiratory failure as the result of pulmonary hemorrhage. But while rituximab works beautifully at cooling off those major disease manifestations, patients are often left with chronic grumbling sinonasal disease – a major determinant of poor quality of life. And even when these patients were treated aggressively with cyclophosphamide or methotrexate, the ENT manifestations did not seem to adequately respond."

Dr. Spiera and others noticed in practice that patients who were prescribed rituximab also seemed to fare better in the ENT domain. Based on these anecdotal observations, he and his colleagues decided to look at this more closely in a retrospective study of 99 of their patients with granulomatosis with polyangiitis (GPA) and severe ENT disease. An otolaryngologist with expertise in GPA provided a score of ENT disease activity. Dr. Spiera and his team reviewed 975 visits among these patients.

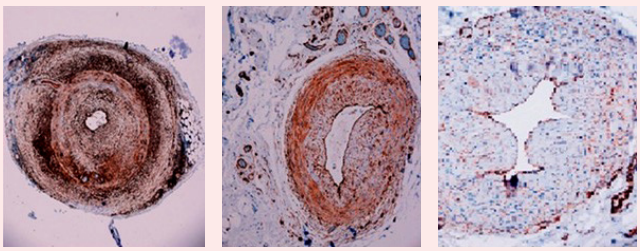
"We found that patients who had been treated with rituximab were 11 times more likely to be in remission in that ENT domain than those treated with cyclophosphamide, methotrexate, or trimethoprim/sulfamethoxazole," notes Dr. Spiera. "This appeared to confirm our clinical impression." Dr. Spiera is now conducting a placebo-controlled pilot study to further evaluate the efficacy of rituximab at inducing otolaryngologic remission in GPA patients with active otolaryngologic disease.

"There's no other disease that causes this kind of destructive sinonasal disease," adds Dr. Spiera. "It's a unique problem for this uncommon disease and successfully treating this manifestation is a major unmet need."

Redefining Diagnostic Tools for Temporal Arteritis

Temporal arteritis is the most common form of vasculitis in people over the age of 50. "The disease can present with systemic and polymyalgia-like symptoms, as well as fevers, but often it presents with severe headaches and severe scalp sensitivity caused by inflammation of the blood vessels going to the head," says Dr. Spiera. "If not properly diagnosed, patients have a substantial risk of vision loss. Like polymyalgia, temporal arteritis is very responsive to steroids. But unlike polymyalgia, it requires high doses of steroids to induce remission, and corticosteroid therapy is generally continued for about a year."

According to Dr. Spiera, temporal arteritis is a bad disease and accurate diagnosis is elusive using temporal artery biopsy, the current standard of care. "Temporal artery biopsies are notoriously inaccurate," notes Dr. Spiera. "Although you don't see false positives, estimates suggest the sensitivity of the test may be as low as 60 percent. If you do biopsies on 10 patients who ultimately have the disease, as few as six of them may be positive. In Europe, researchers are looking at ultrasound to help make the diagnosis, but we felt there might be other ways to look at the biopsies that could increase our yield."



pERM Intensity Score 6
GCA with
Positive Biopsy

pERM Intensity Score 5
GCA with
Negative Biopsy

pERM Intensity Score 3
Control
No GCA

pERM staining was noted predominantly in endothelial cells comprising the intima and vasa vasorum and adventitial fibroblasts.

One pathway, in particular, seemed particularly relevant in the disease. "It is a pathway that is modulated by Rho kinase, or ROCK," explains Dr. Spiera. "This is an important molecule in both inflammatory pathways and in vasculopathy. The molecule is overexpressed in diseases affecting the blood vessels."

Dr. Spiera, Dr. Lally, and their colleagues undertook a study to explore the relationship between temporal artery biopsy results and the activity of ROCK. By staining the biopsies for pERM (phosphorylated ezrin/radixin/moesin), a surrogate for ROCK activity, a

(continued on page 4)

Identifying the Potential for Infections in Lupus *(continued from page 1)*

Dr. Teja M. Kapoor

records themselves," says Dr. Kapoor. "We can 'dive in' and gather very specific information on laboratory data, tissue cultures, and biopsies and confirm whether a diagnosis was an actual diagnosis."

With chart confirmation, overall the investigators determined that the prevalence for PCP in lupus in this cohort was only 0.45 percent – a very low number – while the prevalence of PCP in the patients with AIDS cohort was higher at 5.98 percent. "We were able to screen out patients who were billed as SLE or having PCP infection, but actually did not have the disease or the infection at all," she says. "We also found out that only one patient had actual PCP on histology. The other patients were based on a clinical and radiographic diagnosis for PCP. Remarkably, the one patient with actual PCP had coexisting HIV/AIDS, which is more likely to have put the patient at risk for PCP, rather than the lupus itself."

These results, says Dr. Kapoor, make a strong point against the routine use of PCP prophylaxis in the treatment of lupus patients. "While it is important to prevent infections in patients with lupus, weighing the risks of medications is also key. Their risk for PCP is low, while at the same time, there is a high risk to develop other side effects from the drug."

According to Dr. Kapoor, patients at high risk for PCP are prescribed a PCP prophylaxis – generally trimethoprim/sulfamethoxazole (TMP-SMX), a sulfur-based antibiotic. "The reason why the study results are significant to our care of lupus patients is because a number of lupus patients can have an allergic reaction to medicines with sulfa. It can also lead to a lupus flare in 21 percent of these patients. There are alternatives to TMP-SMX, but the other options can cause gastrointestinal distress, are more expensive, or may not work as well as TMP- SMX," she notes. "Considering the risks and benefits when using TMP-SMX, we find the benefit very low. From our data we've shown that even when they are immune-compromised, there is a low prevalence of PCP in lupus patients overall, and that they may not need PCP prophylaxis unless they have HIV/AIDS."

Historically drug therapies for lupus have come from medications used in other specialties. "The most common are cyclophosphamide and rituximab, typically used in hematological malignancies," says Dr. Kapoor. "We also borrow from transplant, using mycophenolate mofetil or tacrolimus and cyclosporine. There is a hypothesis that hydroxychloroquine, an anti-malarial agent used very commonly in lupus, could be a protective medication against PCP. "

In another study, Dr. Kapoor and the Columbia team examined progressive multifocal leukoencephalopathy (PML), a potentially fatal demyelinating disease in the brain caused by the John Cunningham virus, to evaluate the prevalence of PML in adult and pediatric SLE patients. The researchers focused on validating PML and SLE diagnoses with clinical information again obtained from corresponding medical records in order to better define the risk of PML in SLE. They concluded that the prevalence of PML in adult lupus patients is less than 3/10,000 patients and could not find any PML in children.

Dr. Kapoor undertook another retrospective cohort study of Columbia electronic medical records to establish the prevalence of herpes viruses, both varicella-zoster virus and herpes simplex virus, in SLE patients. "These viruses are very common in immune-compromised patients, and we are finding a high prevalence of these infections in lupus – especially with varicella zoster virus, which causes shingles. In our cohort, not only is there a high rate of shingles, but it is also occurring at a much younger age in lupus patients and causing organ-threatening and life-threatening complications. It highlights the need for having the shingles vaccine for this group, too. Even though they might not meet the age requirement that's now set for the shingles vaccine, lupus patients are at higher risk of developing shingles. Looking into prophylaxis for this infection may be beneficial for our lupus patients.

"We are also studying patients who are in the beginning stages of developing lupus," Dr. Kapoor says. "They are usually categorized as having undifferentiated connective tissue disease. Fewer than 20 percent progress to an autoimmune disease; about 30 percent go into clinical remission; and 50 percent usually continue with just undifferentiated connective tissue disease. We are looking to prevent the progression of lupus by analyzing the biomarkers in the very high-risk patients. If we're able to identify who is in this high-risk group, we can try to treat them earlier and more aggressively to see if we can prevent them from ever developing lupus."

Even with dramatically increased understanding, SLE seems to traffic in a kind of paradox that requires medical detective work to confront it. "As we learn more and more about this disease," says Dr. Kapoor, "we will be better able to create a more targeted treatment approach. There are newer medications that are being tested. Newer research is helping us to clarify who lupus affects and how it affects certain patients, and also to identify the risks of some of these medications."

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Vasculitis: Rethinking Therapeutic and Diagnostic Approaches

(continued from page 2)

pathologist was able to create a scale that measured pERM intensity. The researchers found that using the scoring method dramatically improved the accuracy of the overall test.

"We looked at patients with positive biopsies who had the disease, those with negative biopsies who ended up having the disease, and patients with negative biopsies who didn't ultimately have the disease," says Dr. Spiera. "We found that patients with a positive biopsy would tend to have a high score for pERM staining. Patients with a negative biopsy by routine histology who were subsequently diagnosed with the disease also had a high pERM staining score. Those that didn't have the disease were not likely to have a high pERM staining score." More recently the researchers confirmed the diagnostic utility of assessing ROCK activity to enhance the sensitivity of temporal artery biopsies in a larger cohort of 300 patients. They are now investigating whether altering the pathway can play a therapeutic role in temporal arteritis.

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