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The rheumatology program at NewYork-Presbyterian Hospital is comprised of faculty affiliated with Weill Cornell Medical College 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.

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Addressing the Ongoing Challenges of Systemic Lupus Erythematosus

As founder and Clinical Director of the new Lupus Center and the Director of Rheumatology Clinical Research at NewYork-Presbyterian/Columbia University Medical Center, **Anca D. Askanase, MD, MPH,** is well aware that a comprehensive understanding of lupus continues to elude the rheumatology community.

"We're still in the infancy stage with lupus," says Dr. Askanase, an internationally renowned clinician, diagnostician, and researcher with more than 15 years specializing in lupus. "We need to come up with some unifying diagnoses, outcome measures, and treatment algorithms that work for the whole disease."

Among the challenges, notes Dr. Askanase, are that lupus can range from mild to life threatening and it happens in stages. "It's an accumulation over time of immune system abnormalities that leads to tissue inflammation, pathology, and the signs and symptoms of lupus," says Dr. Askanase. "Many patients may be experiencing some symptoms long before they seek a doctor's opinion. I think the diagnosis is harder when things slowly add up, where it's a process that occurs over a period of years."

> **"We're still in the infancy stage with lupus. We need to come up with some unifying diagnoses, outcome measures, and treatment algorithms that work for the whole disease."**
>
> **– Dr. Anca D. Askanase**

It is an opinion widely shared. "Historically, we've been using classification and diagnosis criteria for

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Systemic Lupus Erythematosus: Understanding and Managing Renal Involvement

Twice a year on a Friday, **Kyriakos A. Kirou, MD, DSc,** Clinical Co-Director of the Mary Kirkland Center for Lupus Care and Director of the Lupus Nephritis Program at Hospital for Special Surgery, and other HSS rheumatologists are joined by nephrologists and a renal pathologist from NewYork-Presbyterian/Weill Cornell Medical Center for the express purpose of an in-depth discussion of the care of challenging cases of patients with lupus nephritis, their optimal therapy, and outcomes. Discussion of lupus nephritis cases continues, less formally, every Friday, and literally at any time there is a need to do so, especially when rheumatology fellows need advice with their cases.

Dr. Kyriakos A. Kirou

"We established the Lupus Nephritis Program to allow us to focus specifically on this disease because it's complicated and it requires a multidisciplinary approach," says Dr. Kirou. "Our goal is to provide the best possible care for our lupus nephritis patients by using the exceptional resources available to us at Hospital for Special Surgery and NewYork-Presbyterian/Weill Cornell. Our approach includes the close collaboration of rheumatologists, nephrologists, a kidney pathologist, our nurse practitioner, and infusion room nurses."

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Addressing the Ongoing Challenges of Systemic Lupus Erythematosus *(continued from page 1)*

lupus," says Dr. Askanase. "There's currently an effort to update those by the Systemic Lupus International Collaborating Clinic [SLICC], which is a group of physicians from around the world trying to redefine criteria and redefine the diagnosis of lupus. The aim of this change is to make the diagnosis criteria more sensitive with an attempt to include a larger number of patients."

Dr. Anca D. Askanase

In addition to her membership on the SLICC, Dr. Askanase serves on the Medical-Scientific Advisory Council of the Lupus Foundation of America, where she and her colleagues are working to define a more user-friendly and comprehensive outcome measure.

These types of initiatives have precedent. "Until relatively recently, the lupus community could not agree on a definition of a lupus flare, a situation that created a barrier to the development of new, safe, and more tolerable treatments for lupus," notes Dr. Askanase. "As a result, the Lupus Foundation of America spearheaded a four-year, worldwide initiative to develop the first universally accepted definition of a lupus flare. It seemed a foundational step that was necessary for us and our patients. Basically we agreed that a flare is a change in lupus signs and symptoms, as well as the way patients feel, that could potentially trigger a change in treatment, and further refinement of the definition is underway."

On the Road to New Therapeutics

The standard armamentarium for lupus includes antimalarials, nonsteroidal anti-inflammatory drugs, corticosteroids, cytotoxics, and immune suppressants – all of which improve disease activity but put patients at risk for long-term consequences from both low-level, active SLE and from the medications themselves. So new therapeutics developed specifically for lupus are desperately needed.

"Steroids are both our 'biggest friend' because of the major impact they have made on the survival rate of lupus patients, but also our 'biggest enemy' because of the long-term damage they can cause," says Dr. Askanase. "There is a strong interest in replacing steroids with effective alternatives; but the major hurdle is that all of the drugs that we've been looking at recently are drugs that require a loading period and time for the biologic effect to take place. Prednisone, non-specifically and indiscriminately, shuts down the immune systems very fast.

"We have also borrowed medications from both the transplant repertoire and the chemotherapy repertoire to suppress the disease's over-driven immune system," says Dr. Askanase. "These include the immunosupressants mycophenolate mofetil and azathioprine, as well as cytoxan and methotrexate. Researchers are continuing to look at drugs used in chemotherapeutic indications, but also at drugs that are more specifically developed for lupus. There is interest in using some of the multiple myeloma drugs, such as Velcade®, and a similar compound, ixazomib, which is currently in clinical trials not only for multiple myeloma but also specifically for lupus."

Dr. Askanase is actively involved in clinical research to develop new therapeutics that could redefine outcomes for lupus. She has been an investigator on multiple NIH and industry sponsored clinical trials, including the Phase III clinical trial and several Phase IV clinical trials that allowed for the approval of Benlysta® (belimumab) – a monoclonal antibody, which represents a breakthrough in lupus drug development and the first FDA-approved treatment for lupus in 50 years.

She also was lead author on a report of observational studies of Benlysta® published in *Rheumatic Diseases Clinics of North America*. The paper discusses three post-marketing experiences that examined the clinical use of belimumab in the treatment of SLE patients outside of clinical trials in real-world practices. "Each of the three observational studies demonstrated that belimumab was generally well tolerated and was safe to incorporate into standard SLE therapy," says Dr. Askanase. "No new safety signals were noted with regards to infections, malignancies, depression, or deaths."

Ideally, down the road, Dr. Askanase hopes researchers will be able to identify what drives lupus manifestations – the cytokine or several cytokines and their role in the pathogenesis of lupus. Out of that discovery could come the right anticytokine, antisignaling molecule, or a combination of both that would enable physicians to control lupus and put it into permanent remission.

"Obviously, there are many pressing questions surrounding this disease that need to be more accurately and rapidly answered," says Dr. Askanase. "Those answers may ultimately emerge from large-scale international collaborations, such as the SLICC, which are pooling cohorts of lupus patients to create a comprehensive database. There is strength in numbers. Having a very large database of patients will help us to answer some of the very important questions. These include actual risk for malignancy or central nervous involvement, long-term sequela of lupus, and whether we are able to make an impact on mortality and morbidity over time."

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For More Information

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Systemic Lupus Erythematosus: Understanding and Managing Renal Involvement *(continued from page 1)*

(From left) Surya V. Seshan, MD, kidney pathologist, Miriam Chung, MD, and James M. Chevalier, MD, nephrologists, and Kyriakos A. Kirou, MD, and Doruk Erkan, MD, rheumatologists, during a weekly conference of the Lupus Nephritis Program

In addition to many other complications of lupus – including cardiovascular, pulmonary, musculoskeletal, gastrointestinal, and neuro-psychiatric – lupus nephritis is a prominent feature of the disease. "Approximately half of lupus patients develop lupus nephritis, usually early in the course of SLE," says Dr. Kirou, "and approximately 10 to 20 percent of those will progress to dialysis or transplantation.

Clinical Presentation of Lupus Nephritis

- Proteinuria
- Microscopic hematuria
- Edema
- Hypertension
- Rising serum Cr level
- Nephrotic syndrome

"When the kidney is affected, a very common finding is swelling of the feet," explains Dr. Kirou. "Blood pressure can be high, which can cause headaches. And in a minority of patients, the urine becomes dark signifying the presence of blood, or foamy because protein is present. These are all clues for the rheumatologist to consider that the patient may have nephritis."

Dr. Kirou notes that as the disease becomes more active, the patient may have a high ANA titer and a positive anti-double-stranded DNA test. "The levels of complement proteins C3 and C4 are often low, especially in lupus nephritis, reflecting the activation of the immune system," explains Dr. Kirou. "Below 90 mg/dl for C3 and below 16 mg/dl for the C4 are considered low, but the lower they become, the more likely they are to be indicative of severe disease."

While symptom presentation and laboratory tests can indicate a diagnosis of lupus nephritis, Dr. Kirou notes that renal ultrasound may be recommended to first rule out other causes of kidney disease. A kidney biopsy is then typically performed on all patients with clinical evidence of previously untreated active lupus nephritis.

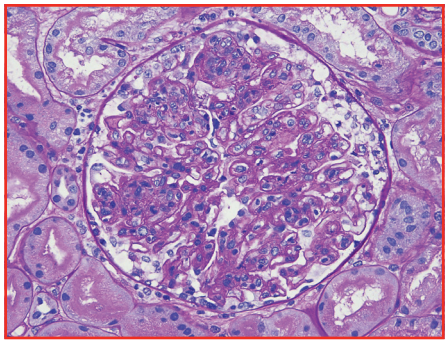
"The biopsy will allow us to determine the degree of activity, the degree of inflammation in the kidney, and the degree of scarring," says Dr. Kirou. "If a lot of scarring is present but not much disease activity, then we generally do not recommend immunosuppressant medications since there's little or no room for improvement. These patients will likely go on to need hemodialysis or kidney transplant. Patients who are active on the biopsy will need aggressive therapy. The biopsy also helps us decide what therapy to administer. Our renal pathologist, Dr. Surya Seshan, reads the biopsies of all of our patients and helps us arrive at the right diagnosis and then the right treatment approach for each patient."

Classifying and Treating Lupus Nephritis

A kidney biopsy also enables the lupus nephritis to be classified according to the International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis and evaluated in terms of its activity and chronicity. The biopsy can also help exclude other causes for the renal disease such as acute tubular necrosis due to medications or hypovolemia.

"Class I represents very minor involvement of the kidneys and is not significant clinically. Class II also indicates a very mild degree of disease, with some inflammation present but not enough to trigger therapy," explains Dr. Kirou. "The disease becomes more serious with Class III and Class IV, representing the proliferation of cells within the kidney or other cells coming from blood in the kidney, which will eventually cause trouble with scarring and kidney function."

Class V may exist by itself or in association with Classes III and IV and is different than those. "With Class V, lupus nephritis is a membranous disease," says Dr. Kirou. "So now the problem is in the basement membrane where the glomerular capillaries – small blood vessels where blood filtration to form the urine takes place – are attached. This Class V lupus nephritis, or membranous nephritis, can be mild or more severe depending on the amount of protein leaking into the urine. Classes III, IV, and V often require aggressive treatment. Most doctors will use steroids or similar compounds because they work quickly. The treatment may begin with a high dosage administered intravenously for one to three days just to get a head start on attacking the inflammation. This would be followed by an oral regimen of about 40 to 60 mg of prednisone per day.



Kidney biopsy from a patient with Class IV lupus nephritis showing a glomerulus with narrowing/closing of the capillaries from an abnormal increase of cells within those vessels. (Courtesy of Dr. Surya V. Seshan, Professor of Clinical Pathology and Laboratory Medicine at Weill Cornell Medical College)

"At the same time we know that the prednisone doesn't have a long-lasting effect so we will start an induction regimen with other agents to bring the disease under control," says Dr. Kirou. "These would be

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classically either cyclophosphamide or mycophenolate mofetil. After we achieve some control, hopefully the disease will respond and we will start to see reduced swelling and a decrease in proteinuria and blood in the urine, as well as an improvement in blood pressure. When we reach that stage, we want to maintain it because if we don't, the disease will come back. It's a relapsing disease. So we will want to give a maintenance therapy for at least two years or so."

Looking Ahead

Dr. Kirou recommends that in the immediate future "physicians should be more sensitized to treating lupus nephritis very aggressively and very early on. "Time is kidney," says Dr. Kirou. "It's important to act quickly and effectively, especially to prevent scarring, which is irreversible. The more attacks there are on the kidney, the more likely the patient will need dialysis."

The work of Dr. Kirou and his colleagues at HSS and NewYork-Presbyterian extends to collaborations with rheumatologists and nephrologists with an interest in lupus nephritis across the country and around the world through organizations such as the Lupus Nephritis Trials Network. The mission of this international organization of clinicians and scientists is to foster collaborations that include clinical trials designed to prevent chronic kidney disease and end-stage renal failure in patients with lupus; develop guidelines for assessing and treating patients with lupus nephritis; and pursue investigations on a wide variety of therapeutic agents, treatment methodologies, and biomarkers of disease.

Dr. Kirou is also an investigator in the ALLURE study, a Phase III randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of abatacept or placebo in combination with mycophenolate mofetil and corticosteroids in subjects with active Class III or IV lupus nephritis. The study is expected to enroll approximately 400 patients in 120 sites worldwide.

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