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While research continues on new therapies for lupus, the 2011 American College of Rheumatology (ACR) was particularly notable for its insights into how to design such trials, according to ALR Scientific Advisory Board Chair Mary (Peggy) K. Crow, MD.

One of the most important and, yes, even exciting presentations came from David Wofsy, MD, professor of rheumatology at the University California-San Francisco, she said. Dr. Wofsy’s presentation, highlighted here, provided a “what if” perspective on the abatacept clinical trial for lupus nephritis, demonstrating that the trial would have had far better outcomes if its primary endpoints had been less restrictive. The exercise demonstrates the importance of choosing the most appropriate outcome measures for clinical trials in lupus, Dr. Crow said, and reiterates the learning curve that still exists in designing clinical trials for what is a very complex and heterogenous disease. “It’s a message to keep an open mind and understand that we still don’t know the best way to design the trials yet, but that we’re learning all the time,” she said.

She also found hope in the results of a large pregnancy study presented at the meeting by ALR grantees Jane Salmon, MD, of the Hospital for Special Surgery in New York, and Jill Buyon, MD, of New York University School of Medicine. The study showed that pregnancy in women with lupus was far safer than previously thought. “The message is that pregnancy is certainly an option for lupus patients,” Dr. Crow said. The study also demonstrated the growing importance of lupus registries of real-life patients in improving our understanding of the disease, its complications, and its progression.

On the basic science side, Dr. Crow highlighted the numerous studies focused on the role of the innate immune system—the part of the immune system designed to respond immediately to threats, versus the adaptive immune system, which takes longer to mount a response—in lupus. “The role of the innate immune system, which was not really recognized as being so significant in lupus pathogenesis not so long ago, continues to be stronger and stronger,” she said. Of particular interest, she said, is the role of neutrophils and immune system nucleic acid-containing complexes that activate the innate immune system, contributing to the production of pro-inflammatory chemicals such as interferon.

More advanced, however, is work on biomarkers in lupus. Dr. Crow highlighted a study she and her colleagues presented, which linked clinical features to gene and protein expression patterns. Once validated in additional studies, she said, it could eventually help clinicians predict the course of the disease and select therapies based on the molecular characteristics of the disease and the patient, just as we’re starting to do today in cancer.

More information about lupus and treatment advances can be found by visiting www.lupusresearch.org.
First Lupus Nephritis Diagnosis and Management Guidelines Released

About 60% of people with lupus will eventually develop lupus-related kidney disease, or lupus nephritis. Yet until now, there was no consensus on the best way to diagnose and manage this common complication. That changed at ACR, when ALR grantee and ALR Scientific Advisory Board (SAB) member Bevra H. Hahn, MD, of the University of California-Los Angeles School of Medicine, presented new guidelines from the American College of Rheumatology. The guidelines, which will be published in an upcoming issue of *Arthritis & Rheumatism*, were developed by a 24-member committee that Dr. Hahn headed, and vetted by separate task force.

The guidelines recommend that physicians perform kidney biopsies on anyone with clinical signs of the disease; classify the disease stage based on the International Society of Nephrology / Renal Pathology Society’s classification; and treat the disease based on that classification.

Other key recommendations include:

- All patients should receive hydroxychloroquine, which can reduce the risk of long-term kidney damage
- Patients may receive azathioprine during the induction phase of therapy, but it should no longer be used as maintenance therapy
- Patients with a proteinuria of 0.5 g/24 hours or greater, or an equivalent protein/creatinine ratio, should receive an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker
- Patients should maintain a blood pressure of 130/80 mmHg or less
- Patients with low-density lipoprotein (LDL) cholesterol levels greater than 100 mg/dL should receive a statin
- Women of reproductive age should be counseled about pregnancy

For induction therapy, the panel recommended either mycophenolate mofetil (MMF) or cyclophosphamide (CYC) in patients with Class III/IV lupus nephritis, but MMF (2-3 g/day for 6 months) for African Americans and Hispanics. All patients should also receive a glucocorticoid IV pulse for 3 days, then prednisone 0.5-1mg/kg per day with eventual tapering to the lowest effective dose.

The guidelines also offer a choice of induction method for CYC: either the low-dose, Euro-Lupus regimen (500 mg IV every 2 weeks for 6 weeks) for those of Caucasian or European background; or the high-dose, National Institutes of Health regimen (500-1000 mg/m² body surface area monthly for 6 months). Both provide similar improvement according to several studies.

If patients fail the first induction drug, they should be switched to the other. If patients fail both MMF and CYC, the guidelines suggest starting rituximab (Rituxan®) or calcineurin inhibitors. Several open-label trials suggest that rituximab may benefit patients with lupus nephritis.

Once the acute phase of the disease improves, doctors can maintain patients on MMF (1-2 g/day) or azathioprine (2 mg/kg/d ± low dose).

Patients with Class V membranous lupus nephritis should start on MMF (2-3 g daily for 6 months) plus prednisone (0.5 mg/kg/day for 6 months) and, if they improve, receive maintenance therapy
with MMF or azathioprine. If they do not improve, they should be started on CYC (500-1000 mg/m² monthly for 6 months), plus a glucocorticoid pulse followed by daily prednisone (0.5-1.0 mg/kg/day).

The guidelines also address management in pregnant women. Women with a history of Class III or higher disease do not require treatment if there is no evidence of disease activity. Those with mild disease activity should receive hydroxychloroquine (200mg-400mg daily), while those with clinically active disease should receive prednisone at doses required to suppress activity and, if necessary, azathioprine not to exceed 2/mg/kg/day).

“These are only guidelines designed to remind clinicians of what is good clinical practice,” said Dr. Hahn. Clinicians can still treat individual patients outside of the recommendations, she said.

**Key point:** *These guidelines represent the best evidence to date about available treatments for lupus nephritis. If your doctor is not treating your disease according to these recommendations, share them and discuss possible treatment changes.*
**The Latest Treatment Advances for Lupus**

**IFNa-Kinoid: A Vaccine for Lupus?**

What if there was a vaccine that could harness the strength of your own immune system to block the activity of a key protein involved in the underlying disease processes of lupus? It’s not as far-fetched as it sounds.

Researchers from the Université Catholique de Louvain, in Brussels, Belgium, presented intriguing data from a small study in 28 patients with mild-to-moderate lupus, 21 of whom received a novel immunotherapy treatment called IFN-a-kinoid, 7 of whom received a placebo.1 The injectable treatment, from Paris-based pharmaceutical company NeoVacs, blocks production of interferon alpha (IFNa) inflammatory cytokines. These cytokines stimulate the autoantibody response that forms the hallmark of lupus pathology.

Participants received increasingly higher doses of the study drug, with the initial, lowest dose injected at the trial’s start; a slightly higher dose a week later; another, higher dose at 1 month; and the final, highest dose, given to half the participants at day 84. All participants were followed for 3 to 15 months.

Other than some mild irritation at the injection site, there were no significant side effects. All patients produced antibodies against IFNa, demonstrating that the vaccine had the desired immunological effect. Participants whose blood was positive for the IFNa signature demonstrated a significant reduction in IFNa activity compared to those receiving a placebo (about two-thirds of those with lupus have the IFNa signature). In addition, there was a statistically significant improvement in complement C3, a biomarker for disease activity; a reduction of the IFNa gene signature; and lower levels of dsDNA antibodies, all of which suggest a reduction in disease activity. The results were so encouraging, researchers said, that they plan to begin Phase II trials in 2012 to assess the ability of the vaccine to prevent lupus flares.

**Key point:** Another possible treatment for lupus is moving forward to the next phase of clinical trials.

**Belimumab (Benlysta) for Renal Nephritis**

In 2011, belimumab (Benlysta) became the first new drug approved to treat lupus in more than 50 years. Now researchers are investigating its potential for lupus nephritis. In a study presented at ACR, researchers evaluated various kidney-related biomarkers from patients who participated in the large, phase III trials that led to the drug’s approval. None had severe active lupus nephritis, nor were the studies designed to evaluate the effect of belimumab on kidney function. Nonetheless, in this secondary analysis researchers found that individuals who received belimumab for 1 year had lower rates of renal flares, higher rates of lupus nephritis remission, and shorter time to first renal remission than those who received standard therapy (the control group). They also showed greater improvement in proteinuria (a marker of kidney dysfunction) and improvement on 2 assessments used to measure renal function, the SELENA-SLEDAI and BILAG.

**Key point:** Belimumab may have some benefits for people with lupus nephritis. Human Genome Sciences, which developed belimumab, is considering whether to begin clinical trials focused on patients with lupus nephritis.
Update on Belimumab (Benlysta)

Several posters presented during the ACR meeting highlighted long-term safety and efficacy outcomes from the pivotal clinical trials that led to belimumab’s (Benlysta) approval. In one study, researchers combined data from 3 clinical trials involving 2,133 patients who received belimumab for 76 weeks. Researchers found similar rates of adverse events overall between the group that received a placebo and the group that received belimumab; as well as similar numbers of participants in each group who dropped out of the trial because of adverse events. Participants receiving belimumab did have higher rates of depression, infection, and reactions at the infusion site than the placebo group.ii

**Key point:** The safety data seen in individual belimumab trials remained relevant even when all the trials were combined.

A second study assessed safety and efficacy data in individuals who had been receiving belimumab for 6 years.iii Researchers reported on 296 patients with lupus who participated in the original clinical trials for the drug. After 6 years, 208 remained on the drug. Rates of adverse events remained stable or actually declined over the time period. Participant scores on the SLE Responder Index (SRI), which measures disease activity, continued to improve, while the number of patients experiencing new flares fell. After the first year on the drug, 38% of patients receiving belimumab experienced at least one BILAG A or 2 new B flares compared to 44% of those receiving a placebo; but by year 6, that figure had dropped to 11%. In addition, while after 1 year on belimumab 84% of participants had experienced an SRI flare (17% severe) compared to 85% (19% severe) on placebo, after 6 years that had dropped to 42% (5% severe). Long-term participants also demonstrated increases in complement C3 or C4 and declining autoantibody levels over the time period. In addition, patients required about a third fewer corticosteroids after 6 years than when they first joined the trial.

**Key point:** Belimumab appears safe over time, with continued increases in efficacy.

In a third study, researchers evaluated various biomarkers in clinical trial participants who received belimumab for 1 year.iv They found that individuals with higher baseline disease activity (a SELENA-SLEDAI score of 10 or higher); positive anti-dsDNA levels; and low complement (C3/C4) all responded better to belimumab than those with lower disease activity. In other words, the sicker the patients, the greater their response. Patients with positive anti-dsDNA and low complement had response rates of 51.5% with the 10 mg/kg dose compared to response rates of 31.7% with placebo. That compares to overall response rates of all participants receiving belimumab of 50.6% and 38.8% for placebo.

**Key point:** Patients with greater disease activity are more likely to respond to belimumab therapy than those with mild-to-moderate disease activity.

In a fourth study, researchers evaluated the effects of lupus on health-related quality of life, a measure that addresses numerous areas in which the disease impacts the quality of life. Other studies find that the impact of lupus is as significant as that of AIDS, rheumatoid arthritis, diabetes, and congestive heart failure. In the clinical trials that led to the approval of belimumab, participants’ quality of life was assessed at the beginning of the trial and again at the end. When researchers evaluated that data, they found that those who benefitted the most from the drug also saw their quality of life improve the greatest. For instance, in response to the question: “Compared with 1 year ago, how are you today?” 76% of responders said they were “somewhat/much better” and 34% responded that they were “much better” compared to just 33.5% and 14.6% of nonresponders, respectively. Responders also experienced significant improvements in fatigue.

**Key point:** People who respond to belimumab experience not just disease improvement, but improvement in their overall quality of life, including less fatigue.
Abatacept (Orencia) for Lupus Nephritis

One reason it has been so difficult to find effective treatments for lupus and lupus nephritis is related not to the potential efficacy of the medication itself, but to the design of clinical trials developed to assess these investigational compounds. That became quite clear during two presentations this year.

Efficacy and Safety of Abatacept Over 12 Months in Patients with Lupus Nephritis: Results From a Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase II/III Study

In the first, researcher Richard Furie, MD, of the North Shore-Long Island Jewish Health System in Lake Success, NY, presented the result of a 12-month study of abatacept in 228 patients with lupus nephritis who also received mycophenolate mofetil (MMF).\(^\text{i}\) The study found no significant improvement compared to participants who did not receive the study drug. One bright spot is that the 122 patients with nephrotic lupus nephritis, a more serious form of the disease, experienced a greater improvement in their urinary protein-to-creatinine ratio in the second 6 months than those in the placebo group, suggesting that more study should be done in this subset of patients. There were no significant safety issues related to abatacept.

Abatacept for Lupus Nephritis: Alternative Outcome Measures Support Opposing Interpretations of Data From a Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase II/III Study

In the second presentation, researcher David Wofsy of the VA Medical Center in San Francisco showed that the results would have been far different if different endpoints, or outcomes, were used.\(^\text{vii}\) In the original study, patients had to achieve a complete response on two successive visits, defined as an eGFR (a test used to measure kidney status) within 10% of the pre-treatment value; a urine protein-to-creatinine ratio less than 30 mg/mmol; and normal urine sediment. This requirement, said Dr. Wofsy, “is a very high bar to meet,” with few, if any, other studies in lupus nephritis requiring such stringent values or requiring that they be met on two successive visits.

Dr. Wofsy’s analysis used a less stringent but still clinically relevant definition of complete response (which is currently being used in another lupus nephritis trial). It required a blood creatinine level that was either normal or less than or equal to 125% of the baseline ratio; a urine protein/creatinine ratio less than 0.5 mg/mg; and a prednisone dose less than or equal to 10 mg/day at the end of the study.

When this criteria was used, he reported, there were significant improvements between those patients who received the study drug and those who did not, particularly among patients with the most severe nephritis when the study began.

“We are locked into a language that is not ours,” Dr. Wofsy said after presenting the data. Phrases like “complete” and “partial” response come from the oncology world, he noted. “We need to get away from this language that doesn’t describe our disease.”

Key point: Abatacept may have some benefit for patients with lupus nephritis; but, more importantly, clinical trial endpoints significantly impact trial results.

Looking Down the Road: New Therapies Under Investigation for Lupus

What’s next in lupus therapies? Here’s a look at one compound still in the very early stages of investigation as a lupus treatment. The results of this trial were presented at the 2011 ACR meeting.

Sirukumab

This human monoclonal IgG1 kappa antibody is being developed by Centocor Research & Development, a division of Johnson & Johnson Pharmaceutical. It targets and inhibits interleukin-6,
which plays a role in autoimmune diseases like lupus. The study presented at ACR was designed to evaluate the safety and pharmacokinetics of various dosages of sirukumab in 33 patients with cutaneous lupus or 15 patients with systemic lupus erythematosus (SLE). The study showed that the drug was generally safe in both groups, with all patients exhibiting decreases in complement C3 and C4. None had any flares, nor did any participants develop antibodies to the drug itself. Sirukumab is also being investigated in a Phase II trial for lupus nephritis.

**Key point:** *This study highlights the potential of another drug to treat lupus.*
A holy grail of lupus is to identify a panel of blood tests that can tell physicians how a patient’s disease will progress and what treatments would be most beneficial. This is particularly difficult given that the disease presents so differently in so many patients. But a poster presented at the ACR meeting by researchers at the Hospital for Special Surgery in New York City, including ALR Scientific Advisory Board Chair Mary “Peggy” Crow, MD, reports on a recent study that may eventually provide that information.ix

The researchers conducted genetic analyses and measured levels of 44 autoantibodies and pro-inflammatory cytokines on 169 blood samples from 23 patients with lupus and 5 healthy donors that had been collected over 3 years. The two most common gene signatures were type 1 interferon (IFN-1) inducible genes and neutrophil granule-related genes. Patients with neither gene signature had only mild disease; while those with both the IFN-1 and neutrophil signatures were more likely to experience vascular complications such as cardiovascular and kidney damage, and much higher levels of anti-SSA/Ro autoantibodies. Patients who expressed the IFN-1 signature only were more likely to have mucocutaneous manifestations, such as those affecting the skin, scalp, and nails, and much higher levels of tumor necrosis factor.

Key point: This study provides promising data on the potential of a biomarker panel to identify subsets of lupus disease that could guide treatment decisions. Additional clinical trials are necessary, however.
One of the most devastating effects of lupus is that it often affects women during their childbearing years. For years, doctors warned women with lupus to avoid pregnancy, citing high rates of complications during pregnancy and delivery, as well as risks to the baby. But the results of a major study presented at the ACR found that women whose disease is stable—even those with lupus nephritis—can have a healthy pregnancy, delivery, and baby.

The Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISS) is designed to find ways to predict the likelihood of problems in women with lupus who become pregnant. Researchers, including ALR grantees Jill Buyon, MD of New York University Medical Center and Jane Salmon, MD, of the Hospital for Special Surgery in New York City, are following 4 groups of women: those with lupus, those with lupus and antiphospholipid syndrome, those with antiphospholipid syndrome only, and healthy women who have already had at least 1 healthy pregnancy and delivery.

The study presented at ACR was based on 333 pregnancies. Most of the women with lupus had markers of serious disease, including a history of lupus nephritis, the presence of anti-DNA autoantibodies, antiphospholipid antibodies, and/or low complement levels.

Overall, researchers reported, about 19% of the women with lupus experienced some type of complication during their pregnancy or delivery compared to 5% of healthy women. However, the complication rate in the general population is about 10%, and other studies have reported complication rates in women with lupus as high as 30%. Those studies, however, had a broader definition of “complications” than this one, Dr. Buyon noted. In this study, complications were defined as miscarriage, stillborn birth, early delivery (before 36 weeks), newborns who were small for their gestational age, and preeclampsia in the mother.

The “extraordinary news,” said Dr. Buyon during a press conference about the study, is that just 15 patients (4%) had a severe flare during their pregnancy, while just 18% experienced a mild-to-moderate flare. Few of the women required steroids during their flares.

Women who had slightly higher disease activity when they got pregnant; anticoagulant antibodies; slightly higher uric acid in the second and third trimesters; and a smaller complement increase as the pregnancy progressed were most likely to develop complications, as were women with a past history of kidney disease.

“What the study says is that even patients with a history of lupus nephritis can do well during pregnancy,” Dr. Buyon said, if they wait to become pregnant until their disease is stable and are closely managed by obstetrical specialists. x

Key point: It is possible to have a healthy pregnancy and a healthy baby if you work closely with your doctor on the timing of pregnancy and are closely monitored throughout pregnancy.
Vitamin D: Intriguing Data

They’ve been calling vitamin D the miracle vitamin for years, implicating low levels of the so-called “sunshine vitamin” in everything from heart disease to autoimmune conditions like multiple sclerosis and, yes, lupus. What is less clear, however, is if supplementing with vitamin D in people with low blood levels has any effect on lupus disease progression or its symptoms. Although the research is still in its infancy, it is providing some intriguing clues. Here’s what we learned at this year’s meeting:

- Twenty people with low-to-moderate lupus disease activity and vitamin D deficiency received 100,000 IU of vitamin D a week for 4 weeks, then 100,000 a month for 6 months. All demonstrated dramatic improvements in their blood levels of vitamin D levels with no safety issues or negative side effects. Perhaps most important is that levels of aberrant T cells declined after 2 months of supplementation, as did levels of 2 inflammatory cytokines and anti-DNA autoantibodies. In addition, the participants demonstrated reduced B-cell activation.

  “These represent very preliminary results,” said lead researcher Benjamin Terrier, MD, of the Internal Medicine Department of the Pitié-Salpétrière Hospital in Paris, France, during a press conference. Given the absence of a control group, he said, he couldn’t even say for sure that the immunologic effects were related to the vitamin D. However, he also called the results “encouraging” because they demonstrated the safety of such high doses of vitamin D in people with lupus.

Next step: Randomized clinical trials

- ALR grantee Michelle Petri, MD, of Johns Hopkins University School of Medicine in Baltimore, presented results from another study of vitamin D in lupus patients. She and her colleagues evaluated vitamin D levels in 922 patients between July 2009 and December 2010. They found that younger age, higher cholesterol levels, higher systolic (the top number) blood pressure, a higher urine protein/creatinine ratio (a sign of renal problems), and obesity were associated with low vitamin D levels. In addition, patients with low vitamin D levels were more likely to have lupus-related kidney and cardiovascular damage. However, supplementing with vitamin D had no effect on patients’ symptoms, although it did lead to a significant reduction in their urine protein/creatinine ratio and an increase in complement C4 and C4, both signs of disease improvement. There was no effect on anti-DNA autoantibodies, however. Yet, Dr. Petri noted, there was a trend towards a reduction in the amount of prednisone patient required to control their symptoms. While the reduction was not statistically significant, it “is suggestive” that increasing vitamin D levels can impact disease severity.

Key point: Supplementing with vitamin D may provide some benefits for people with lupus who have low blood levels of the vitamin, but large, randomized clinical trials are necessary.
Much of what we’re learning about lupus these days comes from patient registries, essentially, large databases that contain numerous types of information, including patient symptoms, treatments, side effects, biomarkers, and genetic analyses. They are invaluable for helping to identify possible problems with treatments, discover new treatment possibilities, or highlight certain clues regarding the progression or regression of the disease the deserve additional investigation. You don’t have to sign up to be in a registry; all information is anonymous and doctors provide the data. In addition to the pregnancy study highlighted here, other registry-related studies included:

**Biologics use in SLE in 23 Centers — Data from the International Registry for Biologics In SLE (IRBIS)**

Although belimumab (Benlysta) is the only approved biologic drug for lupus, physicians use numerous such agents off label. This study analyzed the use of biologics among 359 patients in 23 centers participating in the International Registry for Biologics in SLE (IRBIS). The study found that rituximab (Rituxan) was the main biologic used. Other patients were treated with belimumab, epratuzumab, abatacept (Orencia), etanercept (Enbrel), and adalimumab (Humira), some after participating in clinical trials for the drug. The researchers focused on the outcomes in those patients taking rituximab, finding that about 40% were also receiving cyclophosphamide. Most patients were started on rituximab because they had developed lupus nephritis or blood-related complications. After one year, patients on rituximab had improved SLEDAI scores and taking lower doses of glucocorticosteroids, even without adding any other immunosuppressants.

**Key point:** *Rituximab can provide important benefits for patients with lupus that is not responding to traditional immunosuppressant drugs.*

**Large Scale Analysis of Serum Tumor Necrosis Factor Alpha Levels in Systemic Lupus Erythematosus**

Blood levels of tumor necrosis alpha (TNFα) are high in some patients with lupus but not in others. Researchers studied 653 patients from the Lupus Family Registry and Repository at the Oklahoma Medical Research Foundation to evaluate any correlation between TNF-α levels and disease severity. They found that higher levels of TNF-α were associated with higher levels of the inflammatory protein interferon alfa (IFN-α) regardless of the patient’s ethnic background. However, African Americans were most likely to have the high TNF-α/IFN-α levels, with European-Americans least likely, while European Americans had the greatest proportion of low TNF/low IFN. While IFN-α was associated with the characteristic autoantibodies of lupus, only TNF-α was associated with IFN-α, suggesting some relationship between TNF-α and the characteristics of the disease.

**Key point:** *TNF-α levels may provide an important biomarker for tracking lupus disease progression. More studies are needed, however.*

**The Georgia Lupus Registry: Differences in Age-Specific Incidence Rates Between Black and White Females with SLE**

The Georgia Lupus Registry is a population-based registry designed to estimate the incidence and prevalence of lupus in Atlanta, GA. Researchers reviewed 8,000 medical records and found 332
cases of lupus. Based on census data for the region, they determined that African-American women developed lupus earlier than white women, with the rate increasing more dramatically at puberty and peaking between ages 30 and 39. Rates among white women, however, increased more gradually and peaked between ages 60 and 69.

**Key point:** Although lupus is often considered a disease that affects young women, hormones may have a greater affect on its development in black women than white women.

### Status and Missing Days At Work in a Large Population of Patients with Systemic Lupus Erythematosus (SLE)

Researchers from Toronto Western Hospital in Canada used a large lupus registry to evaluate how the disease affected patients’ ability to work. Of the 1,242 individuals evaluated, with an average age of 40.5, about half were not working, although 80% had previously worked. Among those working, 30% had missed work since their last doctor visit, and half said that their illness make it difficult for them to do their job. Researchers found that the longer patients had the disease, the greater their disease activity, and the more “troublesome symptoms” they had, such as fatigue, weakness, and difficulty thinking, the more likely they were to miss work.xiv

**Key point:** The researchers note that improving work-related interventions could reduce disability among individuals who want to work, but whose lupus interferes in their ability to work.
It has been known for years that lupus affects the central nervous system (CNS) as well as other organ systems, resulting in problems with thinking, remembering, and learning. These cognitive issues, along with other neurologic manifestations such as seizures and psychosis, affect about 80% of patients with lupus, said Robin L. Brey, MD, of the University of Texas Health Science Center in San Antonio, while about 70% of those with lupus experience mood disorders. Her comments came during a talk on cognitive issues in patients with lupus.

Neuropsychiatric lupus (NPSLE) can even occur without any other evidence of the disease, making it difficult to know if the neurological manifestation is due to lupus or some other condition, she said. In fact, a host of other factors can influence cognitive function in normal people and in patients with autoimmune diseases, including sleep, social and cultural issues, psychiatric disorders such as depression and anxiety, preexisting or lupus-related central-nervous system (CNS) disorders, brain damage, medications, metabolic abnormalities and infection.

“The challenge for us is determining whether or not the neurological symptoms are due to the lupus, are primary central-nervous system (CNS) mediated, lupus-mediated CNS pathology, or whether they are secondary to other conditions,” she said.

It may also be that the autoimmune dysfunction itself triggers the cognitive dysfunction, with some studies finding similar levels of cognitive dysfunction in patients with rheumatoid arthritis, multiple sclerosis, and lupus.\textsuperscript{xv, xvi}

“Does this mean that cognitive dysfunction in these patient groups is not related to the underlying disease?” Dr. Brey asked. “I say no, it doesn’t mean that at all.” Instead, she suggested that the underlying inflammation of all three diseases plays a role. Thus, she said, “the quest for looking for a specific cognitive dysfunction pattern in lupus that is not seen in other disease entities will stop us in our tracks in terms of progress.” Instead, what these studies show is that the result of inflammatory damage to the brain can be cognitive dysfunction. “It is a process that you can come to by several different mechanisms.”

Brain involvement in lupus may also be related to the damage that occurs in tiny blood vessels throughout the body, including those in the brain. In addition, she said, there also appears to be dysfunction in the blood-brain-barrier, which may allow autoantibodies access to the brain, leading to the production pro-inflammatory proteins further damaging the brain.

In the San Antonio Lupus Study of Neuropsychiatric Disease (SALUD) study she and her colleagues conducted, in which 65% of the patients were Hispanic, depression, disease activity, prednisone use, persistently positive antibodies, higher SLEDAI scores, were all risk factors for cognitive dysfunction, as was Hispanic ethnicity.\textsuperscript{xvii}

One reason Hispanics may have poorer cognitive function, she said, is that these patients are sicker overall and the effects of lupus in the brain are more pronounced.
More information about lupus and treatment advances can be found by visiting www.lupusresearch.org.

The Alliance for Lupus Research Special Report on the 2011 American College of Rheumatology Meeting was made possible in part by generous support from Genentech.