

# Tips for Predicting High-Risk Pregnancies in SLE

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FROM THE INTERNATIONAL  
CONGRESS ON SYSTEMIC LUPUS  
ERYTHEMATOSUS

VANCOUVER, B.C. — Monthly monitoring by rheumatologists of every pregnancy in every woman with systemic lupus erythematosus may be unnecessary, according to Dr. Michelle Petri.

A relatively small list of criteria can distinguish high-risk pregnancies in women with systemic lupus erythematosus (SLE)—ones that carry a higher likelihood of miscarriage, extreme prematurity, and SLE

flare—from others, and signal the need for intensive monitoring by obstetricians and rheumatologists, Dr. Petri said at the meeting.

At present, however, there is little effort to make such distinctions, so most SLE pregnancies are subjected to monthly visits to rheumatologists and obstetricians, and, starting at week 26, weekly monitoring by obstetricians.

That's not always necessary; women are subjected to needless anxiety and hospital resources are wasted, Dr. Petri said.

Based on the Hopkins Lupus Cohort, a database that has been tracking several thousand

patients with SLE over the past 25 years, Dr. Petri and her colleague, Duke University rheumatologist Megan Clowse, have identified those factors that truly put women and fetuses at risk during SLE pregnancies.

Pregnancy and the postpartum period are hard on the kidneys of women with SLE, though organ involvement elsewhere in the body tends to lessen, said Dr. Petri, professor of rheumatology at Johns Hopkins University, Baltimore.

"Proteinuria from active lupus significantly increases, and this continues even after delivery," she added.

Therefore, pregnant women

with lupus nephritis truly do need close monitoring. Dr. Petri recommended monthly urine protein-creatinine ratios to detect a worsening of the condition and the need for treatment.

In terms of fetal health, the risk of miscarriage doubles if, at the first pregnancy visit, a woman is proteinuric, thrombocytopenic, or hypertensive, or has a history of antiphospholipid syndrome.

The risk triples if two or more of these conditions are present, Dr. Petri said. The presence of antithyroid antibodies also increases the risk of miscarriage.

In addition, active SLE, especially if accompanied by anti-double-stranded DNA antibody or low complement levels, predicts extreme prematurity. Autoimmune thyroid disease also appears to be associated with preterm birth.

Screening for the various factors, "we can predict at the first pregnancy visit if there's going to be a poor outcome," Dr. Petri said.

If the risk factors are present, monthly monitoring by a high-risk obstetrician, followed by weekly monitoring at week 26, are appropriate to gauge if, and when, a rescue delivery is needed. ■

## Vitamin D Repletion in SLE Requires at Least 2,000 IU Daily

FROM THE INTERNATIONAL CONGRESS ON  
SYSTEMIC LUPUS ERYTHEMATOSUS

VANCOUVER, B.C. — A daily dose of at least 2,000 IU of vitamin D is required to elevate serum 25-hydroxyvitamin D levels above 30 ng/mL, the minimum threshold for optimal immune health, according to Dr. Diane Kamen, a rheumatologist at the Medical University of South Carolina in Charleston.

The conclusion is based on an open-label, phase I study of vitamin D repletion in 18 black patients with lupus.

Starting from a baseline mean 25-hydroxyvitamin D (25[OH]D) level of 13.3 ng/mL, six patients received 800 IU vitamin D once daily; six received 2,000 IU once daily; and six received 4,000 IU once daily.

VITALS

**Major Finding:** Five of six black lupus patients who were given 2,000 IU vitamin D daily repleted serum 25-hydroxyvitamin D to 30 ng/mL or more at 3 months.

**Data Source:** A phase I study of 18 patients.

**Disclosures:** The study was funded by the National Institutes of Health. The principal investigator said she had no disclosures.

After 12 weeks, 67% (four patients) in the 800-IU group, 83% (five) in the 2,000-IU group, and 67% (four) in the 4,000-IU group repleted to 30 ng/mL or greater. In the 4,000-IU group, levels in 33% (two patients) rose above 40 ng/mL. That level was not reached at the lower doses.

The results are important, Dr. Kamen said in an interview. Although there is growing awareness that such high doses of vitamin D are needed to restore 25(OH)D levels in patients with autoimmune disease, the rheumatology literature still contains recommendations for doses of 600-800 IU/day.

"That's just not going to cut it; 2,000 IU a day is the minimum effective dose for repletion," especially if patients avoid the sun to prevent lupus flares, Dr. Kamen said.

Rheumatologists "need to know to recommend those higher doses, and to monitor levels" of 25(OH)D to make sure they are maintained, she said.

The 18 patients were enrolled from the Gullah, a population of blacks living on the Sea Islands of South Carolina and Georgia, in whom there is a high incidence of lupus. An earlier Gullah study found that 43% of 187 subjects had 25(OH)D levels below 10 ng/mL; in some, levels were undetectable. Lower levels correlated with higher SLEDAI scores and higher anti-dsDNA antibody levels, Dr. Kamen said.

The mean age in the phase I study was 44 years; mean prednisone dose 4.3 mg/day; and mean SLEDAI score 2.4. In all, 17 of 18 of the subjects were women, 50% (9) took hydroxychloroquine, and 50% (9) were anti-dsDNA antibody positive. Compliance with the treatment regimen was 99%, by pill count. The doses were very well tolerated and safe, Dr. Kamen said.

Although 2,000 IU per day elevated 26(OH)D levels in most patients to at least 30 ng/mL, there's debate about whether target blood levels should be higher in lupus patients.

"We know that 30 ng/mL is the minimum accepted as normal," Dr. Kamen said, noting that secondary hyperparathyroidism can begin below that level. "We also know [healthy] sun-exposed people tend to live closer to 60 ng/mL. The debate is over if the target should be 30, 40, 50, or 60," she said.

"I tell my patients at high risk for conditions influenced by vitamin D, such as osteoporosis and inflammatory conditions, that we want them to stay between 40 and 60 ng/mL," she said, but "it's a gray zone" that awaits further research.

Levels of 25(OH)D are known to be low in lupus patients, but no one can say for sure whether that is a cause or a consequence of the disease, or if it results from the medications used to treat it, such as prednisone and hydroxychloroquine. ■

## Urinary Retention in SLE? Think Gray Matter Myelitis

FROM THE INTERNATIONAL CONGRESS ON  
SYSTEMIC LUPUS ERYTHEMATOSUS

VANCOUVER, B.C. — Fever and urinary retention without obstruction in a patient with active systemic lupus erythematosus should be considered a medical emergency and treated immediately with high-dose intravenous corticosteroids, according to recent findings from Johns Hopkins University.

Those signs signal gray matter myelitis and spinal cord ischemia, and high-dose corticosteroids can prevent a cord infarct and permanent paraplegia, Dr. Michelle Petri said.

Rheumatologists at the school have identified two previously unrecognized forms of myelitis in SLE patients: gray matter myelitis and white matter myelitis.

Both are longitudinal and likely to span three vertebral segments; the nomenclature refers to the type of spinal cord tissue affected.

Gray matter myelitis leads to rapid onset of permanent paraplegia and urinary incontinence in as little as 4 hours. Because it usually presents with acute urinary retention, it is often misdiagnosed and mistreated as a bladder infection.

But the "patient is announcing ischemia of the spinal cord and needs high-dose corticosteroids and to be admitted," said Dr. Petri, professor of rheumatology and director of the lupus center at Johns Hopkins in Baltimore.

If the syndrome—and how to treat it—was more widely recog-

nized, "hundreds of young women would be saved from permanent paralysis," she said.

"When you have to place a catheter because the patient cannot urinate, treatment [with 1,000 mg IV methylprednisolone] should start," Dr. Julius Birnbaum, the lead

VITALS

**Major Finding:** Of 11 SLE patients with gray matter myelitis, a newly recognized form in SLE, 10 presented with urinary retention and fever and were treated for bladder infections; the mistake likely led to permanent paraplegia.

**Data Source:** Retrospective study of 22 patients.

**Disclosures:** The investigators said they had no disclosures. The study was funded by the National Institutes of Health.

investigator on the project and a rheumatologist and neurologist at Johns Hopkins, said in an interview after the conference.

"The overall message is, don't wait to provide treatment," he said.

Gray matter myelitis, which the team considers a vasculopathy, presents with lower motor neuron signs: flaccidity and hyporeflexia, in addition to urinary retention and fever (*Arthritis Rheum.* 2009;60:3,378-87).

On the other hand, white matter myelitis presents with upper motor neuron signs: hyperreflexia and spasticity. The onset is more gradual, antigravity strength is more likely to be preserved; attacks are less severe; and disability comes from repeated episodes that eventually lead to paralysis, in some cases.

It is more likely an antibody-driven phenomenon; white matter myelitis shares features with neu-

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# Belimumab May Be First Biologic Okayed for SLE

BY BRUCE JANCIN

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

ROME — What a difference a year makes.

At last year's rain-drenched EULAR gathering in Copenhagen, earlier optimism regarding the prospects for biologic therapies for systemic lupus erythematosus gave way to a pervasive pessimism. Highly encouraging studies had been followed by a rash of negative major clinical trials, which dashed many observers' hopes that biologics would have a clinically meaningful impact in SLE. But that was then.

"It's a year later now. The sun has been shining every day in Rome, and I can tell you that there are now a lot of reasons to think biologics are going to make a real difference in the treatment of lupus," Dr. Ronald van Vollenhoven said. Clearly, the most exciting recent development is that the anti-B cell cytokine agent belimumab (Benlysta) achieved its primary end points in two separate, exceptionally large phase III clinical trials.

"Safety was excellent in those trials; that's really a great component of the story. So I think belimumab is very likely to become



**Early data from the EMBLEM trial show that epratuzumab halved, rather than eliminated, B cell numbers.**

DR. WALLACE

all baseline BILAG grade A disease to grade B-D, and BILAG grade B to grade C or D, in all body systems; no BILAG worsening in other organ systems; no deterioration in SLEDAI or physicians' global disease activity assessments; and no increase in corticosteroids and/or immunosuppressive agents over baseline levels. Overall, the responder rate index was 43.2 for the 74 patients on a total of 2,400 mg of epratuzumab vs. 21.1 for those on placebo. Especially impressive were the epratuzumab-induced reductions in neuropsychiatric and cardiorespiratory symptoms of SLE, which are often particularly resistant to conventional therapies, observed Dr. Wallace of the University of California, Los Angeles.

"This is a very encouraging result from a relatively small first trial that needs to be confirmed," Dr. van Vollenhoven said. "The size of the treatment effect is pretty impressive. There was a strong positive effect for a total dose of 2,400 mg, but 3,600 mg was not effective. That's a little bit strange. I can't quite put my head around that."

cause our instruments are blunt. The true effect is probably much better than we think."

Atacicept, another anti-B cell cytokine agent, is now in a phase III randomized clinical trial for SLE, he said.

There is further encouraging news. At the Rome congress, Dr. Daniel J. Wallace presented positive results from the phase IIB EMBLEM trial of epratuzumab, a humanized anti-CD22 monoclonal antibody. Unlike rituximab, an anti-CD20 monoclonal antibody that completely obliterates B cells, epratuzumab reduced them by about half in the study.

The EMBLEM trial was a 12-week, multicenter, double-blind, randomized study involving 227 patients with moderate to severe SLE who were already on standard therapy. The key finding was that patients who received a cumulative intravenous dose of 2,400 mg of epratuzumab—either as 600 mg weekly (37 people) or 1,200 mg every other week (37 people)—had a responder rate twice that of controls on placebo (38 people).

EMBLEM's responder rate index end point was a novel composite outcome measure that was aimed at overcoming the sort of limitations Dr. van Vollenhoven cited. It's defined as a reduction of

the first registered biologic for SLE," predicted Dr. van Vollenhoven, senior physician in the department of rheumatology and chief of the clinical trials unit of the Karolinska Institute, Stockholm.

If so, belimumab would also be the first new therapy of any sort approved for SLE in more than 40 years.

Dr. van Vollenhoven, who was on the steering committees of both the BLISS-76 (Belimumab in Subjects With Systemic Lupus Erythematosus-76) and BLISS-52 trials, characterized the demonstrated treatment effect of the anti-B cell cytokine agent as "modest." But he noted that there is a caveat.

"If the effect size isn't so big, how relevant is the treatment clinically? It's a reasonable question. I think the modest effect size is a function of the primitive outcome measures we have for SLE. The [problem with the lupus trials has been]—and still is—that our instruments aren't very good," the rheumatologist said. "I think we're picking up a signal and the signal is weak, but it's not because the true effect is weak. It's just be-

Dr. van Vollenhoven offered the following updates on the status of other major classes of biologic agents in terms of their prospects as SLE therapies:

► **Anti-interferon-alpha.** High serum levels of interferon-alpha are present in SLE. It is produced by plasmacytoid dendritic cells in response to stimulation by immune complexes. Several companies currently have anti-interferon-alpha agents in clinical trials for SLE. The key issue will be safety: Interferon-alpha plays key roles in viral immunity and tumor defenses, Dr. van Vollenhoven noted.

► **Anti-interleukin-6.** Tocilizumab (RoActemra) achieved improvements in SLEDAI and arthritis in a recent National Institutes of Health phase I study in 16 SLE patients (Arthritis Rheum. 2010;62:542-52). Neutropenia was a frequent limiting side effect. Additional interleukin-6 and interleukin-6 receptor antagonists are in early clinical trials.

► **Rituximab.** Early, uncontrolled studies were "exciting and encouraging," recalled Dr. van Vollenhoven, who led several of them. Then came the failed phase III, randomized, double-blind, controlled EXPLORER and LUNAR trials, which contributed prominently to the glum global prospects for biologic therapy of a year ago. EXPLORER established that rituximab (Rituxan) is unlikely to be of benefit in nonrenal lupus. Many rheumatologists have concluded that LUNAR showed the same for lupus nephritis, but Dr. van Vollenhoven, who was on the trial's steering committee, remains unconvinced. In as-yet-unpublished data, he has shown that rituximab works quite slowly in lupus nephritis, with about one-half of treated patients showing a partial response after 1 year, and complete responses being seen only after about 2 years. LUNAR, he noted, was a 1-year trial, so it didn't capture the late responses. "It could be that rituximab doesn't work in lupus nephritis. But I'll reserve my judgment because I've seen such good responses that it still seems to me to be a pretty good option," he said. ■

**Disclosures:** Dr. van Vollenhoven serves as a consultant to GlaxoSmithKline and Human Genome Sciences, which are developing belimumab, and he has received research grants from most of the other companies which make biologics for rheumatologic diseases. Dr. Wallace is a consultant to UCB, which is developing epratuzumab and funded the EMBLEM trial.

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romyelitis optica, Dr. Birnbaum said at the meeting.

High-dose IV methylprednisolone is used to treat both forms of myelitis. Following that, patients at Hopkins are placed on steroid-sparing immunosuppressive regimens, which may include azathioprine, mycophenolate mofetil, or rituximab.

Both forms of SLE myelitis are unlike myelitis that is seen in multiple sclerosis (MS) patients, which tends to be transverse and does not cause the rapid devastation that is seen in gray matter myelitis.

Currently, however, myelitis in SLE and MS patients is often lumped together under the rubric of "lupoid sclerosis," Dr. Birnbaum said.

That's a mistake, he said.

"Under no circumstances should any of these patients be exposed to the armamentarium used to treat MS. Lupoid sclerosis does not exist for these SLE patients," he said.

Interferon, a mainstay of MS treatment, "causes flares and can lead to catastrophic worsening of SLE and SLE CNS disease," Dr. Birnbaum said.

The findings are based on a record review of 22 SLE patients who presented with myelitis to the lupus center or transverse myelitis center at Hopkins in 1994-2007.

Dr. Birnbaum and his colleagues recognized the syndromes through an analysis of histories, physical exams, lab values, follow-up care, and MRIs.

The team discovered that 11 patients had gray matter myelitis, and 11 had white matter myelitis. There were no statistically significant differences between the two groups with regard to age, gender, or ethnicity. Most were women.

Of the 11 patients with gray matter myelitis, 10 presented for urinary retention. Because of the presence of fevers, "all of these patients were unfortunately and erroneously diagnosed as having urinary tract infections. By the

time immunosuppressive treatment was initiated, there had likely already been irreversible injury," according to the study report.

Patients with gray matter myelitis,

**If gray matter myelitis—and how to treat it—was more widely recognized, 'hundreds of young women would be saved from permanent paralysis.'**

compared with those with white matter myelitis, had higher median white blood cell counts (385.5 cells/mL vs. 10 cells/mL; *P* less than .01); higher median neutrophilic pleocytosis (71% neutrophilia vs. 15% neutrophilia; *P* less than .08); higher median total protein levels (254 mg/dL vs. 57 mg/dL; *P* less than .01); and lower central spinal fluid glucose levels (33 mg/dL vs. 54 mg/dL; *P* less than .02), according to the study report.

Cerebrospinal fluid profiles in gray matter myelitis were indistinguishable from CSF profiles in bacterial meningitis, although none of the patients had meningeal signs or positive bacterial, viral, or fungal cultures.

If obtaining an MRI is not feasible, Dr. Birnbaum said, "the spinal tap can support evidence of gray matter myelitis."

He added that in cases in which the differential includes both meningitis and myelitis, concomitant administration of corticosteroids and antibiotics is appropriate. Both are commonly administered for worsening TB meningitis in order to simultaneously eliminate the infection and quiet the cytokine storm it produces.

In all, 12 MRIs were available for patients with gray matter myelitis, and 23 for patients with white matter myelitis.

Cord swelling was seen in 91.7% (11) of the gray matter MRIs and in 21.7% (5) of the white matter images; postgadolinium enhancement was seen in 25% (3) of the gray matter MRIs and in 42.9% (10) of white matter images. ■