Guidelines Define Optimal Lupus Monitoring

BY SALLY KOCH KUBETIN

New guidelines issued by the European League Against Rheumatism on the monitoring of patients with systemic lupus erythematosus offer advice for clinicians and recommendations for the design of observational studies.

The document includes recommendations on 10 components of patient monitoring. An appendix to the document contains a core set of data to be collected in routine clinical practice. Having such standardized data would be a significant help to research, according to Dr. Marta Mosca of the University of Pisa (Italy) and her fellow authors. The panel included dermatologists, rheumatologists, internists, and a nephrologist. They arrived at the following recommendations after a systematic literature review and numerous consultations:

▶ **Patient assessment.** Every visit should include assessments of the patient's disease activity, using a validated index; quality of life, determined either by history alone or in addition to a patient-completed measure such as a 0-10 visual analog scale; and comorbidities and drug toxicity. Organ damage should be assessed yearly.

▶ **Cardiovascular risk factors.** Cardiovascular disease (CVD), including related factors such as smoking, vascular events, physical activity level, oral contraceptive use, hormone therapies, and family history of CVD, should be assessed at baseline and monitored at least once a year thereafter. Similarly, lupus patients also need yearly blood tests for blood cholesterol and glucose levels as well as blood pressure measurement and determination of either body mass index or waist circumference. Patients on glucocorticoids and other lupus patients at particularly high risk for CVD may require more frequent assessment.

▶ **Other comorbidities.** All patients with SLE should be assessed for osteoporosis risk factors, including adequate calcium and vitamin D intake, regular exercise, and smoking habit. They should be screened and followed for osteoporosis according to either of two existing sets of guidelines: those for postmenopausal women or those for patients on glucocorticoids or other medications that reduce bone mass, such as methotrexate. Cancer screening (including Pap smears) is recommended according to guidelines for the general population.

▶ **Infection risk.** Lupus patients should be screened for HIV, hepatitis C virus, and hepatitis B virus, especially before the start of immunosuppressive drugs; for tuberculosis, according to local guidelines and especially before the initiation of immunosuppressive drugs; and for cytomegalovirus. Lupus patients should receive inactivated vaccines for influen-

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Mayo Study Provides Insight Into Nephrogenic Systemic Fibrosis

VITALS

Major Finding: Levels of gadolinium in the involved lower-extremity skin of some affected patients were similar to levels in uninvolved skin of others.

Source of Data: Measurement of tissue gadolinium levels in 13 patients with active NSF, compared with skin biopsies of 13 healthy controls.

Disclosures: Dr. Pittelkow reported no relevant financial conflicts of interest.

BY BRUCE JANCIN

BERLIN — The threshold for developing nephrogenic systemic fibrosis in response to gadolinium deposition in skin and other tissues appears to be much broader than previously recognized, according to Dr. Mark R. Pittelkow.

Precise measurement of tissue gadolinium levels by inductively coupled plasma mass spectrometry in 13 patients with active nephrogenic systemic fibrosis (NSF) demonstrated that levels were consistently higher in involved skin than in skin that was both clinically and histologically uninvolved, Dr. Pittelkow reported at the annual congress of the European Academy of Dermatology and Venereology.

Yet levels of gadolinium in the involved lower-extremity skin of some affected patients were similar to levels in uninvolved skin of others. Moreover, gadolinium levels in uninvolved abdominal skin of patients with NSF were substantially greater than those in skin biopsies obtained from 13 healthy controls, which in most cases showed no detectable gadolinium.

"So one could argue that it's not gadolinium alone in tissue that's actually causing the disease," said Dr. Pittelkow, professor of dermatology at the Mayo Clinic in Rochester, Minn.

Gadolinium levels in the uninvolved skin of patients with NSF varied 100-fold (0.6-68.0 mcg/g). The level of gadolinium in their involved skin was 2.5- to 88-fold greater than the level in their uninvolved skin.

Another key study finding was that the retention of gadolinium in the skin and blood of patients with NSF was protracted. High gadolinium levels were still present in patients with active disease of several years' duration.

Various investigators are now pursuing strategies to remove gadolinium from skin and other tissues, he said. Everyone is eager to learn if this will improve or perhaps even resolve the cutaneous and systemic manifestations of NSF.

NSF is a progressive fibrosing disorder that affects the skin, joints, internal organs, and eyes. Dermatologic manifestations include extensive thickening and hardening of the skin, accompanied by brawny hyperpigmentation along with fibrotic papules and subcutaneous nodules. Dramatic flexion contractures of the extremities are a common feature, with the effects often particularly severe in the legs.

'One could argue that it's not gadolinium alone in tissue that's actually causing the disease.'

DR. PITTELKOW

Dr. Pittelkow called NSF a "fascinating" disease whose pathogenesis is still far from completely understood. The disease has undergone several name changes since its first description by physicians at the University of California, San Francisco, who called it a scleromyxedema-like dermopathy. That term was soon replaced by nephrogenic fibrosing dermopathy, then NSF.

In 2006, Mayo Clinic investigators described an association between NSF and exposure to high-dose erythropoietin-stimulating therapy in patients with chronic kidney disease. This was soon followed by reports from European investigators that exposure to gadolinium-based contrast agents used in radiologic imaging studies was another major risk factor for NSF. ■

FDA: Contrast Agent Black Box Behind NSF Reduction

BY KERRI WACHTER

GAITHERSBURG, MD. — Black box warnings added to the labels of all gadolinium-based MRI contrast agents have reduced the number of reported nephrogenic systemic fibrosis events to almost none in the last year, according to Dr. James Kaiser.

"The numbers of new events have tapered dramatically, probably due to public awareness of the association of NSF [nephrogenic systemic fibrosis] with GBCA [gadolinium-based contrast agent] administration," he said at a joint meeting of the Food and Drug Administration's Cardiovascular and Renal Drugs and Drug Safety and Risk Management advisory committees. Event dates are either the date of administration of contrast or the date of diagnosis of NSF.

The FDA began receiving reports of NSF possibly being linked to gadolinium-based contrast agents in 2006 when 194 event dates were reported. This "probably reflects awareness of the medical community of the potential connection between GBCA administration and NSF and changes in radiologic practice," said Dr. Kaiser of the FDA's office of surveillance and epidemiology. There were 128 reported events in 2007, 55 in 2008, and 6 in 2009 (through September).

In 2007, the FDA asked manufacturers to include a boxed warning on the product labels of all gadolinium-based contrast agents. The warnings caution that patients with severe kidney insufficiency who receive gadolinium-based agents are at increased risk for developing NSF. In addition, patients in need of a liver transplantation, those who have just undergone liver transplantation, patients with chronic liver disease, and patients experiencing kidney insufficiency of any severity are also at risk.

Five gadolinium-based contrast agents have been approved for use in the United States: Magnevist (gadopentetate dimeglumine); Omniscan (gadodiamide); OptiMARK (gadoversetamide); MultiHance (gadobenate dimeglumine); and ProHance (gadoteridol).

As of September 2009, a total of 382 reports of NSF had been associated with Omniscan (GE HealthCare), 195 with Magnevist (Bayer HealthCare), 35 with OptiMARK (Covidien), 1 with MultiHance (Bracco Diagnostics), and 0 with ProHance (Bracco Diagnostics). The numbers are based on cases in which a patient had known exposure to only one gadolinium-based contrast agent.

Though there was no formal vote at the committee meeting, the FDA asked the committees to consider whether warning labels should continue to be grouped together as a class or if there was adequate evidence to single out agents that increase NSF risk.

"The majority of the group feels that at least two of the agents appear to be different from the other agents," said Dr. Robert A. Harrington, who chairs the Cardiovascular and Renal Drugs Advisory Committee. The majority of the group recommended the use of Omniscan and OptiMARK be contraindicated in patients with severe kidney dysfunction. However, there was uncertainty as to how to define severe kidney dysfunction.

There was less consensus on whether a third agent, Magnevist, might also warrant contraindication language. ■

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za and pneumococcus in accordance with guidelines for immunosuppressed patients issued by the Centers for Disease Control and Prevention. It is ideal to do the immunization when the lupus is inactive. The use of other vaccines should be considered on a case-by-case basis. For the exact risk of infection to be determined, lupus patients should be monitored for neutropenia, severe lymphopenia, and low IgG.

► **Frequency of assessments.** Assessment every 6-12 months is adequate in patients with no disease activity, no organ damage, and no comorbidities. Preventive measures should be stressed during these visits. The committee found no data to suggest an optimal frequency of clinical and laboratory assessment in patients with lupus.

► **Laboratory assessment.** The committee recommended that baseline lab assessment include monitoring antinuclear antibody, anti–double-stranded DNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid, C3, and C4. Reevaluation of antiphospholipid antibodies is necessary in previously negative patients prior to pregnancy, surgery, transplant, and estrogen-containing treatments, or in the presence of a new neurologic or vascular event. Before pregnancy, anti-Ro and anti-La antibodies also should be monitored. Remeasurement of anti-dsDNA and low levels of C3 or C4 may support evidence of disease activity or remission.

At 6- to 12-month intervals, patients with inactive disease should have the following lab tests: complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum albumin, serum creatinine (or EGFR), urinalysis, and urine protein:creatinine ratio. Any patient on a specific drug treatment should have that drug monitored as well.

► **Mucocutaneous involvement.** Cutaneous manifestations include lupus erythematosus (LE)–specific lesions, including acute cutaneous LE (CLE), subacute CLE, chronic CLE, and intermittent CLE lesions, and LE-nonspecific lesions. Many conditions may mimic LE and therefore may require an evaluation by an experienced dermatologist as well as a skin biopsy for histologic analysis. Follow-up rebiopsy is recommended if there is a change in the clinical morphology of the lesions, or if there is a lack of response to treatment.

► **Kidney.** Patients with a persistently abnormal urinalysis or raised serum creatinine should have urine protein:creatinine ratio tests, urine microscopy, and renal ultrasound, and should be considered for biopsy referral. Patients with established nephropathy should have protein:creatinine ratio and immunologic tests, urine microscopy, and blood pressure evaluations at least every 3 months for the first 2-3 years. Patients with established chronic renal disease should be followed according to the National Kidney Foundation guidelines for chronic kidney disease (www.kidney.org).

► **Neuropsychiatric manifestations.** Neurologic involvement (central, peripheral, or autonomic) occurs frequently in SLE. The most frequent syndromes observed are headache, mood disorders, seizures, cognitive impairment, and cerebrovascular disease. The assessment of neurologic symptoms is difficult and no specific instrument has been evaluated in clinical practice. Therefore, the guidelines recommend that patients should be monitored by clinical history. Cognitive impairment may be assessed by evaluating memory, attention, concentration, and word-finding difficulties (Ann. Rheum. Dis. 2009 Nov. 5 [doi:10.1136/ard.2009.117200]).

► **Eye assessment.** The incidence of retinopathy among SLE patients who are treated with antimalarial drugs is low (0.5%). Risk factors are age older than 60 years, presence of macular degeneration, retinal dystrophy, obesity, liver disease, renal insufficiency, duration of therapy longer than 5 years, daily dose of hydroxychloroquine greater than 6.5 mg/kg, or chloroquine greater than 3 mg/kg. Recommendations on screening for antimalarial retinopathy include a baseline eye assessment according to published guidelines (Ophthalmology 2002;109:1377-82).

Thereafter, in low-risk patients, no further testing is required for the next 5 years; after the first 5 years of treatment, eye assessment is recommended yearly. In high-risk patients, an eye assessment is recommended yearly. In addition, an eye assessment may be required if there are symptoms suggesting eye involvement by lupus.

In most cases, anything left out of these recommendations should be considered part of standard good clinical practice. In some cases, items were not addressed because of contradictory evidence, wrote the authors, who also included an agenda for future research. ■