LEAP ROUNDS

Johns Hopkins University
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Division of Rheumatology
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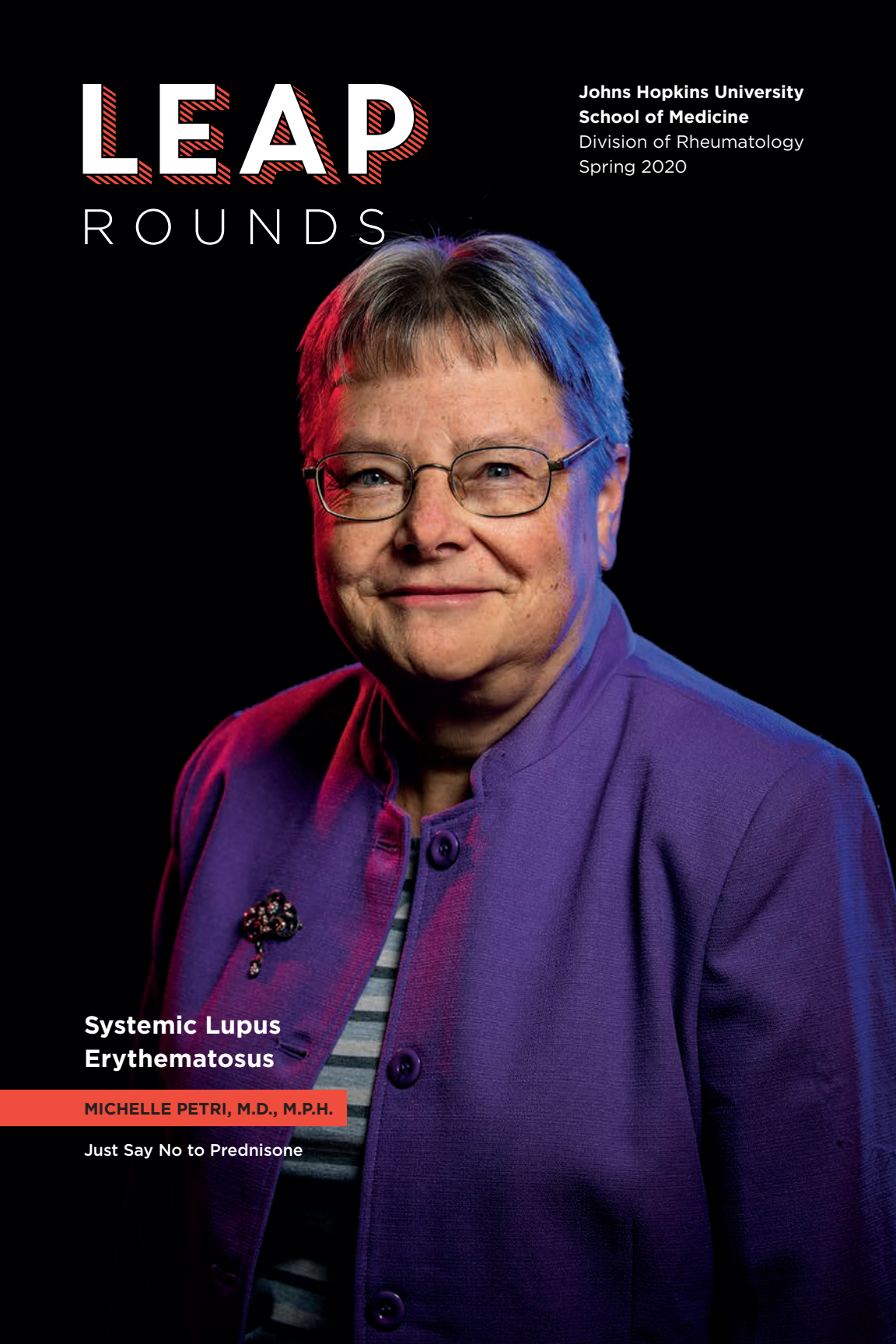

Systemic Lupus Erythematosus

MICHELLE PETRI, M.D., M.P.H.

Just Say No to Prednisone

SYSTEMIC LUPUS ERYTHEMATOSUS

RISK

If the dose is above 6 mg/day, there is a 50-percent increase in permanent organ damage – most commonly, osteoporotic fractures and cataracts – and if the dose is above 18 mg/day, the risk is 2.5 times greater.

INTERVIEW: MICHELLE PETRI, M.D., M.P.H.

Corticosteroids (prednisone) are the mainstay of therapy for systemic lupus erythematosus (SLE). Prednisone works: it has anti-inflammatory and immunosuppressive actions in SLE. This is why doctors who treat lupus patients use it, and why patients accept it — because they often feel better right after they start taking it. But ultimately, it can do much more harm than good.

We have learned that prednisone in doses that used to be considered "safe" is not safe at all.

When we analyzed the permanent organ damage that had occurred in the Johns Hopkins Lupus Cohort patients, we found that to be used safely, the dose of prednisone had to be less than 6 mg/day. This is considered a very, very low dose. If the dose is above 6 mg/day, there is a 50-percent increase in permanent organ damage – most commonly, osteoporotic fractures and cataracts – and if the dose is above 18 mg/day, the risk is 2.5 times greater.

This damage is unacceptable. Yes, the patient can eventually have cataract removal, but may go through years of blurred vision before the cataract has hardened. Osteoporotic fractures should never be considered acceptable; particularly in the lumbar spine – where fractures are not only extremely painful but can drastically affect posture. We have seen women in their 20s and 30s with kyphosis such as a 90-year-old woman might have.

Prednisone stands out as an independent risk factor for cardiovascular disease (CVD) in a dose-response way.

CVD is the major cause of late deaths (more than 10 years after diagnosis) in patients with lupus. Our study showed a 2.4-fold increase if the patient is on 10 mg/day of prednisone, and a five-fold increase with 20 mg/day.

The P in Prednisone stands for poison!

Unfortunately, many doctors think people with lupus get a free pass to prednisone. If the patient is in the ER, the doctor may give prednisone even when it turns out not to be a lupus issue. Sometimes we have to use prednisone in the short-term for the patient who flares, who may need a burst of steroid, but our job is to quickly taper it. We could do that burst of steroid as an intramuscular injection of a long-acting steroid without long-term side effects; or a dose pack of oral methylprednisolone for one week.

What about a patient who's not flaring, but whose lupus is in a chronic activity pattern?

These are the patients who need immunosuppression: methotrexate, azathioprine, mycophenolate. We have to be brave enough to use them and do it in doses that work. It doesn't mean that this solves lupus: it doesn't. Many patients continue to have disease activity in spite of immunosuppressive drugs. Belimumab is one targeted biologic that's been approved, but we desperately need others.

It's been around since World War II, when it was used as an anti-malarial drug.

How to limit prednisone in ways that are safe and easy?

Smarter use of hydroxychloroquine (Plaquenil).

It's been around since World War II, when it was used as an anti-malarial drug. It doesn't immunosuppress; it just immunomodulates. It doesn't increase the risk of infection or malignancy; it is the only medication proven to improve survival. Among other benefits, hydroxychloroquine reduces SLE flares by half, and is particularly effective in treating cutaneous disease and arthritis. It has antithrombotic, anti-diabetic, and lipid-lowering effects. In lupus nephritis, it is an independent predictor of complete renal remission in patients treated with mycophenolate mofetil.

If hydroxychloroquine levels are measured in the blood, you can identify the patients who aren't taking it, or who are not taking it to efficacy.

We found that 50 percent of our patients either weren't taking it at all, or were taking it at subtherapeutic doses. A patient who is taking hydroxychloroquine at a subtherapeutic dose is more likely to end up on more prednisone because the physician assumes hydroxychloroquine is not sufficient. By showing our patients these blood levels and explaining the benefits of taking the therapeutic dose, we were able to increase adherence to 80 percent.

MICHELLE PETRI, M.D., M.P.H.

Co-Director, Johns Hopkins Lupus Center, Professor of Medicine

Michelle Petri, M.D., M.P.H., is a Professor of Medicine at the Johns Hopkins University School of Medicine. She is Director of the Hopkins Lupus Cohort, a longitudinal study of morbidity and mortality in SLE; Co-Director of the Hopkins Lupus Pregnancy Center, and Director of the Hopkins Lupus Center. Petri joined the Hopkins faculty in 1986, after earning her M.D. at Harvard University and completing her medical residency at Massachusetts General Hospital and Rheumatology and Allergy and Immunology fellowships at the University of California-San Francisco. She obtained her M.P.H. at the Johns Hopkins School of Hygiene and Public Health. An internationally respected authority on SLE, Petri is the author of nearly 600 scholarly publications.

Measuring the blood levels has had another important benefit: In 2016, the American Academy of Ophthalmology (AAO) set new guidelines, lowering the recommended hydroxychloroquine dose from 6.5 mg/kg to less than 5 mg/kg to prevent retinopathy. However, it is not clear that this lower dose has the same efficacy for SLE activity, or the same protective role against CVD risk factors and thrombosis. In a recent study, we found that the risk of retinopathy was not as high as the AAO thought. At 16 years, the risk is about 10 percent. Caucasians, older patients, patients with a higher body mass index (BMI) and those with a longer duration of hydroxychloroquine use had a higher risk of toxicity.

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We have now shown that patients with hydroxychloroquine blood levels in the highest tertile are at higher risk of retinopathy.

This blood test is available at Johns Hopkins and a commercial source: Exagen. Some commercial labs offer a plasma level, but hydroxychloroquine binds to *blood*, so the plasma level is not accurate; it underestimates by 50 percent.

Vitamin D. Vitamin D tends to be almost universally low in lupus patients. We replaced vitamin D if we found it was low, and we found less disease activity – including less kidney activity, measured by the urine protein-to-creatinine ratio. We could do this perfectly safely; you only need to achieve a 25-hydroxy vitamin D level of 40; that's nowhere near the toxic level. Vitamin D replacement also helps prevent thrombotic events. It's a really safe way to help keep the disease under better control.

Both hydroxychloroquine and vitamin D are being inadequately used, and both benefit lupus while avoiding major toxicity.

Lupus Low Disease Activity State (LLDAS)

We want to reduce the long-term rates of organ damage in SLE. What should our "treat to target" be? Remission that is durable is very hard to achieve. The lupus low disease activity state (LLDAS) is more achievable. In LLDAS, the prednisone dose must be 7.5 mg/day or lower, which is still higher than our proven safe dose (below 6 mg/day). We recently completed the largest study to date of definitions of remission in SLE (DORIS) remission and LLDAS as predictors of organ damage. We found that even a small percentage of time (less than 25 percent) in DORIS clinical remission cut organ damage by about half. The take-home message from this study is that patients able to achieve LLDAS for 50 percent of their visits have a 50-percent reduction in later organ damage. These results are quite meaningful, as there was a significant reduction in end-stage renal disease, myocardial infarction and osteoporotic fractures.

Don't Treat All Symptoms Like Lupus Symptoms

Patients tend to think that "every reason I'm feeling bad must be my lupus." But after a report from Duke University, we're looking at two types of symptoms. Type I are the classic SLE signs that improve with lupus therapy. Type II are symptoms such as chronic fatigue, sleep disturbance, brain fog, depression, and chronic pain. These are not associated with lupus activity, and they should not be treated with prednisone.

Prednisone remains a problem in the management of SLE.

Conclusion: Prednisone remains a problem in the management of SLE. Immunomodulators such as hydroxychloroquine and vitamin D should be optimized, but over 50 percent of patients may need immunosuppressive drugs, as well.

FURTHER READING

Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy.
Arthritis & Rheumatology
2019, PMID:31532077

Comparison of remission and lupus low disease activity state in damage prevention in a United States systemic lupus erythematosus cohort.
Arthritis & Rheumatology
2018, PMID:29806142

Management strategies and future directions for systemic lupus erythematosus in adults.
Lancet
2019, PMID:31180030

THE COHORT

The Hopkins Lupus Cohor has made important contributions to the understanding of corticosteroid toxicity in SLE, the preventive role of hydroxychloroquine and the pathogenesis of accelerated atherosclerosis.

JOHNS HOPKINS
MEDICINE

Division of Rheumatology
5200 Eastern Avenue
Mason F. Lord Building
Center Tower, Suite 4100
Baltimore, MD 21224

2,300

Number of patients followed by protocol every 3 months in a 27-year longitudinal study.

OUTCOMES

include prediction of disease activity, prevention of organ damage, and improvement in quality of life

HOPKINSLUPUS.ORG
PATIENTS: 410-955-9114