CME

Improving the Diagnosis and Treatment of Lupus: Practical Guidance for the Primary Care Physician

PeerView inPlay

Course Director

Michelle A Petri, MD, MPH
Johns Hopkins University School of Medicine
Baltimore, Maryland

What's Inside

UNIVERSITY OF Cincinnati

This CME activity is jointly provided by the University of Cincinnati and PVI, PeerView Institute for Medical Education.

Participate in interactive questions, download activity slides, and obtain your instant CME credit online.

www.peerview.com/FYE900

Activity Information

Activity Description and Educational Objectives
In this activity, Dr. Michelle Petri discusses strategies to improve the diagnosis and management of systemic lupus erythematosus in the primary care setting.

Upon completion of this activity, participants should be better able to:
- Diagnose systemic lupus erythematosus (SLE) based upon recognition of characteristic clinical manifestations in the setting of supportive serologic studies, after excluding alternative diagnoses
- Outline nonpharmacologic measures and other medical interventions that are important in the comprehensive management of SLE
- Describe current approaches to drug therapy in SLE, recognizing that treatment is highly individualized and depends on the predominant symptoms, organ involvement, response to previous therapy, and disease activity and severity
- Collaborate with SLE patients and other care providers (eg, rheumatologists) to monitor disease activity and therapy, as well as improve treatment adherence, quality of life, and survival outcomes

Target Audience
This activity has been designed to meet the educational needs of primary care physicians and other clinicians involved in identifying and managing patients with systemic lupus erythematosus.

Requirements for Successful Completion
In order to receive credit, participants must view the activity and complete the post-test and evaluation form. There are no pre-requisites and there is no fee to participate in this activity or to receive CME credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

Media: Enduring Material
Release and Expiration Dates: June 12, 2018 - June 11, 2019
Time to Complete: 60 minutes

Faculty & Disclosure / Conflict of Interest Policy
In accordance with ACCME requirements, the University of Cincinnati has a conflict of interest policy that requires faculty to disclose relevant financial relationships related to the content of their presentations/materials. Any potential conflicts are resolved so that presentations are evidence-based and scientifically balanced.

Course Director
Michelle A Petri, MD, MPH
Professor
Johns Hopkins University School of Medicine
Baltimore, Maryland

Michelle A Petri, MD, MPH, has a financial interest/relationship or affiliation in the form of:
Consultant for Amgen Inc.; Bristol-Myers Squibb; Eli Lilly and Company; Inova Diagnostics; Janssen Pharmaceuticals, Inc.; and Quintiles Pharma Inc.
Grant/Research Support from AstraZeneca; Exagen Diagnostics, Inc.; and GlaxoSmithKline.
Other Financial or Material Support from Data Monitoring Board for EMD Serono, Inc. and Merck & Co., Inc.

CME Reviewer
Bruce C. Gebhardt, MD
University of Cincinnati College of Medicine
Cincinnati, Ohio

Bruce C. Gebhardt, MD, has no financial interests/relationships or affiliations in relation to this activity.

CME Accreditation
Jennifer Holzberger, BS
Program Coordinator, Continuing Medical Education
University of Cincinnati
Cincinnati, Ohio

Jennifer Holzberger, BS, has no financial interests/relationships or affiliations in relation to this activity.

Susan P. Tyler, MEd, CMP, CHCP
Director, Continuing Medical Education
University of Cincinnati
Cincinnati, Ohio

Susan P. Tyler, MEd, CMP, CHCP, has no financial interests/relationships or affiliations in relation to this activity.

Medical Director
Kathryn B. Charalambous, PhD
PVI, PeerView Institute for Medical Education

Kathryn B. Charalambous, PhD, has no financial interests/relationships or affiliations in relation to this activity.

Providership, Credit & Support
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Cincinnati and PVI, PeerView Institute for Medical Education. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

The University of Cincinnati designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Providership
This CME activity is jointly provided by the University of Cincinnati and PVI, PeerView Institute for Medical Education.

Support
This educational activity is supported by an educational grant from GlaxoSmithKline.

Disclosure of Unlabeled Use
The faculty of this educational activity may include discussions of products or devices that are not currently labeled for use by the FDA. Faculty members have been advised to disclose to the audience any reference to an unlabeled or investigational use.

No endorsement of unapproved products or uses is made or implied by coverage of these products or uses in our reports. No responsibility is taken for errors or omissions in reports. For approved prescribing information, please consult the manufacturer's product labeling.

The materials presented here are used with the permission of the authors and/or other sources. These materials do not necessarily reflect the views of PeerView or any of its partners, providers, and/or supporters.

About This CME Activity
PVI, PeerView Institute for Medical Education, and the University of Cincinnati are responsible for the selection of this activity's topics, the preparation of editorial content, and the distribution of this activity. Our activities may contain references to unapproved products or uses of these products in certain jurisdictions. The preparation of PeerView activities is supported by educational grants subject to written agreements that clearly stipulate and enforce the editorial independence of PVI and the University of Cincinnati.

Key Concepts in Diagnosing and Managing SLE: An Interactive Game

Dr. Petri: Hello, my name is Michelle Petri. I direct the Lupus Center at Johns Hopkins University School of Medicine in Baltimore, Maryland. Welcome to our educational activity on lupus.

This activity includes a discussion focused on diagnosis and current treatment approaches, as well as an interactive game designed to assess and improve your knowledge of strategies for managing individual patients with lupus in the primary care setting.

Systemic Lupus Erythematosus: Introduction

- Systemic lupus erythematosus (SLE), commonly referred to as lupus, is an autoimmune disease that affects many systems
- Disease course is typically recurrent, with periods of relative remission followed by flares
- Effective management requires regular monitoring

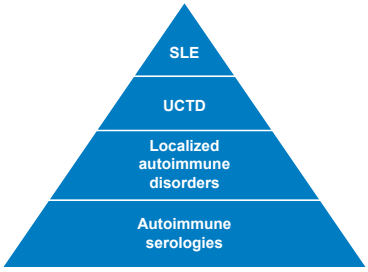
PeerView.com

Systemic lupus erythematosus is an autoimmune disease that affects the skin and musculoskeletal, renal, neuropsychiatric, hematologic, cardiovascular, and pulmonary systems. Its course is typically recurrent with periods of relative remission followed by flares. Establishing the diagnosis may be challenging, and because of the variable disease course, effective management of SLE requires regular clinical monitoring to assess disease activity, alleviate symptoms, monitor side effects related to drug therapy, encourage medication adherence, and coordinate care with the patient's other providers.

With these concepts in mind, let's begin the game portion of the activity. You can earn up to 1,000 points, and you'll see your points and ranking as you go. Are you ready?

SLE Diagnosis: Making It Early and Getting It Right

Systemic Lupus Erythematosus (SLE): The Tip of the Iceberg

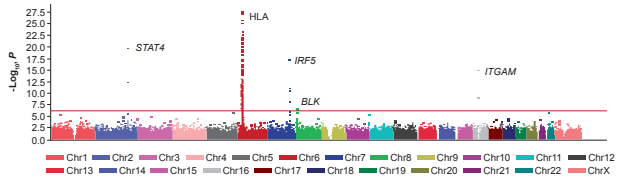


PeerView.com

Dr. Petri: I want you to think of lupus as the tip of the autoimmune iceberg, with autoimmune serologies being most common—that would mean a positive ANA. And the next step in this pyramid is localized autoimmune disorders. The most common one that you'll probably encounter is autoimmune thyroid disease.

Rheumatologists become involved in the next step of the pyramid. Mild systemic autoimmune symptoms are usually labeled as undifferentiated connective tissue disease, or UCTD for short. I put lupus at the top of the pyramid, but, of course, you could put rheumatoid arthritis, scleroderma, myositis.

SLE Is Half Genetics[1]



1. Hom G et al. *N Engl J Med.* 2008;358:900-909.

PeerView.com

I think you'll be very surprised to learn that autoimmune diseases have a very strong genetic component. This is certainly true in lupus, where in terms of causality it's 50% genetics. Here you see an example of a genome-wide association study, or GWAS, identifying the most important genes that contribute to lupus.

There are over 80 that have been identified. The most important individual set of genes are the HLA immune response genes.

But we don't want to think of lupus as a genetic mutation disease. It's not like cystic fibrosis or sickle cell. These are not mutated genes. These are just varieties of genes that any of us might have. But what they share in common is they seem to increase the immune response, the chance that the immune system will make a mistake and attack itself.

Ethnic Differences in Incidence[a]

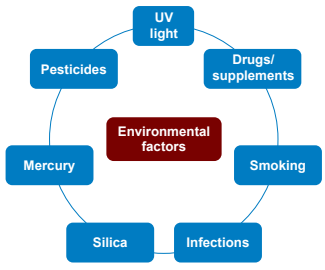
	Caucasian	African American or African Caribbean	Asian	Hispanic
Somers et al. 2004 (MI)[1]	6.3	12.8	–	–
Lim et al. 2014 (GA)[2]	4.7	13.4	–	–
Dall'Era et al. 2017 (CA)[3]	5.3	30.5	7.2	8.9
Izmirly et al. 2017 (NC)[4]	7.1	15.7	6.6	6.5

* Females per 100,000.
1. Somers EC et al. *Arthritis Rheumatol*. 2014;66:369-378. 2. Lim SS et al. *Arthritis Rheumatol*. 2014;66:357-368.
3. Dall'Era M et al. *Arthritis Rheumatol*. 2017;69:1996-2005. 4. Izmirly PM et al. *Arthritis Rheumatol*. 2017;69:2006-2017.

PeerView.com

There are certainly very important ethnic differences in the incidence of lupus in the United States. We will see this in two major populations, an increase in African Americans and an increase in Hispanic Americans. But, in addition, there are some studies that suggest an increase in Asian Americans as well. These are very recent studies predominantly funded by the Centers for Disease Control [and Prevention].

SLE Is Half Environmental[1-8]



1. Parks CG et al. *Arthritis Rheum*. 2002;46:1840-1850. 2. Chiou SH et al. *Lupus*. 2004;13:442-449.
3. Zarmbinski MA et al. *J Rheumatol*. 1992;19:1380-1384. 4. Cooper GS et al. *J Rheumatol*. 2004;31:1928-1933.
5. Costenbader KH et al. *Arthritis Rheum*. 2004;50:849-857. 6. Karlson EW. *Autoimmunity*. 2005;38:541-547.
7. Freemer MM et al. *Annals Rheum Dis*. 2006;65:581-584. 8. Majka DS, Holers VM. *Annals Rheum Dis*. 2006;65:561-563.

PeerView.com

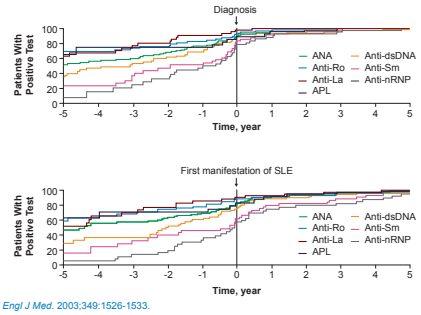
Now it follows if lupus is half genetic, it must also be half environmental. The environmental trigger that most of us immediately recognize is exposure to ultraviolet light. Both UVA and UVB can trigger lupus rashes and sometimes even systemic flares. So it's important that we tell patients to avoid the sun and to use a sunscreen that can block both UVA and UVB wavelengths.

Patients don't realize how little ultraviolet exposure it takes to cause lupus rash. I remind patients that just going from the garage into our clinic building is enough.

There are some very common drugs that can actually precipitate flares or first onset of SLE. This includes echinacea, which some people like to take for the common cold, but most importantly the antibiotic trimethoprim/sulfa. We actually ask patients to avoid this antibiotic entirely. And even when we have to use PCP prophylaxis, we would rather not use trimethoprim/sulfa. Instead, we would ask them to use another therapy.

Smoking is both a risk factor for lupus, but in particular, if someone continues to smoke they are much more likely to have cutaneous activity, including the worst lupus rash, which is discoid lupus. Infections can also trigger lupus. In particular, Epstein-Barr virus has been incriminated, but also several other infections, including parvovirus and CMV. There are several environmental pollutants that increase the risk of lupus, and these include silica, mercury, and pesticides.

SLE Autoantibodies Precede Clinical Manifestations by >5 Years[1]

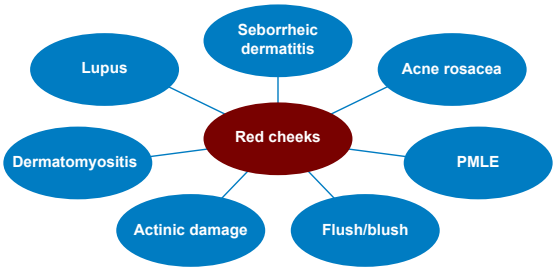


1. Arbuckle MR et al. *N Engl J Med*. 2003;349:1526-1533.

PeerView.com

You'll be surprised to hear that lupus autoantibodies are present in the person for 5 to 7 years before they reach either a clinical onset or a clinical diagnosis. So the patient who wants to blame a very recent event for their lupus is almost certainly incorrect. It's more likely a process that's been going on for 5 to 7 years.

When You Should Suspect SLE



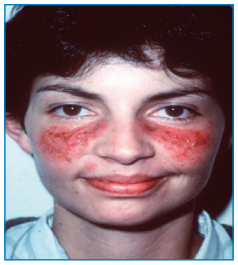
PeerView.com

Early diagnosis really does matter. We want to both control disease activity and prevent damage. So when should you suspect SLE? I want to start with cutaneous manifestations, because nothing is simple in lupus. Some patients often think that any redness of their cheeks is a lupus rash. We see red cheeks all the time that have absolutely nothing to do with lupus—for example, from

seborrheic dermatitis, acne rosacea, a flush or a blush, actinic damage from years of sun exposure may reveal telangiectasias, and then the more complicated differential diagnosis.

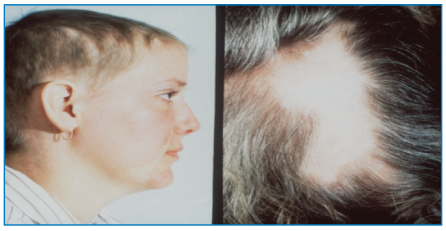
So a rash that occurs within a couple of hours of sun exposure and is gone by the next day is much more likely to be a polymorphous light eruption. Lupus rashes don't occur usually on the same day as the ultraviolet light exposure. They'll occur a day or two later. The lupus rash will be raised, because it's due to inflammation. And it will usually last for days or weeks, not a couple of hours or one day.

Even more confusing is that there is another autoimmune disease that can cause a rash on the cheeks. That is dermatomyositis. But the dermatomyositis rash actually can involve the nasolabial fold, even though that area is at least partially shaded from ultraviolet light.



Courtesy of Dr. Michelle Petri. PeerView.com

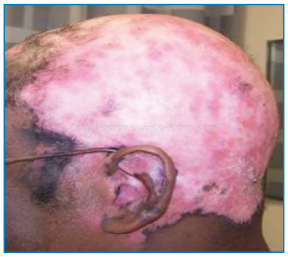
Let's show an example of what looks like the world's worst case of acne, but this is actually a lupus rash. And the reason we can tell that is it's obviously raised, isn't it? And it spares the areas shaded from ultraviolet light. So the nasolabial folds below the nares and below the lower lip are not involved.



Courtesy of Dr. Michelle Petri. PeerView.com

Here is another one of the cutaneous manifestations of lupus. But I want you to pay attention to the left-hand part of this photograph. Here we see someone whose scalp shows through, and the hairs around the frame of the face are broken off and very short. These are the typical findings of SLE. The hair is fragile, so it breaks off; and it's thinner than usual, so the scalp shows through.

The right-hand part of the slide shows a completely separate autoimmune disease. This is alopecia areata. This is one of the localized autoimmune disorders that we discussed on the pyramid of autoimmunity, but it's not part of lupus.

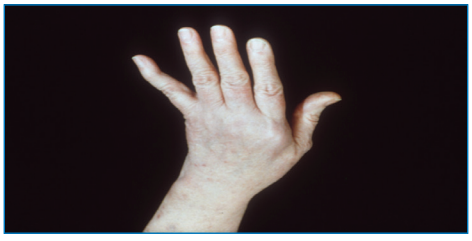


Courtesy of Dr. Michelle Petri. PeerView.com

Here is the worst lupus rash, called discoid lupus or sometimes chronic cutaneous lupus. It is possible to have this rash without systemic lupus, but about 5% to 10% of patients who present with this rash will go on to develop SLE.

This rash is devastating because the inflammation involves the deeper layers of the dermis. When healing occurs, it's like the healing of a third-degree burn. There is major hypo- and hyperpigmentation, and the hair follicles are completely destroyed. This young woman, for example, will have to wear a wig for her entire life.

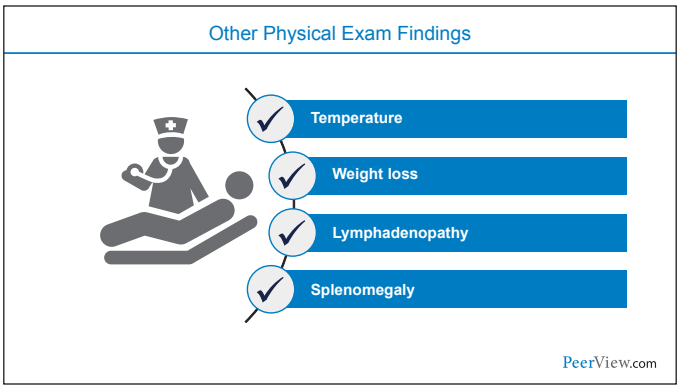
One of my patients who looked like this was hounded in her apartment complex. The other residents thought she had leprosy, and that it might be contagious. You can't even begin to imagine what it is like for a young woman to have to live her life looking like this.



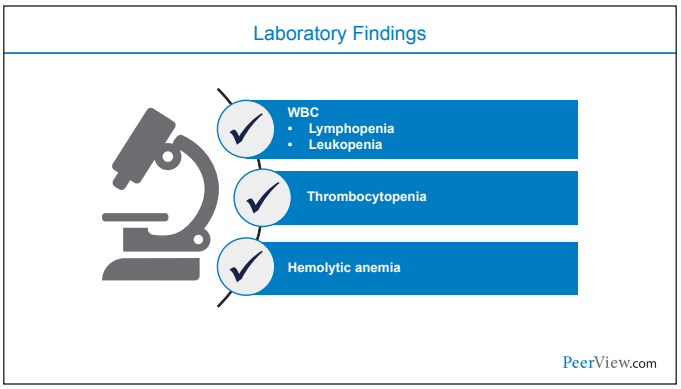
Courtesy of Dr. Michelle Petri. PeerView.com

Here's an example of lupus arthritis. Ninety percent of people with lupus will have joint symptoms. When you look at this photograph, you're thinking this is rheumatoid arthritis because of the deformities. Lupus arthritis is less likely to cause erosive damage, but these deformities, which are called Jaccoud's arthritis, are

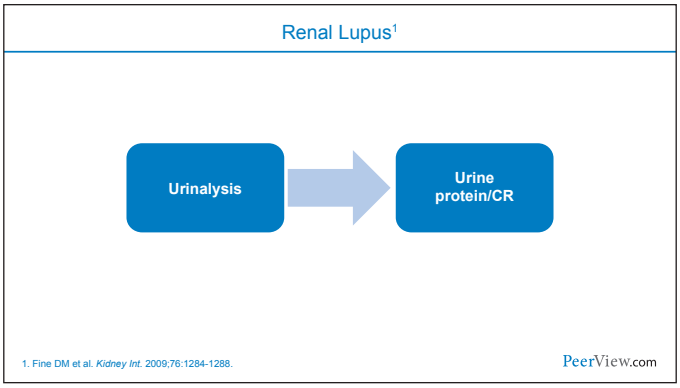
actually due to tendon and ligament laxity. If this progresses, it will be very difficult for the patient to do her activities of daily living.



Other physical exam findings that are important are an actual temperature, a temperature of 101 or greater; weight loss; lymphadenopathy, which we often detect in the cervical region but can occur also in the axillary, inguinal, and femoral regions; and splenomegaly.

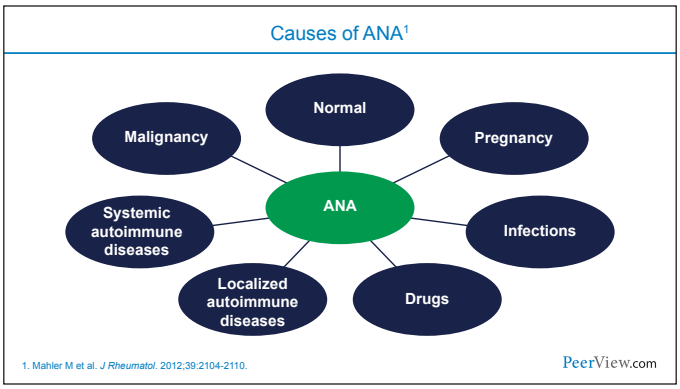


Laboratory findings that are early clues include the hematologic cell lines, so for the white blood count lymphopenia or leukopenia. But do remember that if the patient has been put on prednisone, prednisone itself will cause lymphopenia. Thrombocytopenia, which can be either from lupus or from antiphospholipid antibodies that many people with lupus will have, and hemolytic anemia.



Renal lupus is one of the more devastating complications of lupus. The initial pickup may be on the urinalysis with a urine dipstick, but it's very important to quantify it. So what we prefer is the spot or random urine protein to creatinine ratio.

Don't depend on microalbumin, because in lupus, half of the protein loss is from globulins. So if only microalbumin is measured, it will underestimate the degree of renal lupus by 50%.

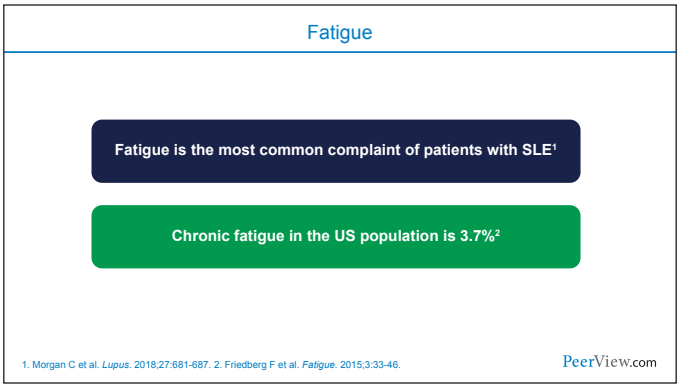


What isn't specific for lupus? Well, it's the ANA. The ANA is not the end-all and be-all for lupus. So a positive ANA is usually not from lupus, and a big surprise even to rheumatologists is that people who have had lupus for many years can sometimes become ANA negative. So it turns out the most common cause of having a positive ANA is being normal.

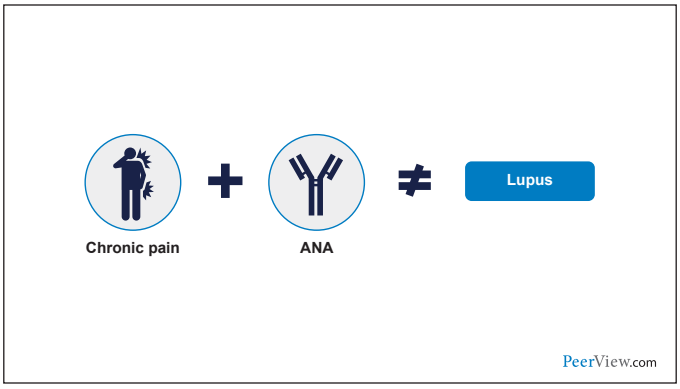
And I'm serious. Twenty percent of normal young women can have a positive ANA. Pregnancy can cause a positive ANA. Many infections can. Many drugs can. And I know you know about drug-induced lupus, and you've heard that the most common causes of drug-induced lupus are things like procainamide, isoniazid, and hydralazine. But many very common drugs will cause a positive ANA without ever causing a drug-induced lupus, and that can include things like statins, for example.

In the autoimmune pyramid, we already discussed localized autoimmune disorders. They will usually have an ANA. We mentioned autoimmune thyroid disease, but every specialty has a handle on autoimmune diseases that affect their organ. And

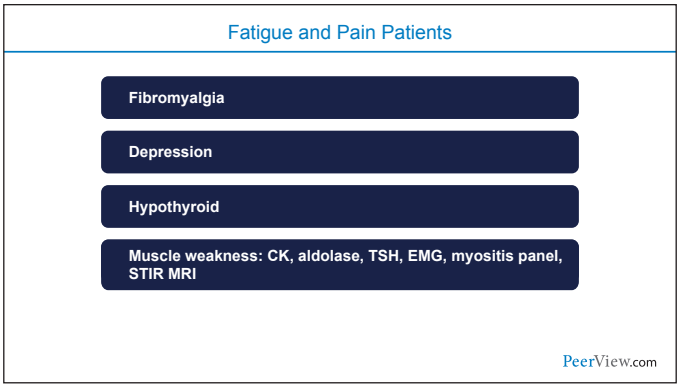
then, of course, rheumatologists will see an ANA in nearly all of our autoimmune diseases, including rheumatoid arthritis, scleroderma, and myositis. And oncologists will find an ANA with many different kinds of malignancy.



Fatigue is the most common complaint of lupus patients. So how dare I tell you that fatigue is not an important specific sign of lupus? It's because chronic fatigue in the United States affects 3.7% [of the population]. It's a very common complaint. And in lupus patients it doesn't associate with our specific organ manifestations. That doesn't mean that we don't care. It doesn't mean that we wouldn't like to fix it, but it means we don't have a causal association with active lupus.



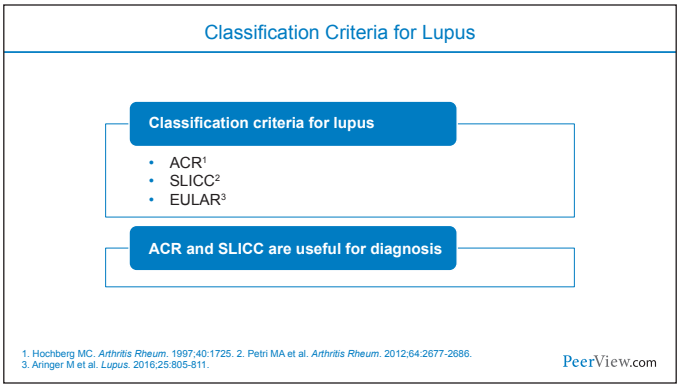
An important take-home message is that a patient who presents with chronic pain and a positive ANA should not be diagnosed with lupus. She is much more likely to have fibromyalgia than she is to have lupus. Lupus is not a chronic pain disease.



So what does cause fatigue and pain? The most common cause is fibromyalgia. This is particularly confusing because over 30% of people with lupus also have fibromyalgia. We don't want to chase their fibromyalgia with lupus treatments, so it's very important to recognize both and to help the patient differentiate muscle pain and chronic fatigue as part of their fibromyalgia.

Depression can cause fatigue and pain. And hypothyroidism should not be missed, because it's going to cause fatigue, muscle, and joint pain. And 10% of people with lupus also are hypothyroid.

Now particularly if the patient is complaining of muscle weakness, do check for myositis with obviously a CK and aldolase, but [also] a TSH to make sure there isn't hypothyroidism. And then becoming more serious about working up myositis, we would want to do an EMG, a myositis panel, and a STIR MRI.



So we now have three classification criteria for lupus. The first and oldest one, you may remember. That's the American College of Rheumatology criteria, where the person had to have 4 of the 11 to be classified as having lupus. Why four? Because if a person just has one or two autoimmune manifestations, we'd rather call that undifferentiated connective tissue disease. Only 10% of people with mild autoimmunity, like UCTD, actually go on to develop true lupus.

But the ACR criteria really didn't represent the autoimmune antibodies to the extent that we wish, and that led the Systemic Lupus International Collaborating Clinics to develop new

classification criteria. These also required a total of four things. But now the rule was that at least one of the four must be a clinical manifestation, and at least one of the four must be an autoantibody.

If the patient had lupus nephritis by a biopsy, you didn't even have to have four things. Lupus nephritis by biopsy was sufficient in and of itself.

Finally, very recently, the European group called EULAR have developed criteria that will be used for clinical research. The first two criteria here, I think are quite useful for diagnosis as well.

SLICC Revision of the ACR Classification Criteria[1]

Clinical Criteria	
1. Acute/subacute cutaneous lupus 2. Chronic cutaneous lupus 3. Oral/nasal ulcers 4. Nonscarring alopecia	Dermatologic
5. Inflammatory synovitis with physician-observed swelling of two or more joints OR tender joints with morning stiffness 6. Serositis 7. Renal: urine protein/creatinine (or 24-hour urine protein) representing at least 500 mg of protein/24 hours or red blood cell casts 8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state)	Four other systems
9. Hemolytic anemia 10. Leukopenia (<4,000/mm³ at least once) OR lymphopenia (<1,000/mm³ at least once) 11. Thrombocytopenia (<100,000/mm³) at least once	Hematologic

1. Petri M et al. *Arthritis Rheum*. 2012;64:2677-2686.

PeerView.com

Here are the clinical criteria that are part of the SLICC classification criteria. The first four are the dermatologic manifestations: the acute lupus rash, the chronic cutaneous lupus rash, oral or nasal ulcers, and the nonscarring alopecia that we saw on the photograph.

The next four are four other organ systems: the musculoskeletal system; serositis, which can present with pericarditis, pleurisy, or even sometimes ascites; renal lupus; and neurologic lupus. You can see the large number of manifestations of neurologic lupus. Luckily, seizures and psychosis are rarer now than they were 30 years ago.

The last three are the three hematologic cell lines: hemolytic anemia, the low white blood count, and thrombocytopenia.

SLICC Revision of the ACR Classification Criteria (Cont'd)[1]

Immunologic Criteria
1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range (except ELISA: >twofold laboratory reference range)
3. Anti-Sm
4. Antiphospholipid antibody • Lupus anticoagulant • False-positive test for syphilis • Anticardiolipin: at least twice normal or medium-high titer • Anti-β2-glycoprotein 1
5. Low complement • Low C3 • Low C4 • Low CH50
6. Direct Coombs test in absence of hemolytic anemia

1. Petri M et al. *Arthritis Rheum*. 2012;64:2677-2686.

PeerView.com

Here are the autoimmune criteria. Now the positive ANA is still there. We can't get rid of it. But the more important ones are below. The anti-double-stranded DNA, I know you've been told it's specific for lupus. But I want you to be particularly careful if your laboratory reports in ELISA units. There, there can be borderline positive titers that we would ask you to ignore. We want the titer to be twice above the laboratory reference range before it should assume any importance.

Anti-Sm actually stands for anti-Smith. The next one on the list, the antiphospholipid antibodies. About 50% of people with lupus will have these antibodies, but you're probably aware that many people can have them who don't ever get lupus or another autoimmune disease. They're particularly important because they represent a hypercoagulable state that can lead to thrombosis or pregnancy complications. The most important one is the lupus anticoagulant.

Next is low complement. Low complement had not been part of the ACR classification criteria. But when complement is low, although it's not specific for lupus, it does make us suspicious, and, of course, we order a more elaborate work-up.

And finally, the direct Coombs test. And you're going to be thinking this is a repeat because hemolytic anemia was on the clinical list. But it turns out that 90% of lupus patients with a direct Coombs test never manifest a hemolytic anemia. So that's why it counts on this list.

Primary Care Algorithm: It Only Takes ONE

- ANA PLUS
  - Rash in photosensitive distribution
  - Morning joint stiffness in autoimmune distribution (PIP, MCP, wrists)
  - Visible hair loss around frame of face
  - Decreased WBC, platelets, and HCT (not because of iron deficiency)
  - Urine protein (preferably urine protein/CR)
  - Temperature elevation in office NOT because of infection
  - Lymphadenopathy
  - Splenomegaly
- Refer to rheumatologist
- Helpful to have ANA >640 but *more* helpful to test for specific autoantibodies (Sm, anti-dsDNA, Coombs), complement (C3, C4), and nonspecific autoimmune antibodies (antiphospholipid, RNP, Ro, La)

PeerView.com

So my primary care algorithm for being suspicious about lupus, it only takes one additional thing on top of an ANA for us to be suspicious and to warrant a referral to a rheumatologist for a complete workup. So that would be an ANA plus a rash in a photosensitive distribution, morning joint stiffness in the autoimmune distribution, which means PIPs, MCPs and wrists.

If a patient is telling you their shoulders and hips hurt, be much more suspicious about fibromyalgia. Those are not areas that are usually part of lupus. And then visible hair loss around the frame of the face, as we saw in the photograph, next, a low hematologic cell line, next, urine protein, next, a temperature elevation that you've documented in your office that's not due to infection, next,

lymphadenopathy and next, splenomegaly. Remember an ANA plus any one of these is worth a referral to a rheumatologist.

It's very helpful if the ANA is over 640, but even more helpful to do the specific autoantibodies, the Smith, the anti-DNA, the Coombs, to check complement, and even to go further and check the nonspecific, but also autoimmune antibodies, antiphospholipid, anti-RNP, anti-Ro, and anti-La.

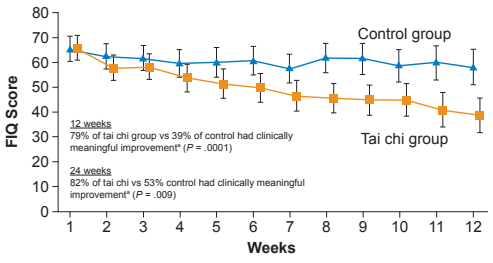
A Closer Look at the Contemporary Management of SLE in Adults

Lupus activity does not manifest as chronic fatigue or pain

PeerView.com

Dr. Petri: In part two of our discussion, we're going to be talking about contemporary management of lupus. Remember, an important take-home message was that lupus activity does not manifest as chronic fatigue or chronic pain. We want to look for objective manifestations of lupus in an organ system.

Treating Pain: Tai Chi[1]



* "Clinically meaningful" change in FIQ = 8.1 points.
1. Wang C et al. *N Eng J Med.* 2010;363:743-754.

PeerView.com

So what are we going to do if a lupus patient has chronic pain? We know from a tai chi trial for fibromyalgia published in the *New England Journal of Medicine* that tai chi can actually lead to 50% reduction in chronic pain.

Exercise for SLE-Related Fatigue[1]

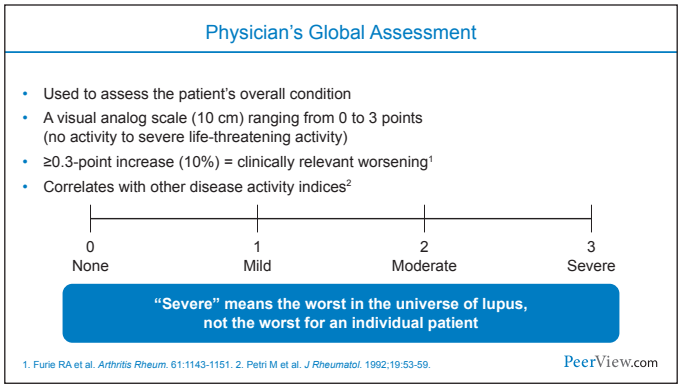
Clinical Global Impression Change Score	No. (%) in Exercise Group (n = 33)	No. (%) in Relaxation Group (n = 28)	No. (%) in Control Group (n = 32)
Very much better	3 (9)	4 (14)	1 (3)
Much better	13 (40)	4 (14)	4 (13)
A little better	5 (15)	4 (14)	3 (9)
No change	6 (18)	10 (36)	13 (41)
A little worse	4 (12)	4 (15)	10 (31)
Much worse	2 (6)	2 (7)	1 (3)
Very much worse	0	0	0

1. Tench CM et al. *Rheumatology (Oxford).* 2003;42:1050-1054.

PeerView.com

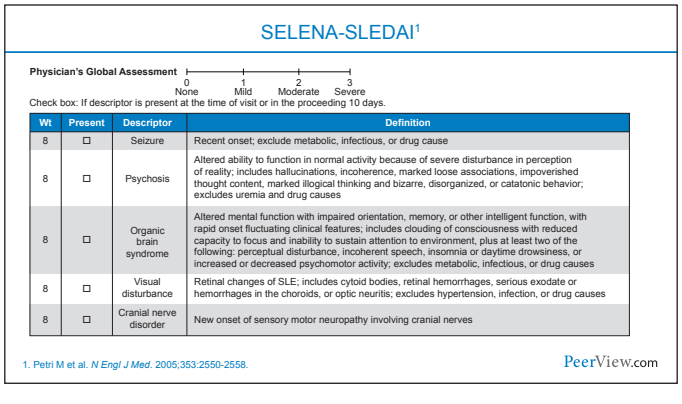
We would then build upon this by asking the patient to do aerobic exercise as well. We don't turn to narcotics. This is the biggest trap in fibromyalgia, because narcotics actually make fibromyalgia pain worse. Remember that fatigue was the patient's major complaint worldwide. So what do we do for the patient who has chronic fatigue?

It does seem counterintuitive, but we recommend the gradual introduction of aerobic exercise. It was shown in this clinical trial that the great majority of lupus patients with chronic fatigue improve with aerobic exercise. It takes time to convince the patient, but this is the right way to go.



I want to show you how we try to measure lupus disease activity in rheumatology. We can use a very simple assessment on a 0-to-3 scale called the Physician's Global Assessment: 1 is mild, 2 is moderate, and 3 is severe. Mild, for example, might be 15 minutes of morning stiffness. Moderate might be a urine protein creatinine ratio of 1 g/day; severe might be a platelet count of 5,000, with the patient actively bleeding and admitted to the ICU.

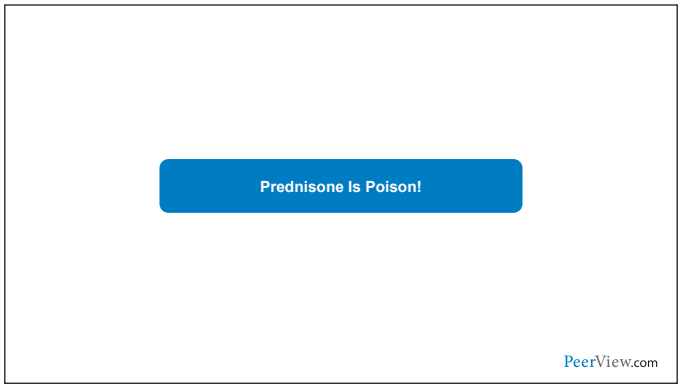
This is a scale where 3 is the worst possible in the universe of lupus. Remember, the things that aren't due to active lupus, like chronic fatigue and chronic pain, are not counted.



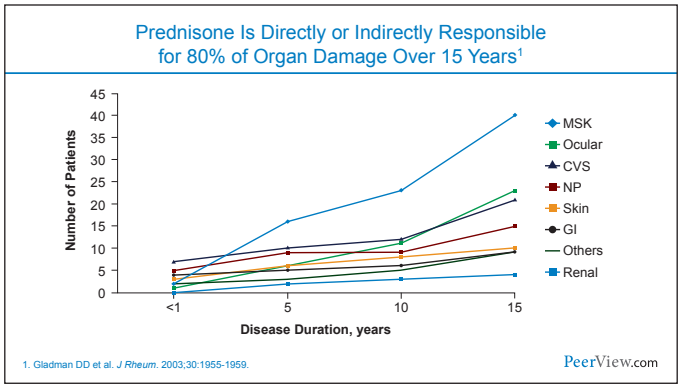
We do have a more elaborate index called the SLE Disease Activity Index Score. This was called the SLEDAI for short. It's a very simple index. We simply circle whether the manifestation is present or absent, and we only circle it if it's due to active lupus.

Here you see a snapshot of the things that are counted under neurologic, but we wouldn't circle seizure if it was a chronic seizure disorder and the patient just had a breakthrough seizure. We would only circle seizure if it was due to active lupus.

I was teaching one of my fellows one day how to complete this index and I called it the SLEDAI score, and I will never forget the patient interrupted me as I was teaching and said, "Dr. Petri, you never told me you could predict when I would die." And I realized how awful the name was. So we renamed it that day. The SLE Day Score, how active the person's lupus is on that day. And I'm trying to convince all rheumatologists to call it the SLE Day.



Now my most important take-home message for this part of the talk is that the "P" in prednisone stands for "poison." I never want you to forget that every time we write a prednisone prescription, we're dooming our patient to long-term organ damage. The modern management of lupus is to avoid prednisone as much as possible.



Prednisone is directly or indirectly responsible for 80% of permanent organ damage 15 years after the diagnosis. Here is the study done at the University of Toronto. You can see in the first 5 years, the slope is reasonably flat. But you see how it starts to take off, especially after 10 years.

The most frequent organ damage is musculoskeletal. Those are osteoporotic fractures or avascular necrosis of the hips. The ocular damage won't surprise you. It's mostly cataracts. Everything we've just discussed is from prednisone.

Effect of Prednisone on Organ Damage[1]

Adjusting for Confounding by Indication Because of SLE Disease Activity

Prednisone Average Dose	Hazard Ratio
>0 to 6 mg/day	1.16
>6 to 12 mg/day	1.50
>12 to 18 mg/day	1.64
>18 mg/day	2.51

A prednisone dose of >6 mg/day increases organ damage by 50%

1. Thamer M et al. *J Rheumatol*. 2009;36:560-564.

PeerView.com

FLOAT Trial Comparison of Oral Methylprednisolone and Intramuscular Triamcinolone[1]

		Methylprednisolone, %	Triamcinolone, %
Complete improvement	1 week	8.3	8.6
	2 weeks	20.8	12.5
	3 weeks	20.8	30.4
	4 weeks	25.0	34.7
Partial improvement	Day 1	41.6	69.5
Health status	4 weeks	66.6	73.9

1. Danowski A et al. *J Rheumatol*. 2006;33:57-60.

PeerView.com

How bad is it? Here is a study that I did showing that if the daily maintenance prednisone dose is above 6 mg, there is going to be a 50% increase in permanent organ damage. If it's above 18 mg, permanent organ damage is going to go up two-and-a-half-fold. So doses of prednisone that used to be thought acceptable for lupus are not.

Now we discussed musculoskeletal and ocular damage. But the most important thing that goes wrong in lupus is accelerated atherosclerosis. It is the most common cause of death after the first 5 years.

Prednisone Itself Increases the Risk of Cardiovascular Events[1]

Prednisone Use	Observed Number of CVE	Rate of Events/ 1,000 Person-Years	Age-Adjusted Rate Ratios (95% CI)	*P*
Never taken	22	13.3	1.0 (reference group)	—
Currently taking				
1 to 9 mg/d	32	12.3	1.3 (0.8-2.0)	.31
10 to 19 mg/d	**31**	**20.2**	**2.4 (1.5-3.8)**	**.0002**
≥20 mg/d	**25**	**35.4**	**5.1 (3.1-8.4)**	**<.0001**
Cumulative past dose				
<3,650 mg[a]	14	9.9	0.9 (0.4-1.6)	.56
3,650 to 10,950 mg[b]	26	13.8	1.2 (0.7-2.2)	.49
10,950 to 36,499 mg[c]	41	12.8	1.1 (0.6-1.8)	.83
36,500+ mg[d]	**30**	**25.3**	**2.2 (1.2-3.7)**	**.0066**

[a] 3,650 mg equals 10 mg/day for 1 year, or an equivalent cumulative exposure. [b] 1-3 years with 10 mg/day or an equivalent cumulative exposure. [c] 3-10 years with 10 mg/day or an equivalent cumulative exposure. [d] 10+ years with 10 mg/day or an equivalent cumulative exposure.

1. Magder LS, Petri M. *Am J Epidemol*. 2012;176:708-719.

PeerView.com

Here is another analysis that we did showing that if the maintenance prednisone dose is 10 mg, the risk of a cardiovascular event goes up 2.4-fold. And if the maintenance prednisone dose is above 20 mg, the risk of a cardiovascular event goes up 5-fold. So prednisone contributes directly to the major cause of death.

These analyses were adjusted for all the traditional cardiovascular risk factors, as well as for the disease activity for which I prescribed the prednisone. Yes, these are all my patients. I am the guilty party. I had to learn about prednisone the hard way.

Now what do we do if the patient is having a flare? I'm not going to tell her, "Go home and suffer in silence." We have to treat flares. The great majority of flares are going to be skin or joint flares. We can fix most of them with a small burst of steroid. We can do this with Medrol Dosepak or with a triamcinolone intramuscular injection.

Now we can't do this all the time or yes even these can cause steroid toxicity. But we could probably do it safely every 3 months. In this trial, the great majority of mild-to-moderate flares were handled by this kind of small burst of steroid without ever increasing the maintenance prednisone.

A triamcinolone injection will wear off in about a month. If the disease activity is right back, that's a clear message to the rheumatologist that the patient is going to need more daily immunosuppressive therapy.

Hydroxychloroquine Should Be Background Therapy in All SLE Patients

Reduction in flares →	Canadian Hydroxychloroquine Study Group. *N Engl J Med*. 1991;324:150-154.
Reduction in organ damage →	Fessler BJ et al. *Arthritis Rheum*. 2005;52:1473-1480.
Reduction in lipids →	Petri M. *Lupus*. 1996;5(suppl 1):S16-S22. Wallace DJ et al. *Am J Med*. 1990;89:322-326.
Reduction in thrombosis →	Pierangeli SS, Harris EN. *Lupus*. 1996;5:451-455. Petri M. *Scand J Rheumatol*. 1996;25:191-193.
Triples mycophenolate response in lupus nephritis →	Kasitanon N et al. *Lupus*. 2006;15:366-370.
Improvement in survival →	Alarcon GS et al. *Arthritis Rheum*. 2005;52:S726. Ruiz-Irastorza G et al. *Lupus*. 2005;14:220.

Hydroxychloroquine is also effective in treating the arthritis associated with lupus

PeerView.com

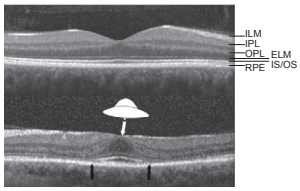
Now what are our current treatment approaches? Hydroxychloroquine is the most important thing that we do for lupus. We feel so strongly about this that we think it should be background therapy in all lupus patients for so many good reasons.

It does help skin and joint activity. Those are the most frequent organ manifestations of lupus. It can reduce flares in half. It reduces later organ damage, has a beneficial effect on some traditional cardiovascular risk factors, and it can reduce lipids and it also reduces diabetes.

For those patients that have the antiphospholipid antibodies, it reduces thrombosis. For patients with lupus kidney involvement, it increases the chance that they will achieve a renal remission. And a good reason to think of the "H" in hydroxychloroquine as standing for "lupus health insurance" is that there are multiple studies showing it improved survival.

Now there are issues with hydroxychloroquine. There's a rare side effect of retinopathy. This is rarely seen in the first 10 years. But after 10 years, a rare patient will develop it. This is the reason that we want everyone on hydroxychloroquine to have ophthalmology monitoring.

Spectral Domain Optical Coherence Tomography (SD OCT) Imaging[1]



Top: Normal spectralis SD OCT image with intact photoreceptor inner segment/outer segment (IS/OS) junction.

Bottom: Spectralis SD OCT from left eye of Patient 10, showing the "flying saucer" sign of hydroxychloroquine retinopathy—an ovoid appearance of central fovea created by preservation of central foveal outer retinal structures (seen between the black arrows) surrounded by perifoveal loss of the photoreceptor IS/OS junction, and perifoveal outer retinal thinning.

1. Chen E et al. *Clin Ophthalmol*. 2010;4:1151-1158.

PeerView.com

There are new, more sensitive tests. Here you see an example of an OCT. That stands for ocular coherence [tomography]. On the top part of this slide, you see that dip in the parafoveal region. This is what the retina should look like. With hydroxychloroquine retinopathy instead you see on the lower part of this slide that that dip is gone, and instead you see what has been nicknamed the flying saucer sign. So yes, ophthalmologists have a sense of humor.

Increasing 25-Hydroxy Vitamin D Helps Disease Activity and Urine Protein/CR[1]

- Model allowing slope to differ before and after 40 ng/mL

Disease Measure	Slope Over Range of 0 to 40 ng/mL (95% CI)	*P*	Slope Over Range of ≥40 ng/mL (95% CI)	*P*
Physician's Global Assessment	-0.04 (-0.08 to -0.01)	.026	0.01 (-0.02 to 0.04)	.50
SELENA-SLEDAI	-0.22 (-0.41 to -0.02)	.032	0.12 (-0.01 to 0.24)	.065
Log urinary protein/ creatinine	-0.03 (-0.05 to -0.02)	.0004	-0.01 (-0.01 to 0.00)	.24

1. Petri M et al. *Arthritis Rheum*. 2013;65:1865-1871.

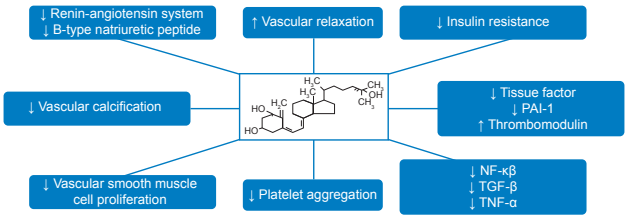
PeerView.com

Vitamin D is our second very safe immunomodulator. By immunomodulator I mean that the drug does not cause infections or increase malignancy.

In a study that we did, we showed that keeping the vitamin D level at 40 ng/mL, we could show a reduction in overall disease activity and a reduction in urine protein to creatinine. We did not need to go any higher than 40 [ng/mL]. So the right-hand part of this slide shows that going over 40 [ng/mL] did not actually achieve any more clinical benefit.

So we can do this very safely, such as with 50,000 units once a week on Sunday. You will find that patients who are particularly obese may need their vitamin D replacement twice a week, for example on Sunday and Wednesday.

Vitamin D May Have Cardiovascular and Hematologic Benefits[1]



1. Targher G et al. *Semin Thromb Hemostatis*. 2012;38:114-124.

PeerView.com

There's a lot of interest in vitamin D right now in general medicine. It may also have cardiovascular and hematologic benefits. We have shown, for example, that vitamin D reduces blood pressure in lupus patients who have hypertension. But what about immunosuppressive drugs for lupus? Remember, we don't want prednisone. So we're going to turn to an immunosuppressive drug if after a burst of prednisone the patient's disease activity comes right back.

Immunosuppressive Approaches

Drugs

- Mycophenolate mofetil[1-3]
- Methotrexate
- Azathioprine

Biologics

- Rituximab[4]
- Belimumab[5]

1. Chan TM et al. *N Engl J Med*. 2000;343:1156-1162. 2. Ginzler E et al. *Arthritis Rheum*. 2003;48(9 suppl):S647. 3. Contreras G et al. *N Engl J Med*. 2004;350:971-980. 4. Leandro MJ et al. *Arthritis Rheum*. 2002;46:2673-2677. 5. Navarra SV et al. *Lancet*. 2011;377:721-731.

PeerView.com

We use several oral immunosuppressive drugs. Remember that these are not smart drugs. They do suppress the lupus part of the immune system, but at the same time they do increase the risk of infection and likely malignancy as well.
We use different drugs for different organ systems, so mycophenolate mofetil is our favorite for lupus nephritis. But we also have a lot of experience that it's helpful for lupus serositis and cutaneous lupus.

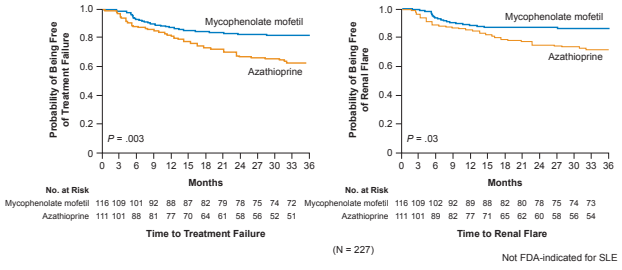
Methotrexate, just like in rheumatoid arthritis, is our go-to immunosuppressive for lupus arthritis. Now we can't use mycophenolate or methotrexate in pregnancy, so if a

woman with lupus has well-controlled disease but requires an immunosuppressive drug to keep it under control, we will transition her to azathioprine before pregnancy.

Now what about biologics for lupus? These are also going to be immunosuppressive, but they're going to be more targeted. They're not going to suppress the entire immune system. One that is not FDA approved, but is used for lupus, is rituximab. We particularly like it for hematologic manifestations, including severe thrombocytopenia or autoimmune hemolytic anemia. And it's also used to treat the catastrophic form of antiphospholipid syndrome.

Belimumab is FDA approved for lupus, and we do use it, particularly in the subset that have low complement and high anti-dsDNA because that's the subset in which it works the best. We also know that it works the best in those that have very high disease activity and have been on prednisone because prednisone works.

Lupus Nephritis Maintenance Therapy: MMF Is Superior to Azathioprine[1]



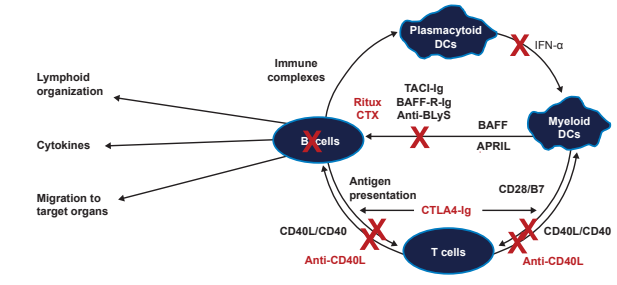
1. Dooley MA et al. *N Engl J Med*. 2011;365:1886-1895.

PeerView.com

What do we do for lupus nephritis? We first start with a kidney biopsy because there [are] many different classes of lupus nephritis. But after the kidney biopsy, we usually turn to mycophenolate for induction, because mycophenolate is as good as cyclophosphamide in Caucasians, but mycophenolate is better than cyclophosphamide in African Americans.

For maintenance therapy, we prefer mycophenolate because of the ALMS trial published in the *New England Journal of Medicine*, which clearly showed that mycophenolate was superior to azathioprine.

Potential Targets for Therapeutic Intervention in SLE[1]



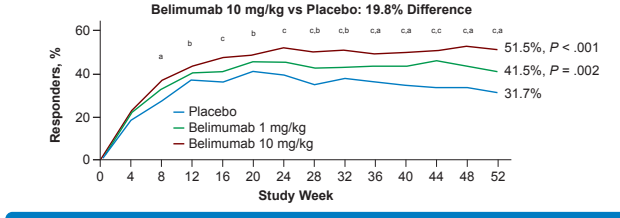
1. Ramanujam M, Davidson A. *Arthritis Res Therapy*. 2004;6:197-202.

PeerView.com

We have many other potential targets for the future in lupus. So, for example, we know that interferon-α gene signature is present in 50% of lupus patients, and there was a very successful phase 2 of an anti–interferon-α receptor blocker that has now moved into phase 3.

We also know that cytokines are important in lupus. Ustekinumab, which you know for psoriasis and Crohn's, had a successful trial in lupus. And there are many others. So there are going to be many opportunities to interrupt the vicious cycle of lupus activity in the future.

Subgroup With Both High Anti-dsDNA and Low Complement Is ~20% More Likely to Respond to Belimumab[1]



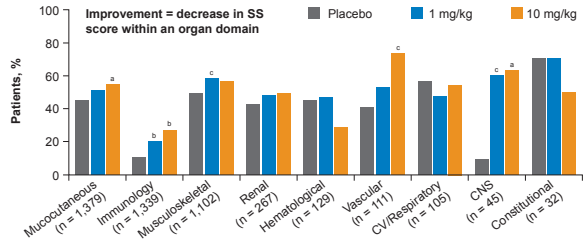
In the pooled analysis of BLISS-52 and BLISS-76, SRI rates at week 52 were 38.8% with placebo, 46.2% with belimumab 1 mg/kg ($P = .006$) and 50.6% with 10 mg/kg ($P < .0001$)

* $P < .01$. † $P < .05$. ‡ $P < .001$.
1. van Vollenhoven RF et al. *Ann Rheum Dis*. 2012;71:1343-1349.

PeerView.com

I want to show you some of the specific belimumab data, because that's the one that is FDA approved for lupus. Here you see that the subgroup that had both high anti-dsDNA and low complement was 20% more likely to have a good response to belimumab than standard of care alone.

A Post Hoc Analysis Shows the Organ Systems That Respond to Belimumab[1]

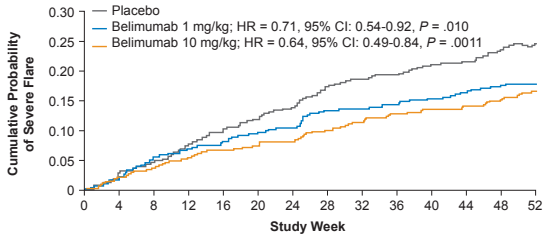


[a] $P < .01$. [b] $P < .001$. [c] $P < .05$.
1. Manzi S et al. *Ann Rheum Dis*. 2012;71:1833-1838.

PeerView.com

A post hoc analysis showed statistical benefit in the cutaneous and musculoskeletal organ systems. Remember, those are the two most common that are going to be involved in lupus.

Belimumab Reduced Severe Flares[1]



1. Cervera R et al. 2011 Annual European Congress of Rheumatology (EULAR 2011). Abstract THU0430.

PeerView.com

Belimumab also reduced severe flares. A small burst of prednisone is never going to be enough for a severe flare. Severe flares usually land patients in the hospital. They're often going to be committed to high doses of prednisone for a long period of time. The reduction of severe flares with belimumab is particularly important clinically.

Seven Year Follow-Up on Belimumab[1]

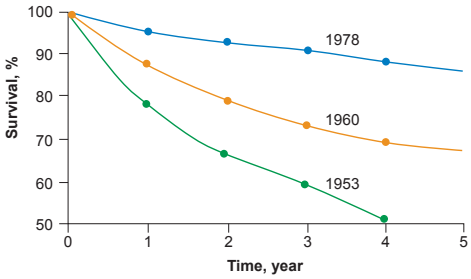
- Open label; 296 patients
- SLE Responder Index
  - Year 2: 57%
  - Year 7: 65%
- Anti-dsDNA : 40% to 60% decrease
- Prednisone: 50% to 55% decrease

1. Ginzler EM et al. *J Rheumatol*. 2014;41:300-307.

PeerView.com

There is a 7-year published follow-up on belimumab showing retention or durability of clinical response, reduction in pathogenic antibodies like anti-dsDNA, and reduction in prednisone in many patients. There is now also a 10-year follow-up about to be published. No new safety problems occurred in these long-term follow-up studies.

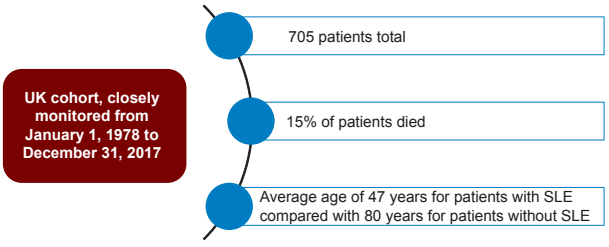
Prognosis in SLE Between 1953 and 1978



PeerView.com

I want to turn now to prognosis. And many people when they look at this slide think that this is one of my good-news slides, because nobody would want to have lupus back in the 1950s where half the people with lupus died in the first 5 years. And you see with subsequent decades improvement in survival.

Death in SLE[1]

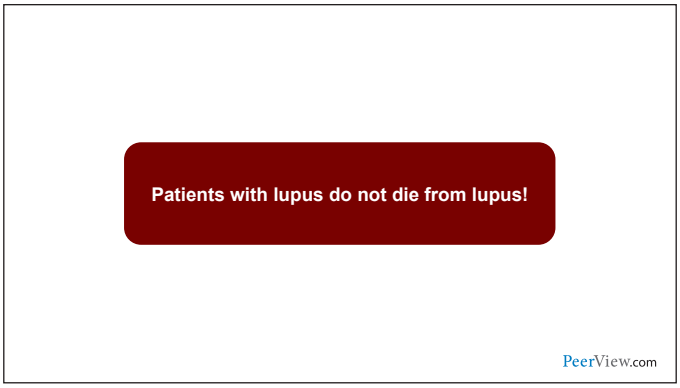


1. Isenberg D. Personal Communication.

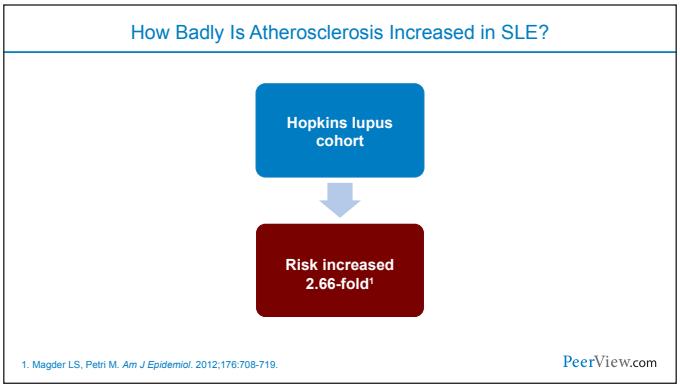
PeerView.com

But now I need to tell you that the survival of lupus patients really plateaued in the 1980s, and we have not seen steady improvement since then. So how is this possible? I want to show you the impact of this. This is a slide shared by David Isenberg, a rheumatologist in London. And he has a very closely monitored cohort, so he's able to track who died.

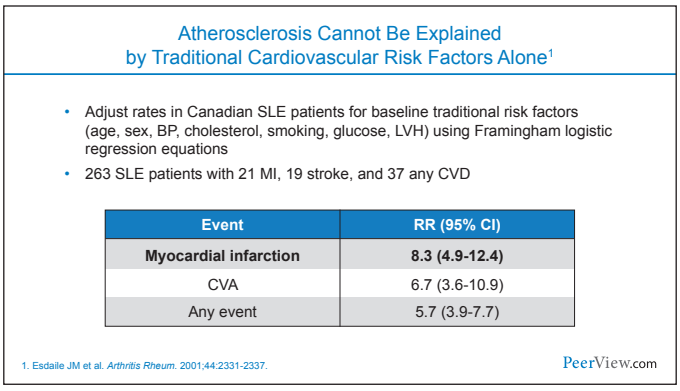
Of his 705 patients, 15% died during this follow-up, and their average age at death was 47 [years]. Please remember that the average age of death for a non-SLE woman is 80 years or more. We don't like to show patients this information, but as physicians we need to know it. Lupus can kill, and it can kill young women.



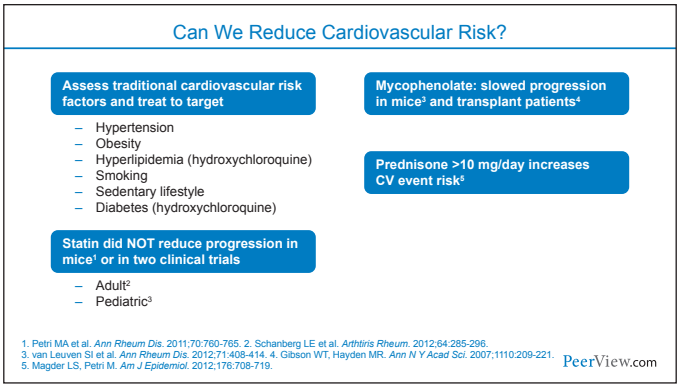
Now this may shock you. Lupus patients usually don't die from lupus. They die from other complications. The most common cause of death after the first 5 years is cardiovascular disease, and infection is number two. Don't forget to vaccinate.



So how badly is atherosclerosis increased in lupus? In our study, we showed that the increase was 2.66-fold. So you know, on a level of diabetes, and everybody knows how strict we have to be in diabetes in controlling traditional cardiovascular risk factors. We need to be equally strict in a young woman with lupus.



In this Canadian study, it was shown that even in a perfect world, if we controlled for all the cardiovascular risk factors, there would still be an eight-fold increased risk of myocardial infarction in lupus patients. Think of that as the lupus part of the risk.



So what can you and I do immediately to reduce the cardiovascular risk in our lupus patients? The first is to assess and treat to target all the traditional cardiovascular risk factors. I do this every day in my clinic, and I've learned not to accept any excuses. And I have heard them all.

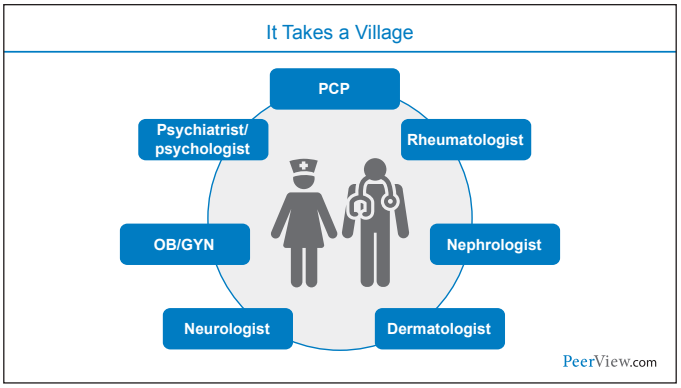
So my patient whose blood pressure is high will tell either the nurse or me that it's because they rushed, or it's because they just took their blood pressure medication, or they just had a cup of coffee. I no longer accept any excuses. I'm a hardliner, and I tell the patient that she must never leave home without taking her blood pressure medication.

I am going to ask you to be equally strict in explaining to patients that it's their job to be adherent to the cardiovascular risk factor therapies. But wouldn't it make sense to give everybody with lupus a statin, since that's what we do for secondary prevention—isn't it—in anybody who has a myocardial infarction?

So I believed that this was the way forward that I actually did a clinical trial of statins in lupus and had no benefit on things like a coronary calcium score, carotid IMT, carotid plaque. And I think many people thought that perhaps my trial was wrong.

So the same trial was done in pediatric lupus with the same result. I think the final nail in the coffin was even in mice with lupus, statins don't work. So, of course, we do give statins for hyperlipidemia, but they're not going to prevent the lupus part of atherosclerosis.

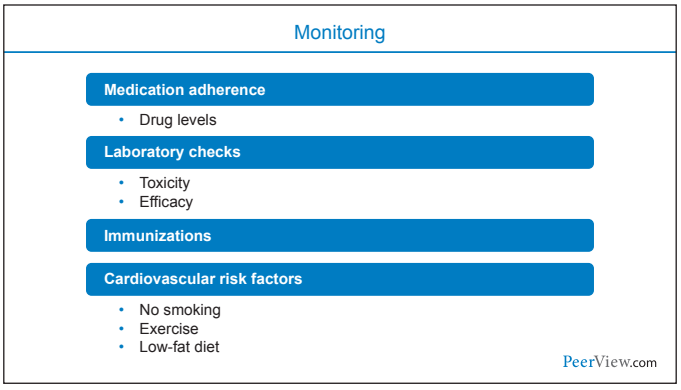
What might? Well, it turns out in mice with lupus, mycophenolate, the immunosuppressive drug we use for lupus nephritis, can reduce progression of atherosclerosis. And also in the renal transplant field, there are data to suggest that mycophenolate may have reduced the risk in transplant patients as well. But we cannot give mycophenolate forever to everyone with lupus, because it has real risk. Now remember from the prednisone slide we must keep the prednisone maintenance dose below 10 mg if we want to reduce cardiovascular risk.



It really does take a village to take care of a lupus patient, and I tell all my lupus patients I want them to have a primary care doctor. I don't want them to think that all their care is going to come from me. And I am going to need help as well. If someone has renal lupus disease, they're going to have a nephrologist. If they have bad cutaneous lupus, they may need a dermatologist. And if they've had a stroke or other neurologic manifestation, they may have a neurologist.

During pregnancy they're going to need a high-risk OB/GYN. It turns out that 30% of people with lupus also have depression. There may be a psychiatrist or psychologist involved. The list goes on and on.

But if it takes a village, it's also going to take communication. And one of the most important things is keeping everybody in the loop. I tell my lupus patients if they go to an emergency room not to leave until the emergency room doctors talk to me, because if I don't know what's going on, I won't know whether the treatment chosen was appropriate.

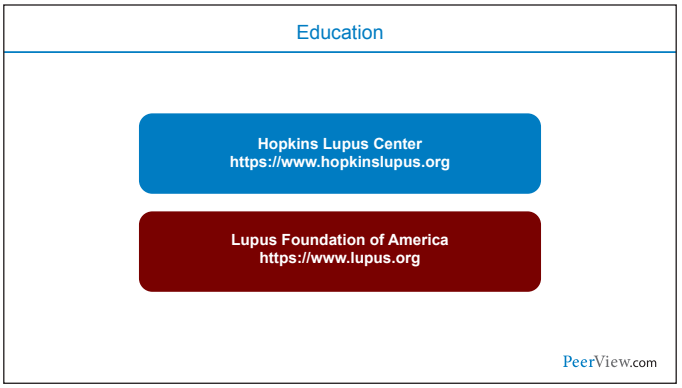


What can the primary care doctor do to help in monitoring? Well, I have a real shocker for you. When we started to measure hydroxychloroquine blood levels, we found out that 50% of my lupus patients were not taking enough to have any therapeutic benefit. And many weren't taking it at all. So I now routinely monitor drug levels for both hydroxychloroquine and vitamin D.

Because I'm often only going to see a patient every 6 months, if there's a primary care visit in between the visit with me, help with adherence is something I would welcome, because this is the most important battle we face. Of course, not just with lupus, with every chronic disease.

Laboratory checks need to be done for efficacy but also for toxicity, especially on immunosuppressive drugs. Remember how important it is to have frequent checks of that urine protein-to-creatinine ratio. We don't need 24-hour urines anymore. A random urine is fine.

We need to make sure immunizations are up to date; flu vaccine for everyone, the once-a-lifetime pneumonia vaccine, and the pneumonia vaccine booster for everyone. And then, of course, monitoring and treating the cardiovascular risk factors as well.



In terms of education, I wanted to give you two sites that I think are very useful. On the Hopkins Lupus Center site, we have many articles written for patients, and the Lupus Foundation of America remains one of the greatest educational resources for our patients with lupus. Thank you.

Narrator: This activity has been jointly provided by the University of Cincinnati and PVI, PeerView Institute for Medical Education.

CME

Improving the Diagnosis and Treatment of Lupus: Practical Guidance for the Primary Care Physician

PeerView inPlay

This CME activity is jointly provided by the University of Cincinnati and PVI, PeerView Institute for Medical Education.

This educational activity is supported by an educational grant from GlaxoSmithKline.

UNIVERSITY OF Cincinnati

Sign up for email alerts on new clinical advances and educational activities in your specialty: **www.peerview.com/signup**

@PeerView

www.peerview.com/FYE900

New and improved source for free CME/CE

PeerView.com