EMERGING CONCEPTS IN THE RECOGNITION AND MANAGEMENT OF SLE

OVERVIEW

Michelle Petri, MD, MPH, and Daniel J. Wallace, MD, FACP, MACR, provide their experience and insight into the diagnosis and management of systemic lupus erythematosus (SLE), with perspectives for both general practitioners and rheumatologists.

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

Rheumatologists:

- Develop SLE treatment plans based on individual patients' disease characteristics and treatment goals
- Identify a validated SLE disease activity measure for regular patient monitoring
- Incorporate recommendations for the use of existing and newly approved treatments for SLE into clinical practice

Primary Care Physicians:

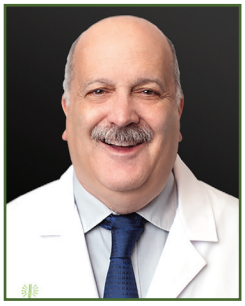
- Apply the ACR diagnostic criteria to recognize patients who may have SLE
- Utilize and interpret laboratory findings to investigate possible SLE
- Develop SLE treatment plans based on individual patients' disease characteristics, treatment goals, and consensus recommendations
- Identify a validated SLE disease activity measure for regular patient monitoring

CE STATEMENT

Target Audience

This activity was developed for rheumatologists, family physicians, internal medicine physicians, nurse practitioners, nurses, physician assistants and other health care professionals who have an interest in systemic lupus erythematosus (SLE).

FACULTY



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Editor's Note

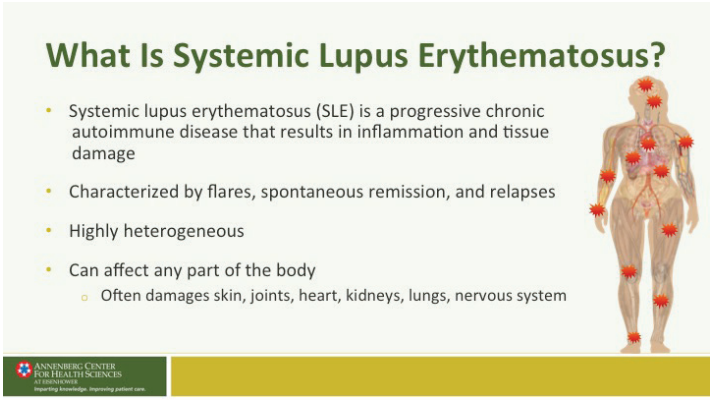
This is a transcript of the Daniel J. Wallace, MD, and Michelle Petri, MD, MPH, presentation "Emerging Concepts in the Recognition and Management of Systemic Lupus Erythematosus."

EMERGING CONCEPTS IN THE RECOGNITION AND MANAGEMENT OF SLE

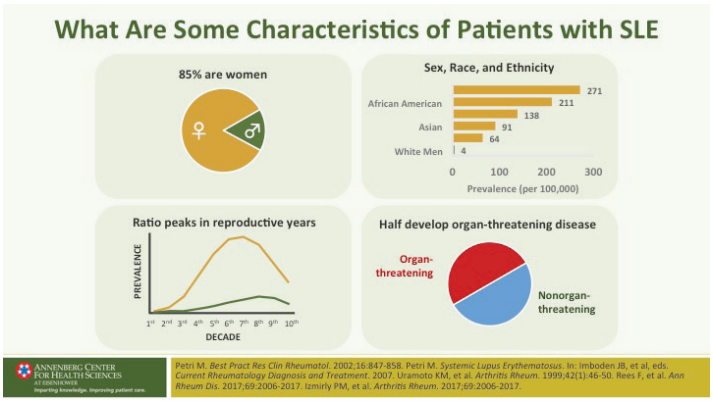
Daniel J. Wallace, MD, FACP, MACR

Systemic Lupus Erythematosus (SLE)

What is SLE? Or Systemic Lupus Erythematosus? It's a progressive, chronic, autoimmune disorder that results in inflammation and tissue damage. It's a very heterogeneous disorder. It's manifested and characterized by flares, remissions, and relapses and it's further complicated by the fact that it can affect any part of the body. Skin, joints, heart, kidneys, lungs and the nervous system, among others.



To give an idea of what we see with lupus, approximately 85% are female. Whereas maybe 1 in 10,000 white males develop lupus. One in 70 Native Americans develop the disease. 1 in 250 African American women. And it is more common in people of color such as Hispanic and Asian. It is seen in 1 in 1,000 Caucasian females. Lupus tends to peak during the reproductive years between the ages of 15 and 45. And half with lupus develop organ threatening disease, defined as heart, lung, kidney, liver, brain or bone marrow. Non-organ threatening would be considered to be people who are tired, achy, have swollen glands, low grade fevers, swollen joints, or rashes and perhaps some colitic discomfort.



The primary care physician is usually the first stop on the road to diagnosis of lupus. (If) it is suspected, usually they will send the patient to a lupus care specialist who will establish the diagnosis and stage it or assess its activity and severity. There have been several criteria for SLE. The original criteria in 1972 was revised in 1982 and again revised in 1997 by the American College of Rheumatology. There were 11 criteria of which 4 are skin, 4 are systemic, and 3 are laboratory. The skin criteria being a butterfly rash or sensitivity to ultraviolet light in the malar region of the cheek which is angled to absorb more ultraviolet light. Discoid rashes or thick plaque like adherent rashes are seen in about 20% with the disease at any given time. Two thirds of all lupus patients are sensitive to ultraviolet A and B light and oral or nasal ulcerations and even pelvic ulcerations or vaginal ulcerations can be seen in approximately 20%.

The systemic criteria included markers of inflammation. An inflammatory arthritis affecting at least 2 joints, such as pleurisy or pericarditis, is seen in approximately 20% to 30% of patients with lupus during the course of their disease. Renal disorder manifested by proteinuria at least a third of all lupus patients at some point. And neurologic disease for this criteria was defined as seizures or psychosis and its inadequacy was one of the reasons why the criteria has been further revised.

The laboratory criteria include: cytopenia, in other words in a CBC a hemolytic anemia, leukopenia, or thrombocytopenia along with a positive ANA, which is seen in close to 98% with the disorder.

And an immunologic disorder such as either markers of hypercoagulable state such as anti-phospholipid antibodies for lupus anticoagulant or the false positive serology as well as that, plus the presence of anti-DNA or anti-SM. Symptoms must have been going on for at least 3 months (and) another possibility, such as a virus, needs to be ruled out.

The Systemic Lupus International Collaborative Clinics revised this criteria in 2009. The reason why the revision was necessary was one could have lupus nephritis on a kidney biopsy but not meet the criteria. The definitions for continuous disease inflammatory arthritis were further refined.

Renal disease was further defined and neurologic disorders were expanded to include mononeuritis multiplex myelitis, peripheral or cranial neuropathy or cerebritis.

The hematologic criteria was the same. And the laboratory criteria, for the first time, allowed well complement to be included, as well as a direct

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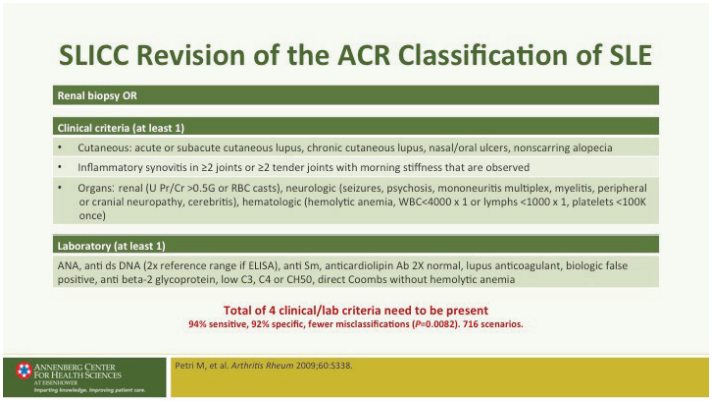
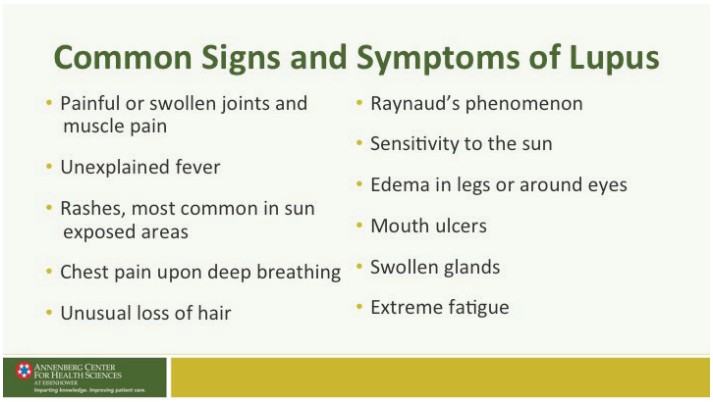
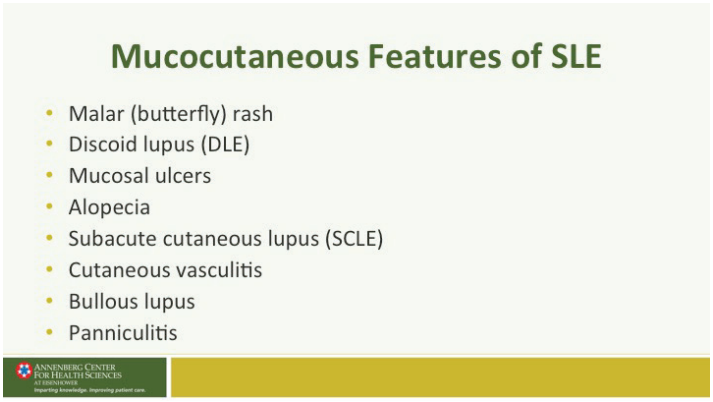


Coombs without hemolytic anemia, along with the ANA. In order to meet the (SLICC) classification, one had to have 4 clinical or laboratory criteria to be present. This particular classification was 94% sensitive and 92% specific, with fewer misclassifications, and it was done based on 716 scenarios with people who had SLE and other rheumatic disorders.

The most common signs and symptoms of lupus include: painful or swollen joints, low grade fevers, or fevers without infection, rashes usually in sun exposed areas, chest discomfort on deep breathing, such as you would see with pleurisy, unusual hair loss, Raynaud's phenomenon in about 20% to 30%, exquisite sensitivity to ultraviolet light, swelling, cutaneous ulcers, adenopathy, and in about 70% to 90%, significant fatigue.



So, the clinical and laboratory manifestations of SLE from a study of 2,000 patients is summarized in this slide. It includes that the overwhelming majority with SLE have a positive ANA, joint pain, a little over two thirds have some skin manifestations, between half and two thirds have myalgias and low compliment. About 40% to 50% at times have fever and elevated anti-double stranded DNA, low white count, and pleurisy or serositis with protein in the urine, and anemia. Approximately one third have anti-cardiolipin antibody, and some CNS or central nervous system manifestations—of which there are many. Elevated gamma globulin or polyclonal gammopathy can be seen in up to one third. 12% at some point had serositis, and adenopathy in 10%.



We mentioned that lupus can affect the skin. It can produce a butterfly rash or malar rash. Lupus means wolf in Latin and it's the distribution one sees when in the cheeks. Discoid lupus we've already discussed. Alopecia or hair loss can be focal, called alopecia areata or diffuse alopecia universalis, or one can develop discoid lesions in the scalp. Subacute cutaneous lupus is a variant of SLE that affects the dermis rather than the epidermis and it is harder to treat, relatively easy to diagnose. And it's associated with the antibodies to SSA and these individuals are exquisitely sensitive to sunlight. Cutaneous vasculitis usually seen in the fingers and toes, but it can occur anywhere in 5% to 10% with SLE. Lupus subsets sometimes associated with rather more discoid cutaneous lupus rather than systemic lupus include one that we would see bullous or a dermal lesion where it's inflammation of fat pads or a panniculitis.

The butterfly rash of lupus is where we get hyperkeratosis, follicular plugging, and dermal atrophy. It tends to spare the nasolabial fold. These rashes can come and go. They can be plaque-like, thick and scaring.

Discoid lupus is defined as this thick plaque-like adherence scaring. If it exists with any of the criteria for lupus it's called SLE. It can also exist in isolation without any organ involvement. 10% with discoid lupus patients, we now call it chronic cutaneous lupus, will ultimately develop SLE. These plaques, as shown, can expand, they can produce scaring, hyperpigmentation, vacuolization, and they can occur anywhere on the

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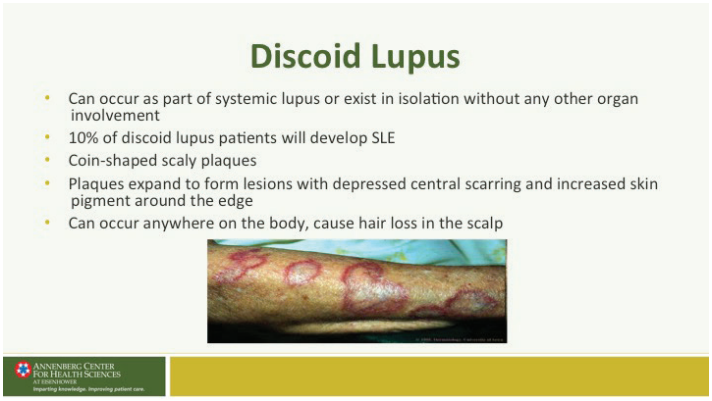
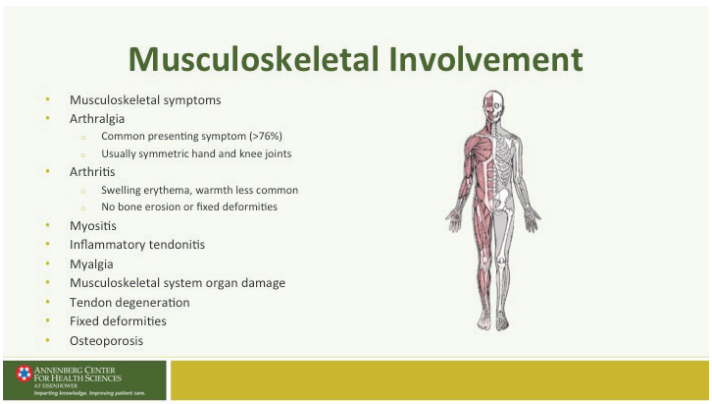
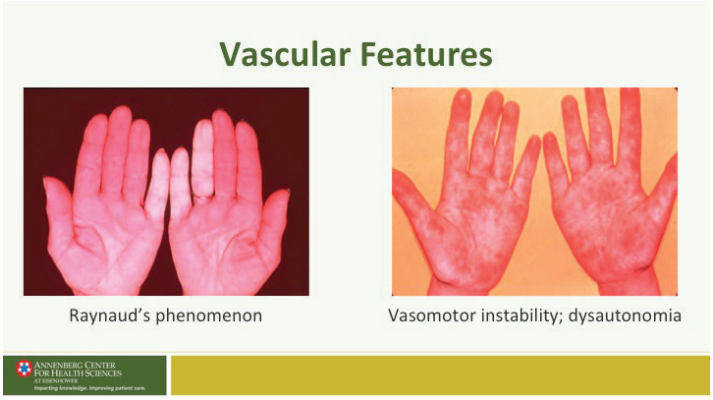




body, especially in the scalp, but they usually occur in sun-exposed areas.

Nervous System, Cardiopulmonary

The autonomic nervous system controls our pulse and blood pressure and dysautonomia is very, very, common in SLE. In some forms it can manifest as Raynaud's, where the fingers turn more red or purple with warmth, and they turn more blue or white with cold. Or they can be both at the same time. This is a manifestation of vasomotor instability, or dysautonomia, as shown on the right side of the screen. We can also get

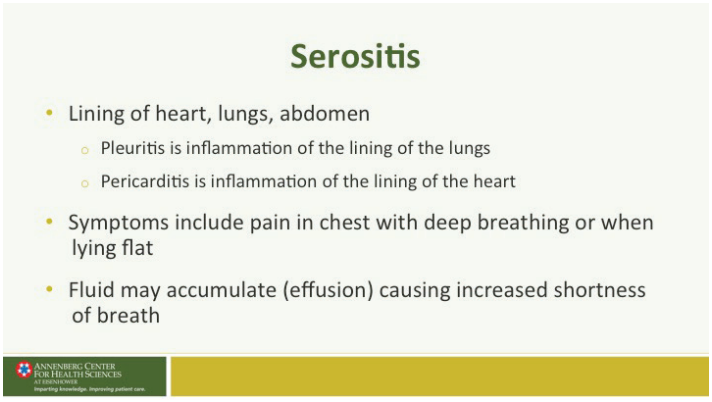


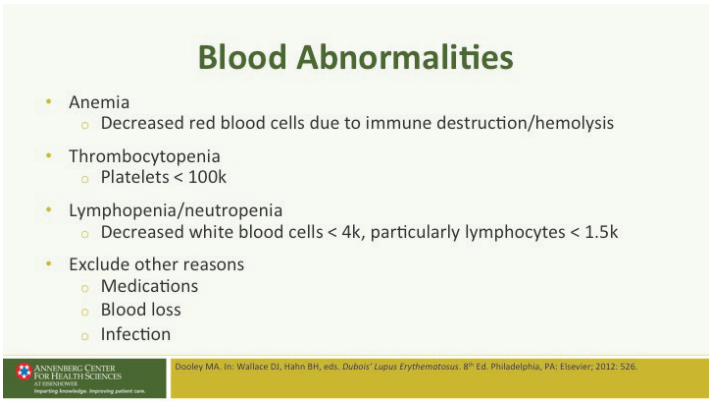
autonomic features that cause cognitive impairment. We could get vasodilation in the cerebral area that causes headaches, vasoconstriction which causes a lupus, partly responsible for a lupus fog. We can get microvascular angina so it's sort of like a migrainous-type of phenomenon with migrating pain that can be in any part of the body.

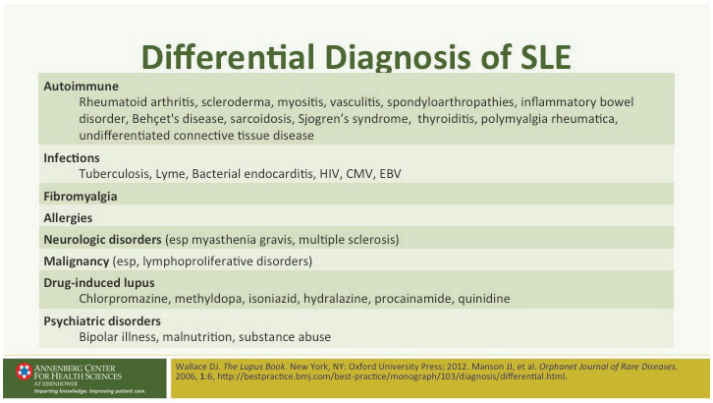
Let's turn now to the musculoskeletal system. You know we have 640 muscles in our body and 210 bones, 100 joints, and the only joints that are involved in SLE are those that are lined by synovium which is 80 of the 100 joints. In other words, it does not include the sutures in the brain and anywhere from C4 to the bottom of the spine. Most patients with SLE have arthralgias or aching. About half, at some point, have inflammation of the joints with swelling and edema. And only about 5% to 10% develop erosive disease, as we would see with rheumatoid arthritis, which is often an overlap known as lupus. But mostly there are no erosions.

Myositis or elevation of muscle enzymes can occur in 10% to 15% of lupus, unlike dermatomyositis or polymyositis, muscle enzyme levels are usually below 500 but they can be slightly elevated. Anywhere there is synovium, such as the tendon sheath, can be inflamed. Someone can get trigger fingers, and cystitis, and inflammation of the supporting structures. Muscle aches can occur, but need to be differentiated from fibromyalgia. Fixed deformities of the hands and feet and other joints are seen in less than 10% with SLE. And long-term management with anti-inflammatories, or years of inflammation, leads to ultimate osteoporosis. Especially if corticosteroids are being used.

I like to say when God created our heart and lungs they came gift wrapped. And the gift wrapping of these regions is a layer, normally, of loose connective tissue that's 2 or 3 layers thick, and it has some collagen and fibroblasts, but when it gets inflamed, it gets thick, and







sometimes even adherent. So we can get inflammation of the heart, pericarditis, of the lung, pleuritis, of the abdomen, peritonitis, and of the joints, synovitis. The major symptom of serositis is pain in the chest on taking a deep breath. Around the pericardium it's a form of chest pain that can be differentiated from let's say esophageal spasm, and that it improves when one leans forward. The fluid itself can be a transudate or an exudate. And the fluid does accumulate and it can cause shortness of breath.

Some of the blood abnormalities seen in SLE include cytopenias, that we've already discussed. But it's not just being anemic, it's specifically immune destruction or autoimmune, usually Coombs direct positive hemolytic anemia. 10% are Coombs positive but a smaller percentage develop hemolysis. Hemolysis is a serious complication of SLE that shortens lifespan and worsen prognosis and needs aggressive management. Platelets less than 100,000 are not uncommon in SLE, but generally we only treat it or worry about it if it gets down to 20 or 30,000. With regard to white blood cells, either the lymphocytes or neutrophils can be decreased, and leukopenia is far more common. When we do see cytopenia, especially anemia, we need to make sure that it's not due to blood loss from heavy menstrual flow, any ongoing infection, medications commonly can suppress bone marrow production of red cell elements, there are many other causes of anemia as well.

Diagnostic Workup

Before we label a patient as having SLE we need to rule out other disorders. In other words, lupus is only one of many autoimmune conditions that is associated with inflammatory arthritis with constitutional symptoms of fatigue and aching. A third of lupus patients have a positive blood tests of rheumatoid arthritis. Some lupus patients have overlapping features with scleroderma and sometimes the presence of Raynaud's could be either lupus or scleroderma. Myositis, to a mild degree, is seen in lupus—to a greater degree in polymyositis or dermatomyositis. ANCA-positive vasculitis is often mistaken for SLE. Also mistaken for lupus are the spondyloarthopathies because one can get inflammation in the hands and feet and the sacroiliac area. Inflammatory bowel disease sometimes smolders for years before it's ultimately diagnosed. Some patients with low titer anti-nuclear antibodies could be told that they have lupus when they turn out to have inflammatory bowel disease.

Behçet's is manifested by large numbers of oral ulcerations, but has unique features like erythema nodosum, HLA-B51 is more common in this group. One third of all lupus patients in the United States are African American, and sarcoidosis is extremely common in this group and sometimes the presentation can overlap. An ANA in this population is uncommon. Sjogren's syndrome, which is dry eyes and dry mouth with arthritis, is usually seen (in) an older age group than we usually see in SLE, but a third of all lupus patients ultimately have dry eye and dry mouth and there is a lot of overlapping.

10% to 15% with SLE have Hashimoto's thyroiditis or even Graves' disease. And it seems that 20% of individuals with one autoimmune disease have a second one. In older patients we like to rule out polymyalgia rheumatica which gives a very high sedimentation rate along with stiffness and aching. And there's a large group of patients, probably more than even have SLE, who have an ANA, may be tired and achy and have some swollen joints, but don't meet established criteria for SLE. We call them UCTD. Over a 10-year follow-up period, the patients with Undifferentiated Connective Tissue Disease—in about a third—the condition goes away and (in) about a third it stays the same, and about

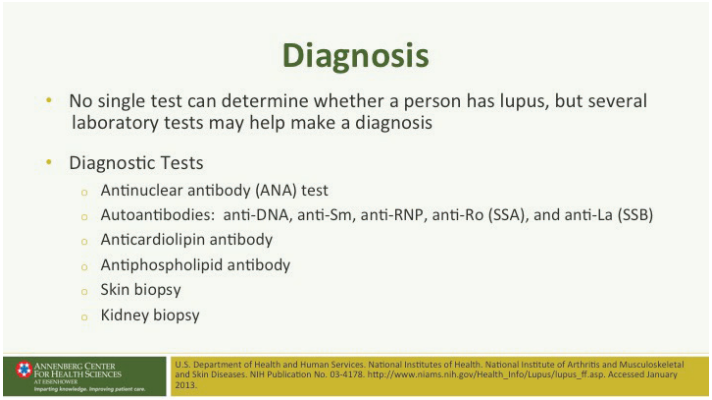
20% of these individuals go on to develop rheumatoid arthritis, lupus, or scleroderma.

I might want to mention here that there is a new classification or criteria being developed for SLE, in collaboration with the American College of Rheumatology and the European League Against Rheumatism, that is attempting to address some of the difficulties and uncertainties, and we expect these to be published in the next year or 2. Infection can also mimic lupus. Lupus patients and rheumatoid patients have infections. Patients with infections often have ANA and rheumatoid factors. Viral conditions such as Epstein Barr and cytomegalovirus are often mistaken, and since the false positive syphilis serology reflects a spirochete, which is Lyme also being a spirochete, that sometimes with Lyme and lupus, and vice versa, have false positive tests for the other.

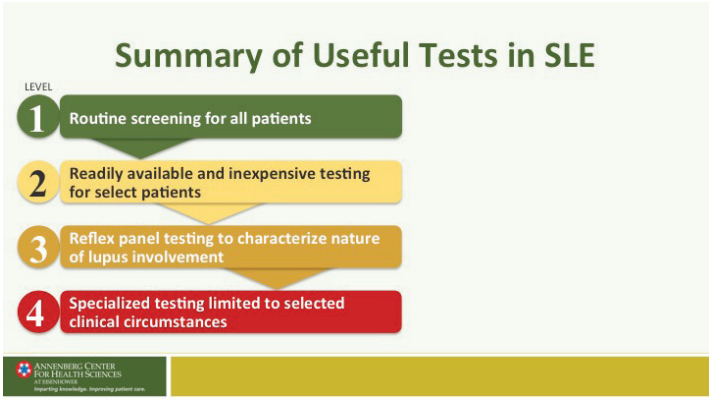
Fibromyalgia is not a disease. It's a syndrome. It's a pain amplification syndrome of the afferent sensory system where they lead to muscle discomfort. About 20% to 30% with lupus have fibromyalgia. This can be caused by medication such as corticosteroid used to treat lupus and it also can be caused by the stresses of coping with the disorder. And it's important that, with fibromyalgia patients, we don't treat them with anti-inflammatories because it is not an inflammatory process. Sometimes acute allergic reactions are mistaken for lupus. Sometimes early myasthenia gravis or multiple sclerosis is mistaken, as well as an early Hodgkin's or lymphoma, as other malignancies can be mistaken for SLE.

There are 15,000 cases in the United States of drug-induced lupus, where certain agents, especially antiarrhythmic, anti-TNF given for rheumatoid arthritis, statins, anticonvulsants, can be mistaken for SLE. Drug-induced lupus is not SLE, because it goes away when the offending drug is removed. The exception to this would be minocycline. And finally, some patients have low titer ANAs, and low titer white counts, and low levels of white count, and they don't have lupus, and sometimes, in young women who are malnourished or have substance abuse (disorder) or (are) bipolar, this is often a confounding factor.

No single test can determine whether a patient has lupus, but several laboratory tests help make the diagnosis. In everybody we get an ANA or antinuclear antibody. We often do a reflex panel which includes other serologies—DNA, SM, RNP, SSA, SSB. The latter 2 standing for Sjogren's syndrome, RNP mixed connective-tissue disease, SM usually confirmatory for lupus, as is the anti-double stranded DNA. Anticardiolipin antibody



is seen in one third of lupus patients, either that or an antiphospholipid antibody, and one third of them, or one third of one third, or one ninth, or 11% of lupus patients have a high thromboembolic complication as a result of the disease. One can have antiphospholipid syndrome without having lupus. Skin biopsies confirm lupus, and I've already discussed the pathologic features. Renal biopsies have been used as well.

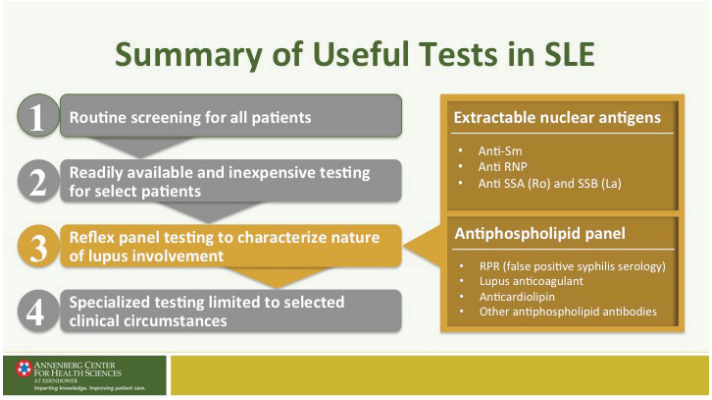


We screen our patients. We try to first use readily available and inexpensive testing, then we do the reflex testing which we showed above, and then for niche conditions, or confusing conditions, or to stage specific organ manifestations, we do more specialized testing. So the easy tests to do, that are very easy to get no matter what health plan you have, and are usually affordable for the uninsured, include a CBC, CMP, urine, muscle enzymes, acute phase reactant such as a C-reactive protein or sedimentation rate, and screening for organ involvement if there is a complaint, such as doing an EKG or chest x-ray as well as getting ANA, C3 and C4 compliments and anti-double stranded DNA.

(If) we are suspicious of rheumatoid arthritis, we would get a rheumatoid factor, anti-CCT and image the joints to see if there are classic rheumatoid features such as erosive disease. We like to see if there is a

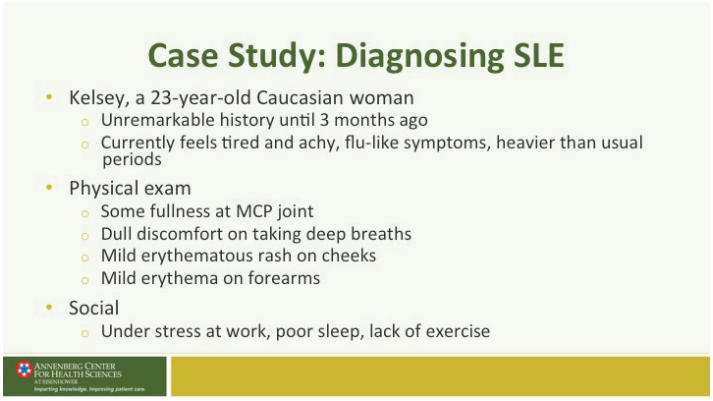
prolonged clotting time that may be associated with antiphospholipid syndrome and 2-D echoes are very good screenings for pericarditis or pulmonary hypertension which is often early and can be diagnosed in a lupus patient. And finally, for $200 or less, one can do a bone densitometry because there is a high prevalence of osteoporosis in patients who have the disease over years, and if we can have a baseline we can look for change in bone mineralization and be proactive.

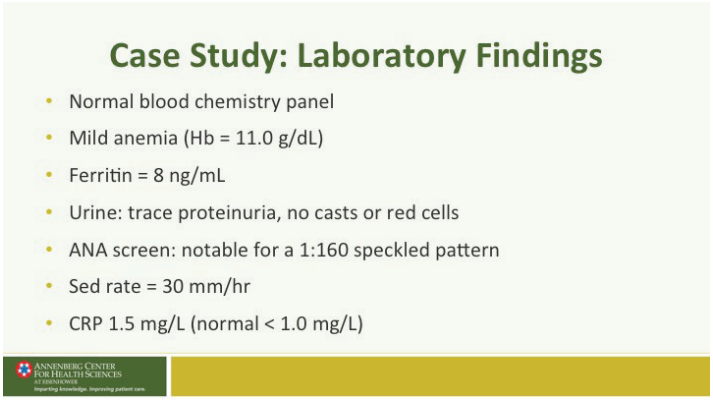
Regarding reflex ANA panels, we already mentioned what the antibodies do. They're relatively inexpensive and usually part of a reflex panel. Sometimes we need CT or MR imaging to figure out what's going on in somebody with central nervous system complaints. We might want to get a better look at somebody with a seizure-like condition or muscle inflammation. Sometimes a bone scan is used to look for inflammation when acute-phase reactants are negative. And then there is a variety of niche serologies that we can do under certain circumstances, when warranted.

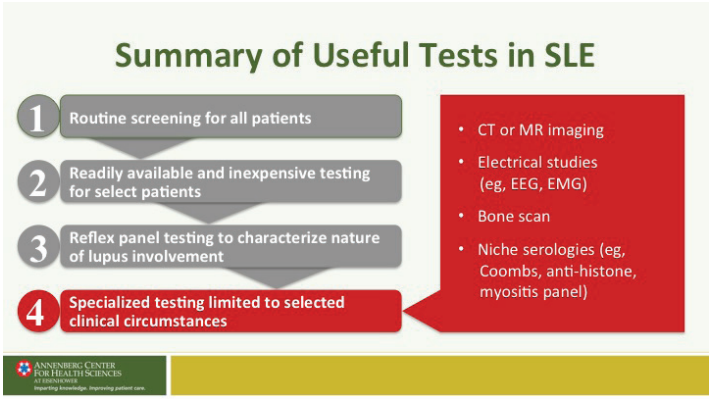


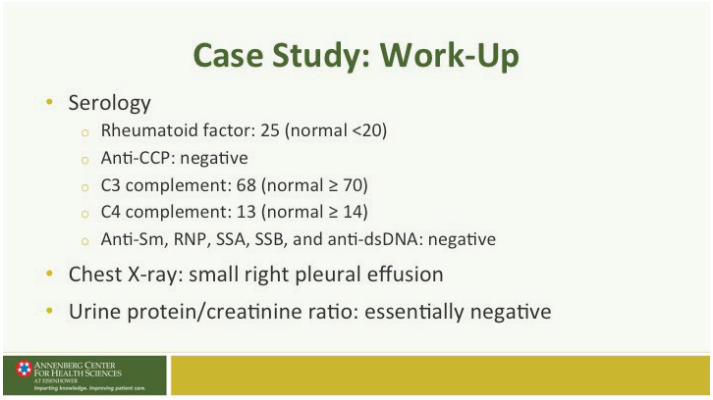
Case Study: Kelsey

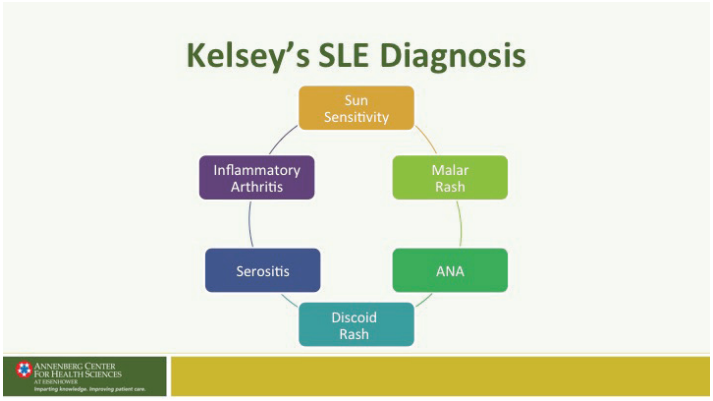
Kelsey is a 23-year-old Caucasian female with an unremarkable history in the past. But over the last 3 months she's been a bit tired and achy with flu-like symptoms and heavier than usual periods. When you examine her, she has some fullness at her MCPs, maybe some minimal discomfort on taking a deep breath. What you think is probably a rash on her cheeks, with some erythema on the forearms, and she clearly has been under (a) significant amount of stress, and hasn't been taking care of herself, sleeping well, or exercising.







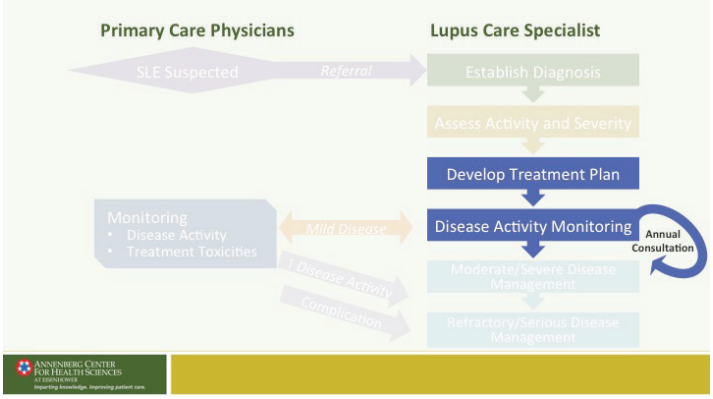




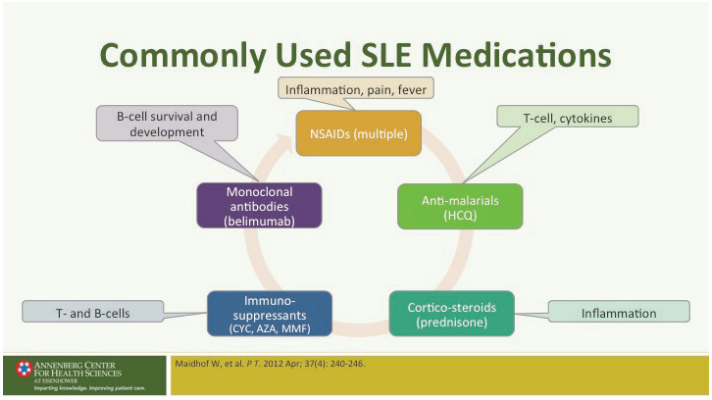
When you do your basic panel, you find that she's iron deficient, which could be heavy period or a chronic disease, but she has a mild anemia, a little protein in the urine which is hard to characterize, and an ANA of 1 to 160 with a slightly elevated sedimentation rate and C-reactive protein. This warrants further testing, and she might have a little rheumatoid overlap with the rheumatoid factor that's positive. Slightly low complements, which would suggest lupus. There's a little small pleural effusion on the right, and the amount of protein that she has is not really significant. So we are saying that she's sensitive, has a butterfly rash, inflammatory arthritis, a little pleurisy, probably a cutaneous rash and ANA, so this is probably lupus.

Principles of Treatment

Let's take a closer look at what we're going to do with regard to treatment in a primary care setting and general treatment strategies. So, we need to work with the lupus care specialist. It can be an internist, a rheumatologist, a nephrologist, a hematologist, even a dermatologist. Then develop a . . . if the organs are not involved . . . develop a treatment plan and monitor the disease and usually touch base with the lupus care specialist on at least an annual basis.

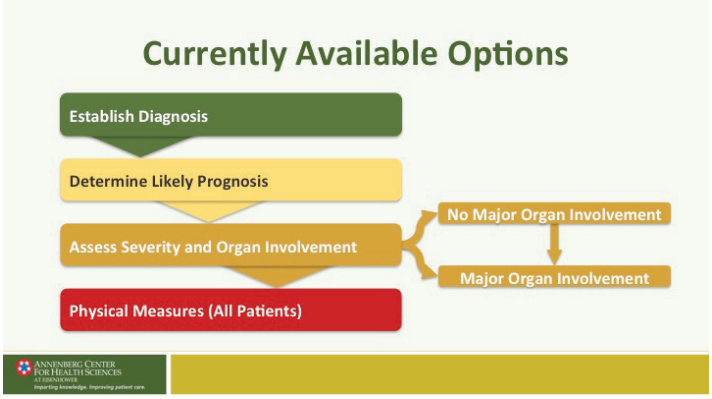


Most commonly, we use nonsteroidal drugs. Approximately 80% of all lupus patients take non-steroidals sometime in the course of their disease. Of course, because it's GI, renal and liver toxicity, one has to be very careful, and we are using a lot of diclofenac gel, which is only 6% systemically absorbed. Recently, the orthopedic society recommended that diclofenac gel be the first line treatment for osteoarthritis of the hand. It appears to be very safe. It helps serositis and headaches and joint pain, but unfortunately it does not do anything for the underlying disease.

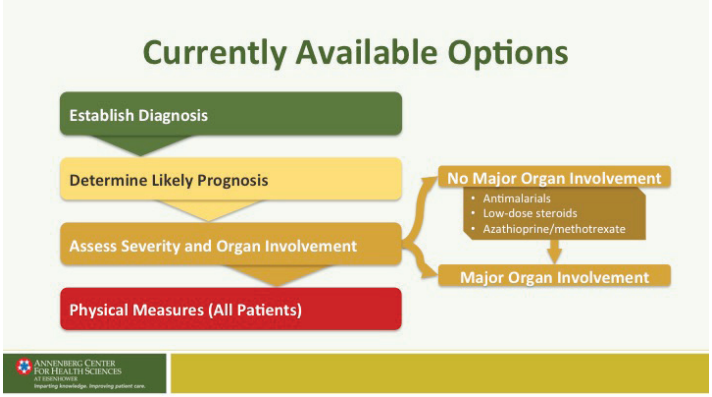


And we're going to go through the next level, which would be antimalarials, followed by corticosteroid, immune suppressants and, ultimately, targeted therapies. So, the nonsteroidals treat inflammation, pain and fevers, and the mechanism of action of the antimalarials is that it raises the pH of the cell so that acid cells become basic, and when you raise the pH of the cell cytokines, such as interleukin 1 and interleukin 6, (they) cannot signal to promote more inflammation. The immune suppressors and biologics of course target (T cells and B cells) and corticosteroids, all inflammation.

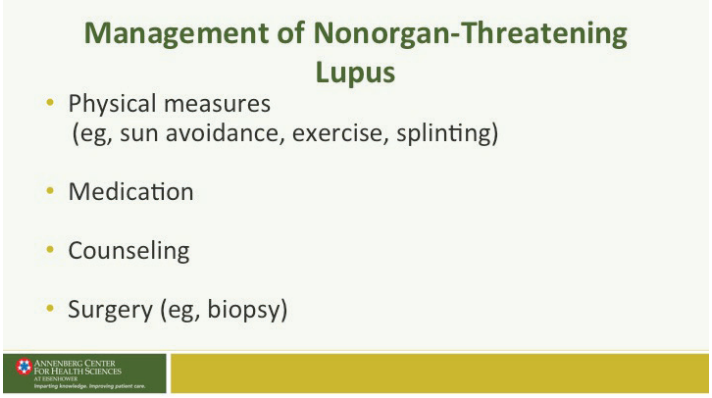
We have to decide if the patient has organ threatening disease or non-organ threatening disease. In other words, heart, lung, kidney, liver, bone marrow, or brain is



organ threatening, and it's treated one way, and non-organ threatening disease, which (is) fatigue, aching, joint pain and rash, is treated totally differently.



If the organs are not involved, we usually manage the patient with nonsteroidal anti as needed, antimalarials which are disease-modifying, low dose corticosteroids, and if we cannot keep the patient below about 10 mg of prednisone or if there's another indication, often use an immune suppressant, and in those without organ threatening disease, it's usually azathioprine or methotrexate.

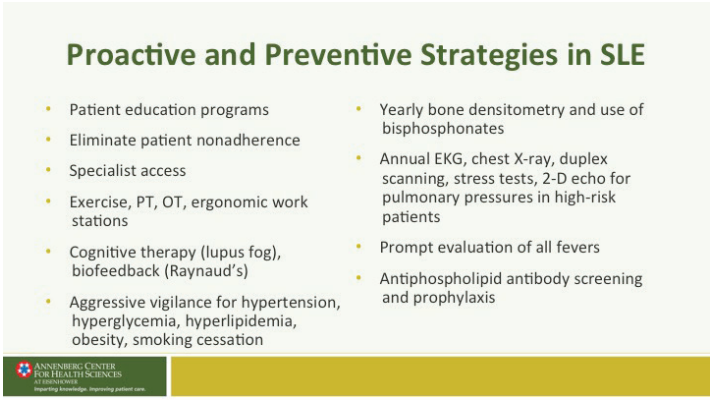


For non-organ threatening disease we often—before we go to medication—look at other measures. The measures, in addition to medication, include physical measures, counseling and surgery. The physical measures include telling patients to avoid ultraviolet light, to do stretching, or isometrics as opposed to isotonic exercise. Counseling is that the head bone is connected to the immune bone. And if we can alleviate their anxiety and educate them about the disease with literature from lupus advocacy groups or websites or blogs, we've come a long way. We've tried to temper their expectations. Sometimes we need to get tissue in order to help the patient, and that's what the surgery component is.

Also, from the physical measures we use sunscreen SPF or some protection factor between 15 and 50 (to) block ultraviolet A light, and they are often very useful. Changes in the barometer can make lupus patients have worse symptoms. It does not matter if it's hot or cold or wet or dry, but if the barometer goes from hot to cold or wet to dry, lupus patients are more symptomatic. We use heat or moist heat rather than dry heat for chronic injuries whereas we use ice for cold. Occupational therapy helps patients to use assistive devices and maybe prevent carpal tunnel syndrome while on the computer. Get on and off the toilet seat. In and out of their bedroom. In and out of the car. And sometimes patients, let's say farmers or fishermen who are outside all the time, or construction workers, would do well with being trained for more of an indoor job.

Diet, there is no special lupus diet. Although we think that fish or fish oil is useful. Vitamin D is often low in lupus and it might be helpful. And there is some evidence with work evolving and understanding our microbiome, that there may be a lupus diet, but it is not yet determined what the best diet would be. The best way to treat fatigue without medication is to pace yourself. If you lay in bed all day, 20 hours a day, a young housewife, she's going to be only more tired. If she's wonder woman and works 20 hours a day she will be wiped out for days at a time. So be active for a couple of hours. Pace yourself. Rest for 20 minutes. Be busy for another couple of hours. Take a lunch break. If you take 4 or 5 breaks during the day, most lupus patients with non-organ threatening disease, can get as much done as any other woman with the disease.

In addition to educating the patient . . . If you don't take a drug it won't work! And nonadherence or noncompliance is a major issue. Patients need to have access to the specialist even if they don't have a rheumatologist, their primary care doctor usually can always call one on the phone or consult somebody.

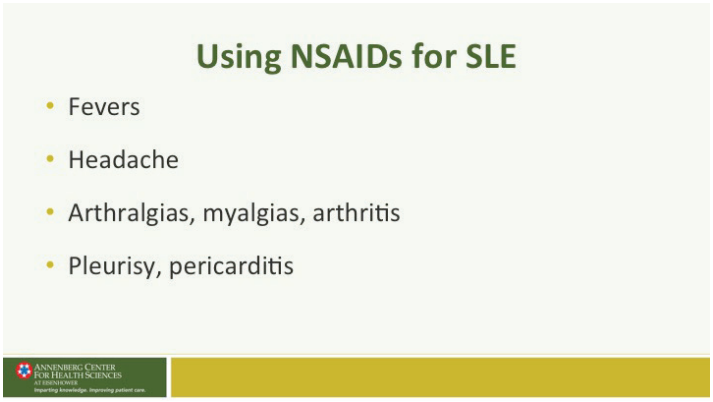


Cognitive behavioral therapy or biofeedback helps Raynaud's, helps dysautonomia, and are anxiolytic. And we screen patients on a regular basis for the development of hypertension, hyperglycemia, hyperlipidemia, and obesity, especially in those who are on corticosteroids, with at least annual screenings.

Hydroxychloroquine is not absorbed as well in patients who smoke. Raynaud's gets worse in patients who smoke. We do annual bone densitometry in people who've had the disease for a long time or we get it at least on a regular basis. We screen patients for cardiopulmonary disease in those at risk. Anybody with lupus who develops a fever needs to see a physician. And we need to, in those who are high risk of having a thromboembolic event, we need to either prophylax them with asprin or some type of blood thinning regimen.

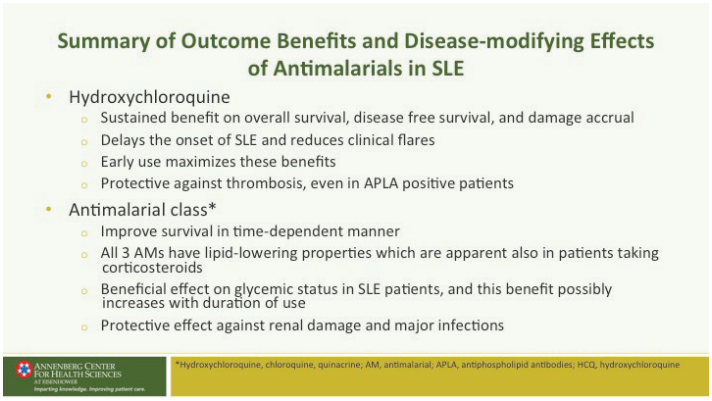
Overview of Pharmacotherapy

We have already talked about the use of NSAIDs in lupus. For fevers, headache, aching and even serositis, the treatment algorithm is such that for those with constitutional symptoms of fatigue and aching we can use steroids, hydroxychloroquine, or combination, and sometimes we have to use azathioprine methotrexate or mycophenolate. We would rarely need something stronger. With widespread cutaneous disease, antimalarials are the first line, along with corticosteroids. Systemic drugs rarely have to be used for cutaneous disease, but mycophenolate, cyclosporine A, azathioprine, methotrexate, and belimumab can be used. And for those who have digital or cutaneous vasculitis we may have to be more aggressive with immune suppressant regimens. Sometimes being more quick to use methotrexate, mycophenolate, or even intravenous cyclophosphamide.



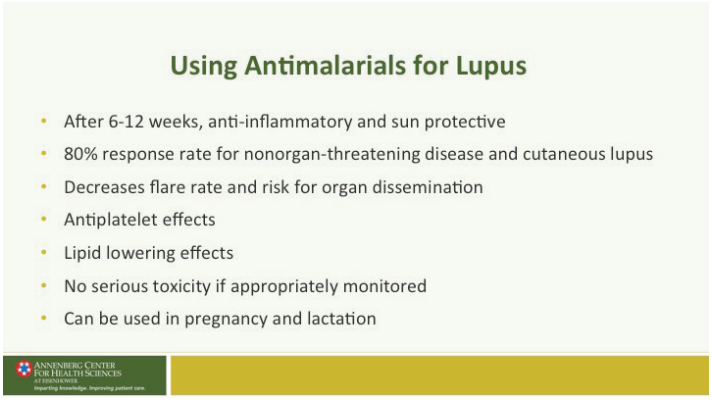
Antimalarials

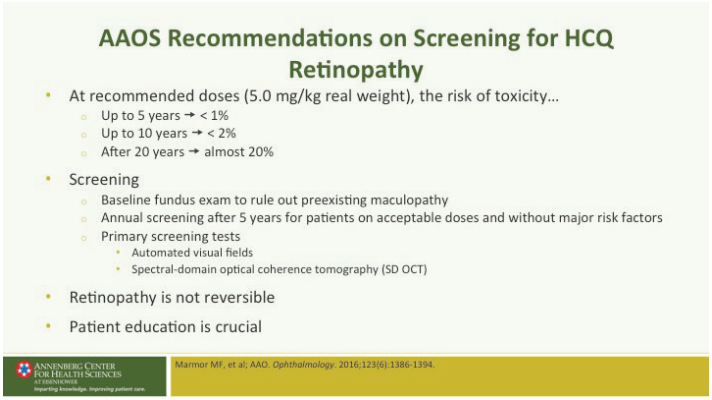
We talked about hydroxychloroquine and in Dr. Petri's talk you're going to hear a lot more about it, but it has a sustained benefit in overall survival. Disease free survival damage accrual. It slows the process of the disease. It



reduces flares and its early use is maximized with these benefits. And these have been shown in controlled trials where patients were doing well on antimalarial drugs such as hydroxychloroquine, and these agents were withdrawn and there were more flares. Our work has also shown that hydroxychloroquine is associated with fewer thromboembolic events, even in those that have phospholipid antibodies. And as a class, when I say class I mean hydroxychloroquine, chloroquine, or quinacrine, they do improve overall survival. They lower lipid levels by an interaction with LDL receptors. They can lower blood sugar by 10 to 20 points and are protective against renal damage and they are associated with fewer infections.

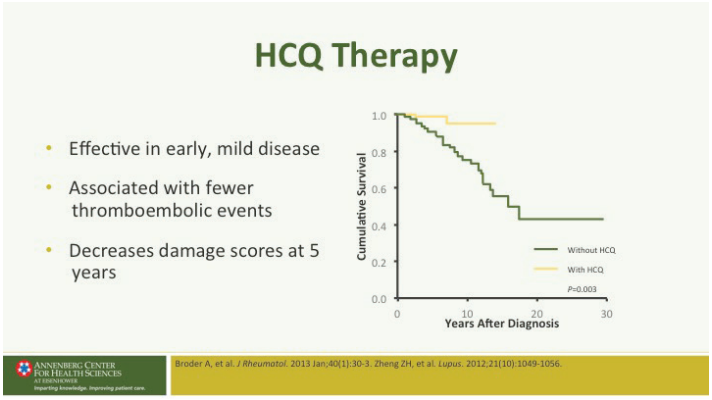
In a new lupus patient, we give the agent for 6 to 12 weeks, and there's about an 80% response or improvement with non-organ threatening disease. The flare rate and risk of organ dissemination is improved.





There's no serious toxicity of this and antimalarials have been used in pregnancy and lactation without any untoward effects.

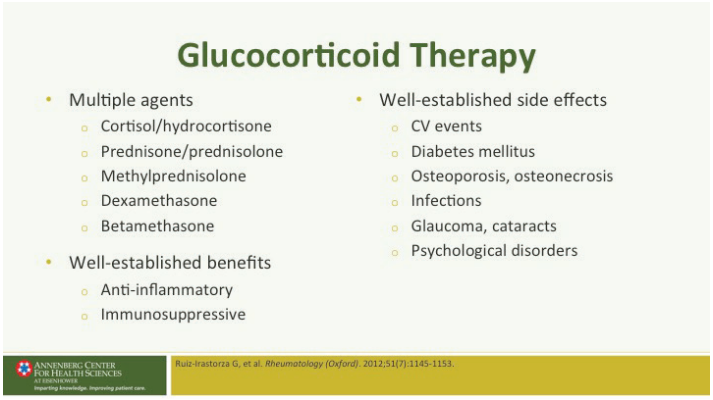
The major thing we need to monitor with antimalarials is the eyes. Plaquenil or hydroxychloroquine does not really affect the uvula area, it only affects the cornea in making one more light sensitive, and (in) a small percentage it's reversible with the discontinuation, and one can even restart. But retinopathy in recommended doses should be used in 5 mg per kg doses. At 5 years the risk of retinopathy is close to zero used in recommended doses. At 10 years its almost 2%. But after 10 years the eye toxicity from hydroxychloroquine increases radically and it's often as high as 20% in 20 years. Patients should have a baseline fundus exam to rule out pre-existing maculopathy and screening at least at year 5 and sometimes before. There is a newer methodology for looking for retinopathy called OCT. Which is a spectral domain optical coherent tomography which can identify retinal disease before the patient even has symptoms. Retinopathy, once it occurs, is rarely reversible, so we need to be very emphatic with our patients about making sure they get eye exams when necessary. As you can see,



hydroxychloroquine therapy is statistically associated with less inflammation, fewer clots and less organ involvement.

Steroids

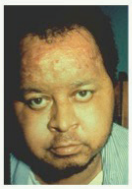
Moving on to corticosteroids. If one has organ threatening disease we need to use 1 mg per kg per day in most cases at onset. If one has non-organ threatening disease, we usually use 10 mg of prednisone a day or less. If they cannot get by with that, we have to then go on higher doses and usually use a steroid-sparing drug. There are many steroid preparations. Most newly used is prednisone or prednisolone, which is also known as Medrol. We usually use prednisone. In children there is more prednisolone. There is a brand-named prednisolone that some people prefer. There is no brand name for prednisone.



Dexamethasone is sometimes used in those with organ threatening disease, especially in the central nervous system, because it crosses the blood-brain barrier. Cortisol or hydrocortisone works in 15 minutes intravenously, and is used in more emergency settings in those with high fevers. Betamethasone is often used in joints and it crosses the placenta and it might help early hyaline membrane disease, or an underdeveloped lung in pregnant patients. Steroids or anti-inflammatory and immunosuppressants that have low established side effects, such as promoting accelerated (adipogenesis) raising the blood sugar, thinning the bones, promoting infections, cataracts, glaucoma, and mood disorders.

Corticosteroids suppress virtually every component of the immune response but expose people to greater risks. There have been relatively few trials of steroids in phase 3, but some have been done, mostly comparing them with other drugs on the market, because it has not been patent-protected for decades. But post-talk

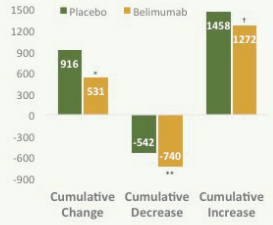
Corticosteroids and Immune Suppression



- Suppress virtually every component of the immune response
- With chronic administration, expose patients to greater risk of viral and fungal infections

Steroid Use in Phase 3 Trials

- Post-hoc analysis of 2 randomized trials
- Trial designs allowed for steroid dose-adjustment based on patient's disease activity
- Patients treated with belimumab had a smaller increase in cumulative corticosteroid dose because of greater decreases and smaller increases in doses



*P<0.0001; **P=0.0165; †P=0.0005
van Vollenhoven, et al. *Arth Rheum*. 2016;68:2184-2192

Effect of Prednisone on Organ Damage

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

*Adjusting for confounding by indication due to SLE disease activity
Thamer M, et al. *J Rheumatol*. 2009;36:560–564.

analysis of randomized trials shows that using let's (say) a targeting agent such as belimumab, is steroid sparing, and it also showed that steroids are very effective. From a damage point of view the work from Dr. Petri from Johns Hopkins has demonstrated that if one is on 6 mg or less—in other words below adrenal replacement levels—organ damage is very slight. But once you end up on a higher dose of steroids, organ damage is much greater. So, this is the reason why steroid-sparing agents are important.

Whereas 80% of all rheumatoid arthritis patients in the United States are taking methotrexate, studies in lupus are limited, but it appears to be effective in about 20% of all lupus patients in the United States (who) are taking methotrexate at any given moment. It does tend to lower the SLEDAI score and have an effect on being steroid sparing. This drug is well known, appears to be generally quite safe and is taken weekly. For those with more serious disease, mycophenolate and azathioprine can be used. We generally restrict mycophenolate to more renal or pulmonary disease, whereas azathioprine can be used in non-organ threatening lupus for just about any manifestation. Both are steroid sparing.

Mycophenolate and Azathioprine

- Mycophenolate
  - Primarily used for renal, or pulmonary involvement
- Azathioprine
  - Can be used for renal, hematologic, musculoskeletal, dermatologic involvement
  - Can be steroid sparing

Then there's the group that we call niche therapies that are only used for specific organs or areas of involvement. For cutaneous disease we might use retinoids, some of the anti-leprosy drugs such as dexamethasone, some of the topical calcineurins such as pimecrolimus and tacrolimus. For low platelet counts we might use an androgen-like hormone such as danazol or intravenous immunoglobulin. Rituximab appears to be particularly effective, as is splenectomy.

Other Agents Used to Manage Lupus

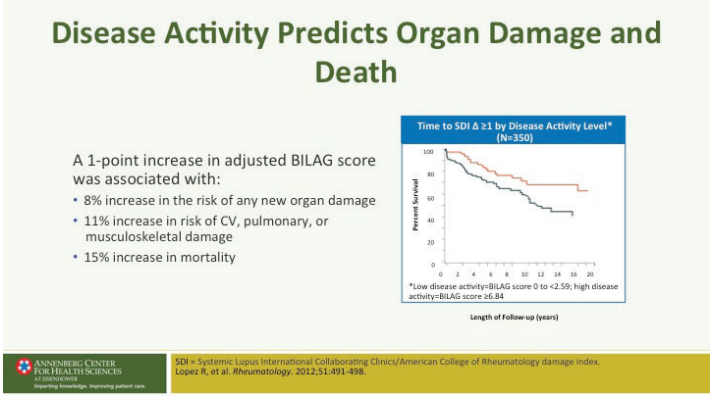
- Specific agents for cutaneous subsets
  - Retinoids, antileprosy drugs, topical pimecrolimus or tacrolimus
- Immune thrombocytopenia (ITP)
  - Danazol, intravenous immunoglobulin (IVIg), splenectomy, rituximab
- CNS
  - Intrathecal methotrexate, cyclophosphamide, rituximab
- Antiphospholipid antibody syndrome (APS)
  - Warfarin, heparin, platelet antagonists
- Raynaud's
  - Calcium channel blockers, phosphodiesterase inhibitors, nitrates
- Pulmonary hypertension
  - Prostaglandins, phosphodiesterase inhibitors, endothelin blockers

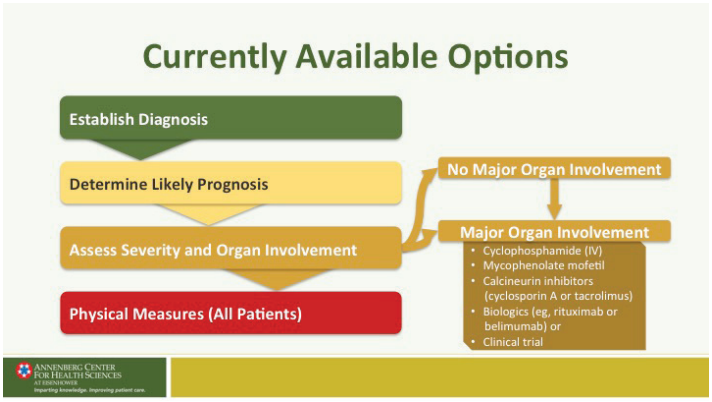
For those with central nervous system disease, if it's very serious we might want to use intrathecal methotrexates like cyclophosphamide, or rituximab for those who've had thromboembolic events, who've had thinners, for those who have vasomotor instability and dysautonomia, calcium channel blockers and

vasodilators such as phosphodiesterase inhibitors. Especially if one has pulmonary hypertension, then we add the endothelin inhibitors and prostaglandins.

Organ Threatening Disease

If there's organ involvement we tend to use cyclophosphamide, mycophenolate, calcineurin inhibitors targeted therapies or biologics. And since there are some aspects of lupus where patients cannot take all the agents that would be best for them, we sometimes enroll them in clinical trials.





mortality and increase in damage score. We try to restrict this.

For lupus in the kidney, which is seen at some point in a third of all patients, it usually manifests as urine protein excretion which leads to low albumin and edema. Especially in nephrotic ranges. A sediment which can include red cell counts, granular counts, hyaline counts, white cell counts, and decreased renal function and hypertension. The American College of Rheumatology guidelines for monitoring lupus nephritis activity include looking at urine, blood pressure, kidney function, compliments, anti-DNA and protein/

Prevalence of Serious Organ- or Life-Threatening Complications With Idiopathic SLE

Complication	N	%	Complication	N	%
Nephritis	128	28	Psychosis	24	5
Thrombocytopenia	73	16	Organic brain syndrome	22	5
Cerebritis	49	11	Lupoid hepatitis	22	5
Thromboemboli	36	8	Retinal vasculitis/ infarct	17	4
Hemolytic anemia	34	8	Myocarditis	12	3
Seizures	30	6	Mesenteric vasculitis	4	1
Lupus pneumonitis, alveolar hemorrhage, or pulmonary hypertension	29	6	Thrombotic thrombocytopenic purpura	4	1
Avascular necrosis	25	5	Total	252	54

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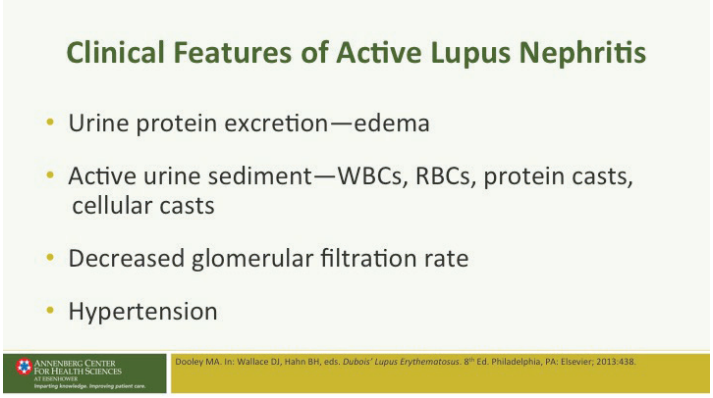
Pistiner M, et al. *Semin Arthritis Rheum.* 1991;21:55-64.



About half, as I mentioned, with SLE have organ threatening disease. Most common is kidney. Second most common is low platelet. Third would be central nervous system. But one must also be aware that lupus can attack the lungs with the interstitium or cause a pneumonitis, it can attack the liver, produce retinal vasculitis, myocarditis, microvascular angina, mesentric vasculitis, and sometimes more serious complications such as TTP.

Disease activity predicts how one is going to do. There is something called the SLICC damage score. And those who have higher activity tend to have a greater

ACR Guidelines for Monitoring Activity of Lupus Nephritis[1]

Recommended Monitoring of Lupus Nephritis (monthly monitoring intervals)*						
	BP	UA	Protein:CR	Serum CR	C3/C4 Levels	Anti-DNA
Active nephritis at onset of treatment	1	1	1	1	2†	3
Previous active nephritis, none currently	3	3	3	3	3	6
Pregnant with active GN at onset of treatment	1	1	1	1	1	1
Pregnant with previous nephritis, none currently	1	1	3	3	3	3
No prior or current nephritis	3	6	6	6	6	6

*Values are the monthly intervals suggested as the minimum frequency at which the indicated laboratory tests should be measured in the SLE scenarios shown in the left-hand column.
†Opinion of the authors based on a study published after the Task Force Panel had voted.[2]

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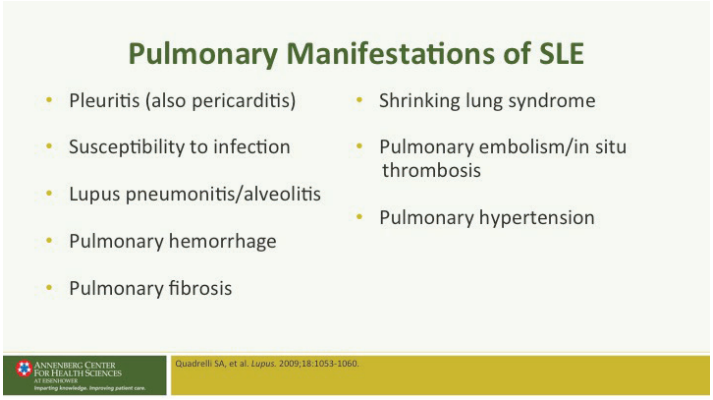
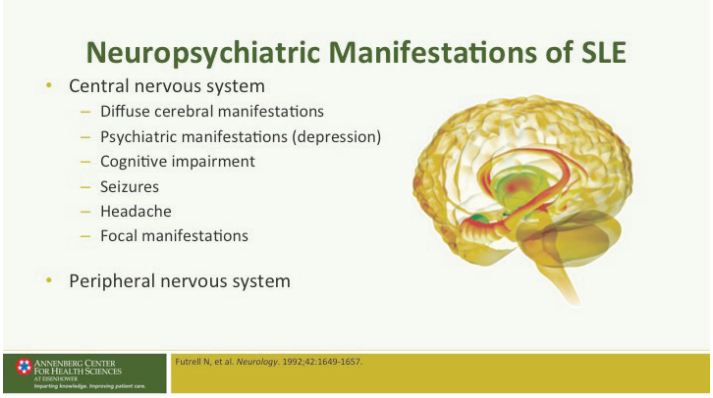
GN, glomerulonephritis; BP, blood pressure; UA, urinalysis; CR, creatinine.
1. Hahn BH, et al. *Arthrit Care Res.* 2012;64:797-808.
2. Grootscholten C, et al. *Kidney Int.* 2006;70:732-742.

creatinine ratios. And, on the basis of that, we usually determine treatment, which can include, in most cases, prednisone, mycophenolate, and sometimes calcineurin inhibitors rituximab and azathioprine, or some of the newer biologics that are being studied.

For involvement of the heart, we have a large menu of involvement. We've already talked about serositis. Some people can have myocarditis or congestive heart failure. 25% with SLE have hypertension. About 2% have actual vasculitis which is intimal proliferation, medial necrosis, and adventitial fibrosis of the coronary vessel. One can get valvular deposits without infection, such as Libman-Sacks endocarditis, or with infection, we actually do develop endocarditis. The problem with endocarditis is that these deposits can break off and become thromboembolic. Valvular insufficiency is not uncommon. And, as a consequence, lupus patients have a 7- to 10-fold increased risk of coronary heart disease and stroke.



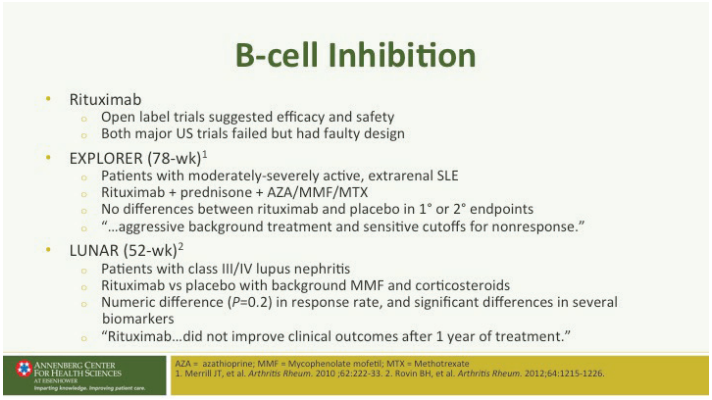
In the lungs, in addition to pleurisy, and susceptibility to infection, that we've mentioned, one can bleed into the lungs, scar the lung, acutely inflame the lung, or chronic pleurisy can lead to diaphragmatic atrophy with adhesions and scaring that produces something called interstitial or shrinking lung syndrome. About 10% or less with SLE develop pulmonary emboli, and pulmonary hypertension is seen in approximately 10% with SLE.



Neuropsychiatric manifestations range from acute inflammation in the brain to organic brain syndrome to seizures, headache, focalized manifestation. One can also get involvement of the peripheral nervous system as well.

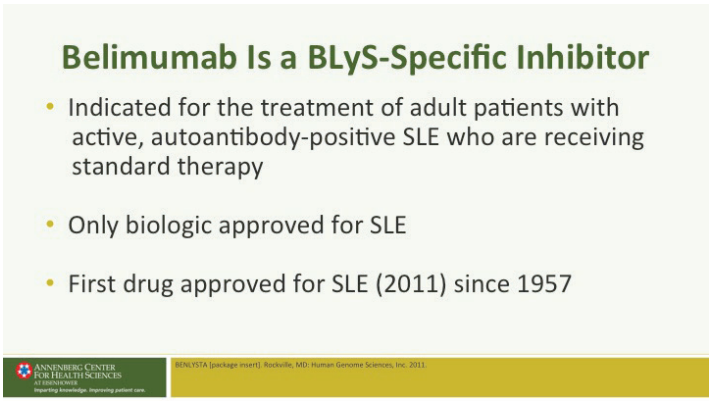
Rituximab

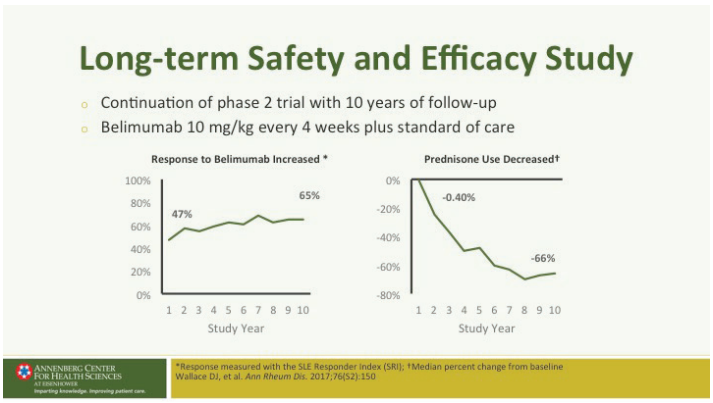
In treating organ threatening disease, there are a lot of people in the United States that use rituximab. Unfortunately, the open label trials—even though they suggested efficacy and safety—were not confirmed by 2 large trials from the sponsor of the drug. Unfortunately, the drug study design was highly flawed in that patients in both arms of the study got high doses of prednisone which will treat anything. So, as a result, we are looking at this again, and as a result of some studies that have been done more recently, we have concluded that even though none of these uses are FDA-approved, that it does appear in series to help central nervous system lupus once steroids and cyclophosphamide have failed in its use for ITP and hemolytic anemia. And it is extremely good in patients who not only have thromboembolic events but also have inflammation, which is part of the catastrophic antiphospholipid syndrome or CAPS. And it is also approved for rheumatoid arthritis. A third of all lupus patients have rheumatoid factor and sometimes we use it for refractory inflammatory arthritis.



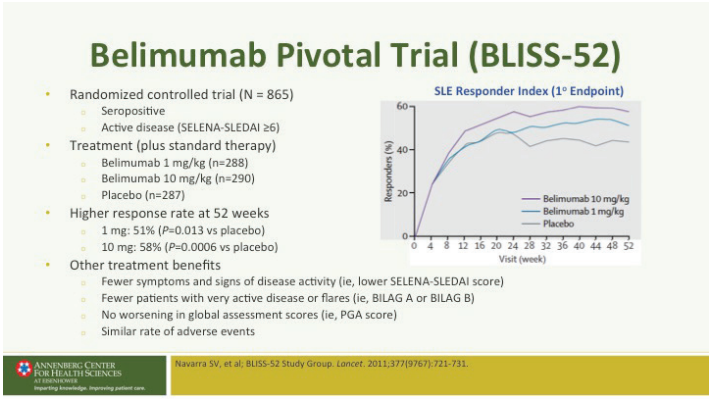
Belimumab

Belimumab is a BLyS-specific inhibitor. Unlike rituximab, which kills B cells, this modulates B cells. It inhibits soluble BLyS, which is on the surface of developing B cells. It's



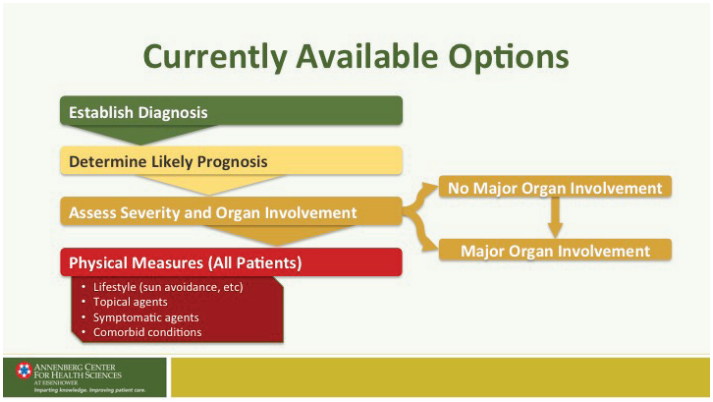


not in the bone marrow, it's not in the plasma cell, as of this presentation, it is the only biologic approved for lupus, and, in fact, the only drug approved for lupus since Eisenhower was president. So, it is indicated for adult patients who have auto-antibody positive lupus who still have active disease despite standard of care treatment. In the pivotal trials that were published in



The Lancet as one can see–using belimumab versus with immunosuppressant suppressive steroids, non-steroidals, and antimalarials, vs no belimumab there was a 13 point differential in the responder index that's most commonly used in clinical trials. And belimumab appears to have long term safety effects. It continues to work over time. It is steroid sparing and has an outstanding safety profile.

Lifestyle is very important. You can also use topical agents for lupus which go from sunscreen to anti-inflammatory agents to diclofenac gel. We also need to treat the symptoms of patients that may not be inflammatory, such as depression or anxiety. And comorbid conditions that are more common, such as hyperlipidemia or accelerated atherosclerosis.



Case Study/Kelsey Continued….

I don't want you to think that we forgot about Kelsey, so treatment with her should begin initially with prednisone and hydroxychloroquine. And we should also consider giving her NSAIDs as needed. And treat her iron deficiency anemia from her heavy period. But would we escalate the therapy? If her symptoms are not resolving, or she develops new organ involvement, or if she has serious side effects, we need to escalate therapy. But there's no point in escalating therapy if there's not adherence. Because we've got to talk to her about adherence. If there's serologic or complement changes and evidence for more information, then we need to work with our rheumatologist and treat the refractory or serious disease.

Assessing her, we need to really find out if she is taking her medicine. We used to call this compliance, but really the correct term is adherence. We don't say, "Have you been taking your medicine?" Because Kelsey will say, "Yep." Because we're intimidating her. We need to say, "How many doses did you miss last month?" And ask questions in a way such as, "Are these symptoms from lupus, or are they from something

in your lifestyle going on; with what's happening?" That way we can usually find out. Now there are ways to do blood levels for hydroxychloroquine. Draw blood levels are available for methotrexate as well.

And it turns out in the United States that if a practitioner prescribes hydroxychloroquine there is a 20% to 30% chance that the patient will not fill the prescription. There's a 20% to 30% chance they will not take it as directed, and there's a 20% chance that they won't make the next visit at the time it was supposed to happen. So, medicine nonadherence is one of the major reasons for emergency room visits, flares, and poor prognosis. It is extremely important that we hone in on this issue.

With Kelsey, it appears that she's evolving towards more organ threatening disease and we really need to educate her and talk to her. We talk about the benefits of educational sessions. We don't want to scare the patients such that the benefits are outweighed by perceived risks. 95% of people who take hydroxychloroquine have no real issues.

So, the main points that I wanted to emphasize is that we talked about the diagnosis and treatment of lupus. That a rheumatologist is important to be involved at some point, especially in those with serious disease, unless it's a nephrologist for kidney disease. We need to screen for organ threatening disease. In other words, somebody who comes in with a rash might turn out to have protein in their urine and we would never know it unless we get a urine. We need to treat early with safe, or rather effective, inexpensive medication such as nonsteroidal corticosteroids, and the overwhelming majority with SLE should be on antimalarial. We should monitor patience for adherence, and the lupus patient should have a lupus care specialist involved in the care system at least at some point.