Contemporary Management of Patients With Systemic Lupus Erythematosus: A Case-based Approach

Editor's Note: This is a transcript of an online course released in June 2023. It has been lightly edited for clarity.
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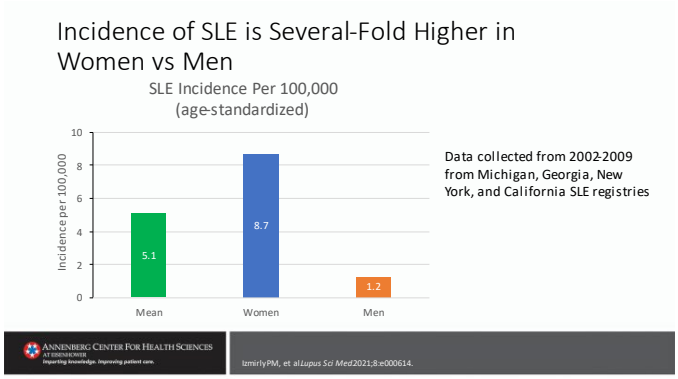
SLE OVERVIEW

Diane Kamen, MD: What is lupus and why are we talking about this condition today?

Well, it is a prototype autoimmune disease, and I say that to mean, if we could figure out lupus and all its complexities, we could come a long way to figuring out a lot of other autoimmune diseases which are very highly prevalent in the world.

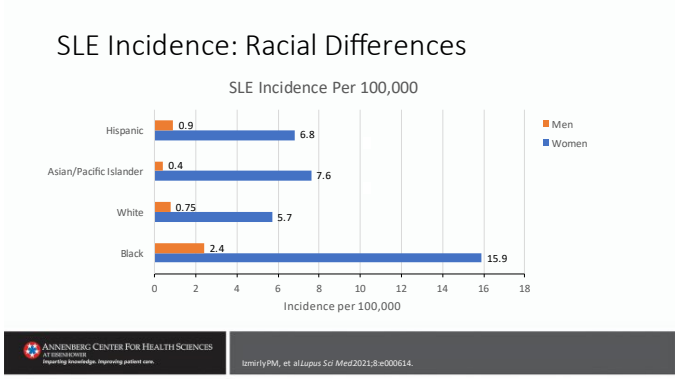
It's also a highly impactful, chronic disease, lifelong disease, with no cure as of yet. It can be potentially fatal and affecting, often, very young people. … The overall prevalence looks low when you look at the United States. That seems like it would be a fairly rare disease, but in certain populations it's not rare at all.



Izmirly PM, et al. *Lupus Sci Med.* 2021;8:e000614.

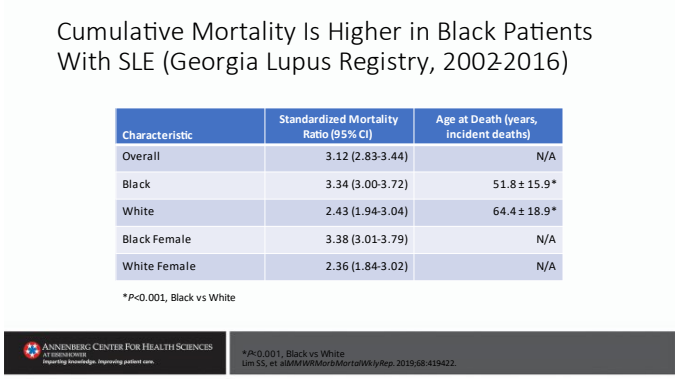
SLE Incidence: Racial Differences

Within certain populations, particularly Black or African American community members and Hispanics, the incidence is actually much higher, and even 1 out of 200 African American women in their lifetime are at risk of development of lupus … in certain populations, again particularly in health disparity communities, unfortunately there's still a big gap, and people still are dying early from lupus, unfortunately.



Izmirly PM, et al. *Lupus Sci Med.* 2021;8:e000614

Mortality in Select Population



Lim SS, et al. *MMWR Morb Mortal Wkly Rep.* 2019;68:419-422.

Social Determinants of Health in Lupus

Socioeconomic status within the community has a big influence on who gets in, who gets access to care, who gets treated more aggressively or appropriately. There's sort of more tendency to have people on things like chronic steroids which can lead to a lot of damage compared to patients with more access and a better socioeconomic status. The latter are the ones more likely to be on some of the newer therapies and not have the damage and effects of steroids over long periods of time. Though, even though there's no significant difference in the prevalence between socioeconomic groups, we do see the outcomes being drastically different, depending on socioeconomic status.

It's women who are at greater risk of lupus overall, with a 9 to 1 ratio of women to men developing lupus. But when men get lupus, they're more likely to have lupus nephritis, with some of the more severe organ involvement.

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Severe SLE Manifestations Are More Common in Racial and Ethnic Minorities

	Non-Hispanic Black[a]	Hispanic[a]	Asian/Pacific Islander[a]
Mucocutaneous	NS	NS	NS
Serositis	NS	NS	NS
Cardiovascular	NS	NS	NS
Pulmonary	NS	NS	NS
Gastrointestinal	NS	NS	NS
Renal	**1.74 (1.4-2.16)[b]**	**1.35 (1.05-1.74)[c]**	**1.68 (1.38-2.05)[b]**
Musculoskeletal	**1.35 (1.05-1.74)[c]**	NS	NS
Neurologic	**1.49 (1.12-1.98)[c]**	NS	NS
Hematologic	**1.09 (1.04-1.15)[b]**	NS	**1.07 (1.01-1.13)[c]**
Serologic	NS	NS	NS

[a]Non-Hispanic White reference population; [b]$P<0.05$; [c]$P<0.0001$

Maningding E, et al. *Arthritis Care Res (Hoboken)*. 2020;72:622-629.

Lupus in Adolescent Populations

- Between 5000-10,000 patients with childhood SLE
- Similar demographic patterns as in adults
  - More common in females
  - Higher incidence in Asian, African, Native American, and Hispanic/Latino populations
- Rare before 5 years of age
- More aggressive disease course and earlier renal and cardiac damage
- 10%-20% of all SLE cases present in childhood

Disengagement from the Healthcare System

I like this figure or this diagram because it shows how the patient is central to a lot of external factors that end up influencing, to a great degree, how much access they're going to have to care, how well they're going to do with being able to get their medications, take their medications, make it to follow-up appointments.

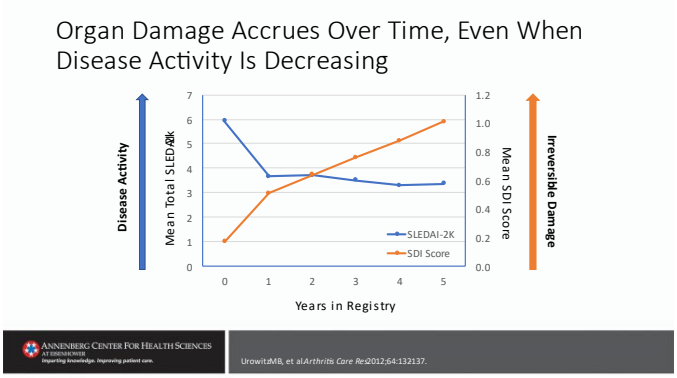
Overview: Key Points

It's important to understand that there you can see lupus in any group of patients, but the Black or African American patients are at more risk at a younger age for more severe disease. And men, especially Black men, are more at risk for kidney disease and often require more aggressive treatment.

DIAGNOSIS

Longer Time to Diagnosis Negatively Affects Outcomes: German LuLa Cohort

Anca Askanase, MD: Let's dive into making a diagnosis of lupus and why it is critical that that diagnosis is timely. These are data from the LuLa cohort in Germany where, based on patient reports, they are able to make the point that delayed diagnosis, even by 6 months, is associated with increased disease activity and damage. This study is an attempt to making it clear that early diagnosis is a big priority for people taking care of lupus patients, but also for people with lupus themselves.



Urowitz MB, et al. *Arthritis Care Res.* 2012;64:132-137.

The big reason for this increase in damage is the cumulative steroid dose. We use steroids to quench disease activity. Over time, the cumulative steroid dose increases and damage parallels that increase in cumulative steroid dose.

ACR (1997) Revised Criteria for Classification of SLE

What have doctors done to provide the tools for rheumatologists to make an earlier diagnosis of lupus? These are the first American College of Rheumatology criteria, 1982. It's been a while since these criteria were thought of and they were revised in 1997, as our understanding of our immunity improved there was a need to revise the criteria. And basically, it relies on the fact that because lupus is complex and heterogeneous, there isn't 1 thing that makes the diagnosis of lupus.

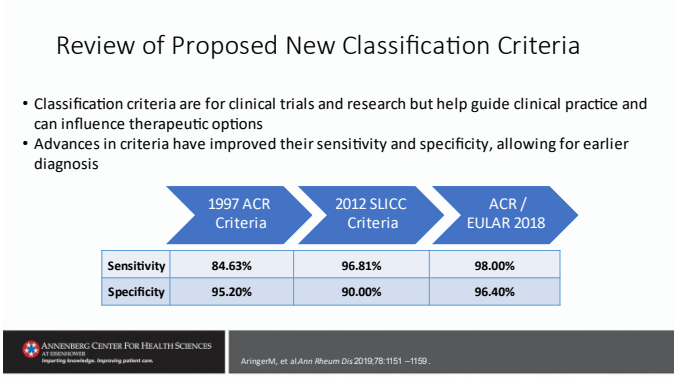
2012 SLICC Revision of the ACR Classification Criteria

These 1997 revised criteria are very specific for a diagnosis of lupus, however we've learned that early diagnosis is critical. We've understood that diagnosis criteria that increase the sensitivity and allow for an earlier diagnosis are critical. And that took us to the 2012 SLICC revision of the ACR classification criteria. The big innovation here is that criteria that are significantly overlapping with the ACR criteria are now divided on clinical and immunologic criteria.

Proposed ACR/EULAR Classification Criteria

ACR and EULAR got together and and came up with a set of classification criteria. While both the ACR and the SLICC criteria have been used for both classification and diagnostic purposes, the ACR/EULAR 2018 criteria are clearly put together as classification criteria and for inclusion in clinical trials. And as we learned, lupus is a disease of autoantibodies, so the entry for these criteria is ANA positivity. Unless you have an ANA-positive, you won't even think about these criteria and the ANA test is very sensitive for a diagnosis of lupus, yet not specific. Sensitive, 100%, according to these criteria of lupus people, have an ANA-positive, yet 5% to 10% of normal healthy individuals also have an ANA-positive. Entry criteria for ACR/EULAR criteria, ANA positivity and then clinical and immunologic criteria much like we've seen for the original ACR criteria and the SLICC criteria, just putting together clinical manifestation and immunological changes to come together and make a diagnosis of lupus.

This is a set of criteria that takes into account how important manifestations are in the overall diagnosis. The older criteria, things are created equal. Here, having class 3 or 4 lupus nephritis automatically allows you to make the diagnosis of lupus and some other manifestations, like fever or nonscarring alopecia, are weighted less. To make a diagnosis, you need 10 points based on the weights of how important that manifestation is to overall lupus and putting together the diagnosis of lupus for clinical trials.



Aringer M, et al. *Ann Rheum Dis.* 2019;78:1151–1159.

Incomplete SLE

There are people that have clinical signs of lupus and have very clear symptoms of lupus, yet they don't meet classification criteria. And some of these people have serious organ involvement, but they don't meet these classification criteria. We call these people incomplete lupus and a good portion, about 55% of these people, ultimately progress and meet the classification criteria.

Summary

Because we understand that time to diagnosis is critical to improving outcomes, and cumulative steroid use is associated with organ damage, there has been a lot of effort to improve the tools available to make a diagnosis of lupus. And because of this, classification criteria have evolved to allow for more sensitivity and earlier diagnosis of lupus. The big changes have been trying to make the balance between autoantibodies and clinical manifestations and we now have criteria that are meant for diagnosis and classification and inclusion in clinical trials.

MONITORING

Regular Monitoring to Assess SLE Symptoms and Organ Involvement is Needed

Diane Kamen, MD: Once you've made a diagnosis of lupus, how can we best work with our patients and monitor their disease and monitor their response to treatment?

There are many, many validated instruments to measure different domains of lupus, whether it's their disease activity, their disease damage, their quality of life, whether or not they're having a flare vs continuous high activity vs being in remission, being in clinical remission or serologic remission. And then there's organ-specific endpoints as well. It's very complex, but what I usually recommend is not to try to do all

of these in your clinical practice because that would not be feasible, but to find any measure of lupus disease activity that's specific to lupus that you're comfortable with, that fits well into your practice and then also to definitely be monitoring damage.

Goal: Prevent Damage

- Organ damage predicts long-term prognosis for patients with SLE
- 30%-50% of organ damage occurs in first 5 years
- Most common manifestations:
  - Cardiovascular
  - Neuropsychiatric
  - Musculoskeletal
  - Renal
- 80% of damage attributable to corticosteroid use
  - Damage is dose-dependent

Glucocorticoids Are Associated With Damage in SLE

Steroids are tightly associated with damage accrual and this is just data from a meta-analysis of many publications, just emphasizing that fact. On top of the damage we see from steroids in patients with lupus, we also know that there's an increased infection risk that sometimes can be mitigated with using more specific targeted therapies and to be able to reduce that kind of overall immunosuppression. And again, we'll talk more about that in a little bit, but you really want to think carefully about steroids as a bridge in order to minimize the harm from overdosing with the steroids compared to their known life-saving abilities and their importance, certainly, with severe activity from lupus, but to try to minimize them as much as possible.

It is dose-dependent, as I mentioned, so even at a low dose of 6 mg to 12 mg a day, there is a significant increase in the hazard ratio for organ damage. Even at the low doses, when you think about less than 20 mg a day, you can see that every milligram really makes a difference. When you're trying to taper your patient, you can tell them that even tapering down a milligram, you can consider that a small win.

Disparities in Cardiovascular Events

We see disparities in cardiovascular events, as well, which we see over the surveillance period of several years before or after the lupus diagnosis. Black patients had a 7-fold increase in cardiovascular events compared to White patients with lupus. That was statistically significant.

Attributable Risk for Cataracts and Osteoporosis Due to Steroid Exposure

This is more data emphasizing that link between corticosteroids and damage, this time looking at cataracts and osteoporosis, and emphasizing the need for regular visits. Certainly, if they're on hydroxychloroquine, hopefully they're already going yearly to the ophthalmologist, but bone density screening, as well, being important in prevention of future osteoporosis and prevention of fractures, certainly important. And more at risk for those on steroids.

EULAR Quality Indicators in SLE Care

- EULAR management recommendations, updated in 2019, developed into 44 QIs
- 18 selected as "most feasible" – checklist includes:
  - Screening-diagnostic QIs (eg, labs every 3-6 months, stratification for CVD risk)
  - Treatment QIs (eg, add ACE-I or ARB for proteinuria)
  - Monitoring QIs (eg, use SLEDAI and PGA at each visit, monitor SLICC/ACR damage annually)

Suggested Plan for Assessing and Monitoring

Assess at Each Visit

- BILAG or SLEDAI*
- Full blood count
- Erythrocyte sedimentation rate
- C-reactive protein
- Urea, creatinine, electrolytes
- Liver function
- Double-stranded DNA titer
- C3/C4
- Urinalysis
- Blood pressure

Annual Assessments

- SF-36
- SLICC/ACR

Annual monitoring for patients with suspected or known renal disease

- Cr-EDTA glomerular filtration rate

Monitoring for patients with known osteoporosis

- DXA bone density scan to monitor treatment response (adjust interval based on severity)

*Faculty recommend SLEDAI as a more practical alternative to BILAG for an objective measurement of disease activity
Fernando MMA, et al. *Ann Rheum. Dis* 2005;64:524-527.

SLEDAI Disease Activity Calculator

I think in a clinical practice, SLEDAI is quite feasible and practical. It doesn't take too long to do and it combines clinical manifestations that tend to be weighted somewhat appropriately to how much they're impacting that patient's functioning, as well as sort of the best we currently have as far as lab markers of disease activity. It includes things like cytopenias and double-stranded DNA positivity and low complement.

Shortcomings of the SELENA-SLEDAI

- Devised in 1992 and never intended for use in clinical trials
- 24 items with a maximum score of 105
- Not sensitive to change in joints, blood counts
- No subjectivity
- Weighted against laboratory tests (6 points)
- Heavily weighted towards CNS and kidneys (56 CNS, 24 kidneys).
  Lupus headache does not exist.
- Ignores pulmonary hypertension, TTP, hemolytic anemia, interstitial lung disease
- Validated for clinical activity, but a poor measure of change in activity

Patient Reported Outcomes (PROs)

Patient-reported outcomes, as I mentioned, are absolutely critical to include and I would say, even in the clinical practice, super-important and even getting medications approved by insurance companies now are often asking for this data. Having it collected over time to be able to show response to certain treatments or lack of response to treatments is an important part of quality care for our patients.

In my clinic, we use the RAPID3 which includes the health assessment questionnaire and some visual analog scales about pain and quality of life, but your practice might have other instruments that you use.

There's, of course, the fact that patient-reported outcomes don't always align with our own SLEDAIs and physician-reported outcomes, so that's important to note that you can't only rely on one or the other. They're best when they're in combination.

Vitamin D Deficiency

- High prevalence in SLE because of sun avoidance and photoprotection, renal insufficiency, and treatment side effects (eg, steroids, antimalarials, and calcineurin inhibitors)
- Can be a risk factor for SLE onset and disease activity
- Can also be related to bone disease, cardiovascular disease, and renal disease

There's been studies of whether vitamin D deficiency in addition to being a risk factor for future osteoporosis and being important in fracture prevention, there's been studies of vitamin D deficiency as being a risk factor for lupus onset and disease activity as well. And from the study from Dr. Petri and her group, we have seen increasing 25 hydroxy-D levels being associated with lower protein creatinine ratios as well.

Summary

- Disease monitoring can be overwhelming
  - Use quality measures as a guide for what to monitor
  - Don't overlook patient reported outcomes, activities of daily living, and quality of life
  - Engage other healthcare providers (eg, case managers or nurses), or use technology, to reduce the burden of monitoring
- Monitoring frequency
  - No defined guidelines
  - Increase monitoring frequency in patients who are in a high-risk demographic group
- Monitoring includes
  - Lupus-specific risk factors such as bone health and cardiovascular health
  - Routine health maintenance monitoring for traditional risk factors (eg, hyperlipidemia and hypertension)

TREATMENT

Discordance in SLE Treatment Goals: Clinical Measures vs Quality of Life

Anca Askanase, MD: As physicians taking care of people with lupus, we are all aware of the discordance in lupus treatment goals. The clinicians tend to prioritize disease activity, long-term outcomes and reducing damage. On the other hand, patients prioritize their symptoms, the personal impact, how they feel, their quality of life. I think that part of the task for lupus researchers is to try to reconcile this discordance so that the goals are aligned. Now, obviously, the ultimate goals are aligned, but the day-to-day goal of taking care of lupus people should be better-aligned and better tools to measure the impact on patients hopefully will allow us to align our goals of treatment better.

Understanding Differences Between Lupus Type 1 and Type 2

Type 1

- Inflammatory, immune-mediated etiology
- Severity varies with disease activity, parallels lab biomarkers
- Responds to conventional immunosuppressants

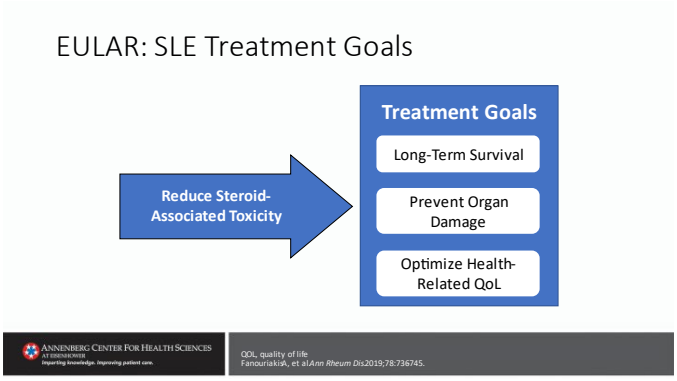
- Examples: nephritis, inflammatory arthritis, cutaneous rash, mucocutaneous ulcers, alopecia, vasculitis, cytopenias

Type 2
- Noninflammatory etiology
- Often persistent and chronic
- Usually does not respond to conventional immunosuppressants
- Examples: fatigue, widespread or diffuse pain, cognitive dysfunction, sleep disturbances, depression or anxiety, brain fog

Overarching Strategy to Address Pain and Fatigue in SLE

This is a proposed strategy to start to address some of that. When you're thinking about assessing lupus activity, think about using validated instruments and evaluating contributing factors. Sometimes the symptoms are related to disease activity; some other time the symptoms are related to non-lupus problems. Evaluate the situation, both in terms of lupus activity, but other causes and contributing factors and then tailor your treatment to control disease activity when the problem is disease activity, controlling the pain, develop psychological and social intervention and lifestyle changes.

Treatment Goals



Fanouriakis A, et al. *Ann Rheum Dis.* 2019;78:736-745.

EULAR: Treatment Targets

How do we put this together? … the target of our treatment is low disease activity or remission and this is the proposed strategy from our colleagues at EULAR on how to achieve that.

You will note that the backbone of treatment for lupus is hydroxychloroquine and still, to this day, sort of the second line we still rely heavily on steroids. And you will also note that these, the hydroxychloroquine and steroids, have the highest grade of evidence behind them. Some of the immunosuppressants have lower grade of evidence and belimumab has accumulating over time high-grade evidence. The use of belimumab is supported by high-grade evidence.

At the time when these treatment guidelines were developed, anifrolumab was not available yet, so we're proposing that its place in the treatment of lupus is in the treatment of moderate, refractory and possibly severe lupus. Hopefully, more evidence will be accumulating shortly.

It also has been recognized that adjunctive therapy, adjuvants, things that help increase the efficacy of our treatment modalities, are important in lupus.

Antimalarials
- After 6-12 weeks, anti-inflammatory and sun protective
- 80% response rate for non-organ-threatening disease and cutaneous lupus
- Decreases flare rate and risk for organ dissemination
- Antiplatelet effects
- Lipid lowering effects
- No serious toxicity if appropriately monitored
- Can be used in pregnancy and lactation

Other SLE Treatments

Methotrexate for Moderate to Severe SLE
- Most commonly prescribed disease-modifying drug for rheumatoid arthritis
- Not FDA-approved for SLE
- Use in patients who
  - Cannot tolerate or do not respond to HCQ
  - Need continued steroid treatment for disease control
  - Have disease activity that could be responsive to methotrexate (eg, arthritis, skin manifestations, possibly serositis)

Mycophenolate and Azathioprine
- Mycophenolate
  - Primarily used for renal involvement
  - Can be used in moderate to severe lupus for organ-threatening or non-organ-threatening disease
- Azathioprine
  - Used for nephritis
  - Can be used for hematologic, musculoskeletal, or dermatologic involvement
  - Can be steroid sparing

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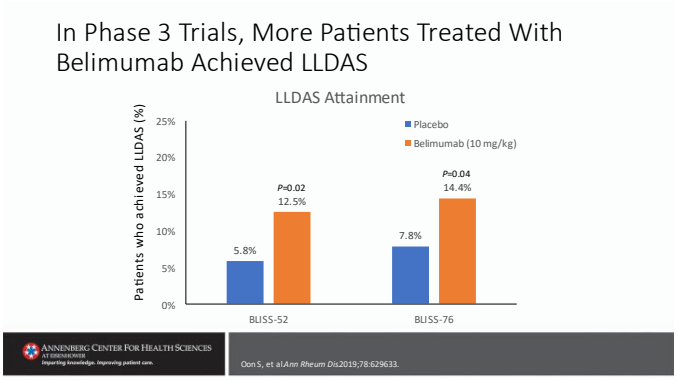
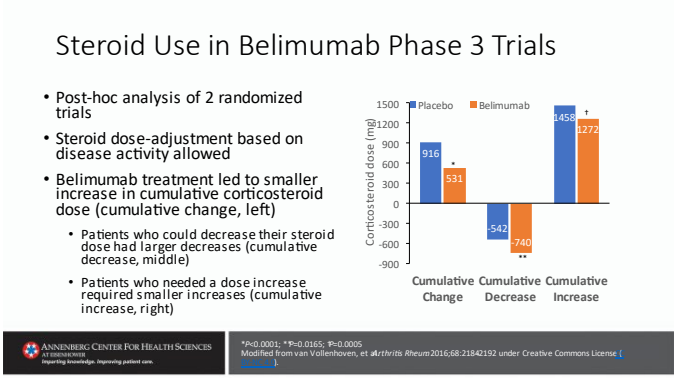
Treating Specific Manifestations

- 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

SLE Biologics

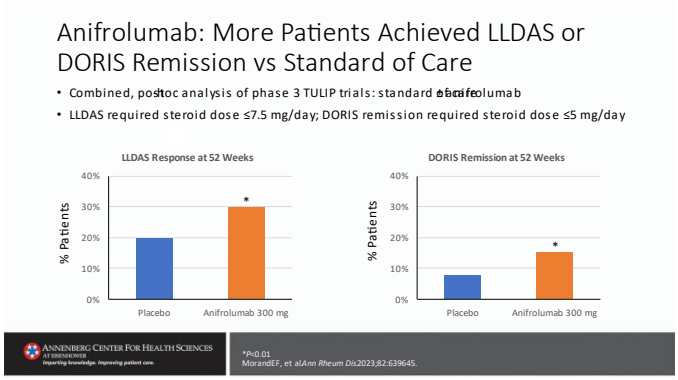


Oon S, et al. *Ann Rheum Dis.* 2019;78:629-633.



*P<0.0001; **P=0.0165; †P=0.0005

Modified from van Vollenhoven, et al. *Arthritis Rheum*. 2016;68:2184-2192 under Creative Commons License (CC BY-NC 4.0).



*P<0.01

Morand EF, et al. *Ann Rheum Dis.* 2023;82:639-645.

EULAR: LN Treatment Goals

Switching gears and now thinking of the lupus nephritis treatment goals, they're aligned and they're very similar to the nonrenal treatment goals, yet have a little more emphasis on preserving renal function. Managing comorbidities. People with lupus nephritis have hypertension because of the steroid use. They can develop steroid-induced diabetes. So, pay attention. These are sicker patients, higher disease activity overall. Pay attention to managing comorbidities.

ACR Guidelines for Monitoring Activity of Lupus Nephritis

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

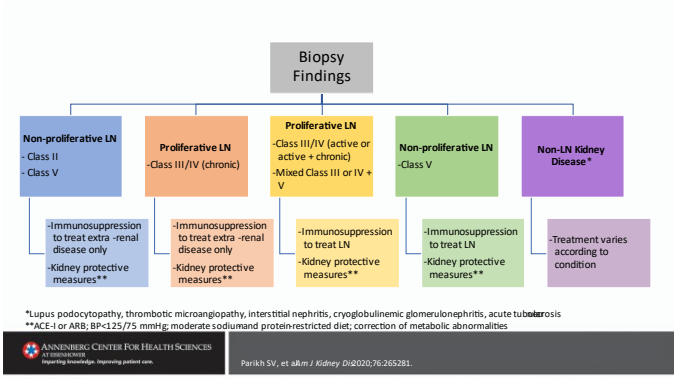
*Values are the monthly intervals suggested as the minimum frequency at which the indicated laboratory tests should be measured in the SLE scenarios shown in the left-hand column.
†Opinion of the authors based on a study published after the Task Force Panel had voted.

Every month | Every 2 months | Every 3 months | Every 6 months

Hahn BH, et al. *Arthritis Care Res*. 2012;64:797-808. Grootscholten C, et al. *Kidney Int.* 2006;70:732-742.

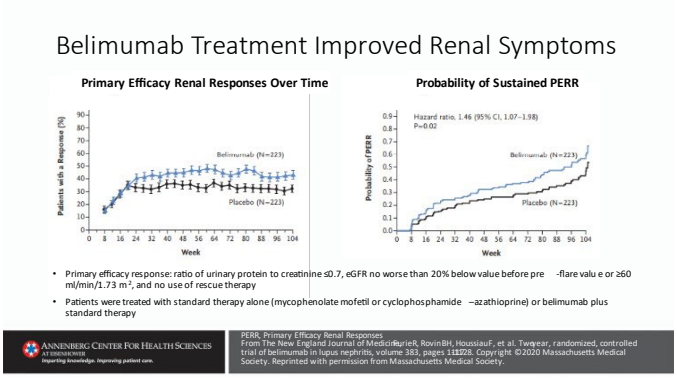
- See patients with active lupus nephritis monthly to monitor their progress and to respond quickly to changes in disease activity (renal or nonrenal)
- For patients who have never had lupus nephritis, monitoring is based on disease activity

Lupus Nephritis Monitoring and Treatment Algorithm

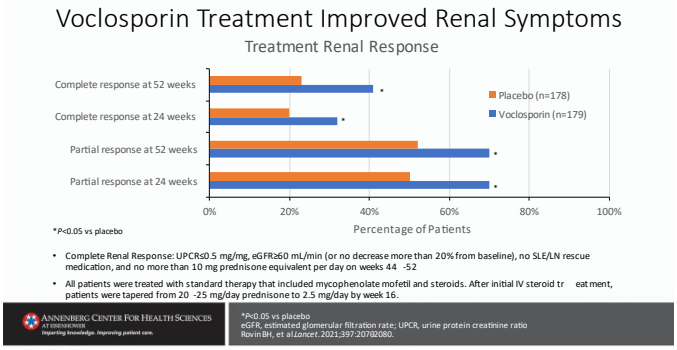


Parikh SV, et al. *Am J Kidney Dis.* 2020;76:265-281.

Lupus Nephritis Treatment



Furie R, et al. *N Engl J Med.* 2020;383:1117-1128



*P<0.05 vs placebo
eGFR, estimated glomerular filtration rate; UPCR, urine protein creatinine ratio
Rovin BH, et al. *Lancet.* 2021;397:2070-2080.

- Complete Renal Response: UPCR≤0.5 mg/mg, eGFR≥60 mL/min (or no decrease more than 20% from baseline), no SLE/LN rescue medication, and no more than 10 mg prednisone equivalent per day on weeks 44-52
- All patients were treated with standard therapy that included mycophenolate mofetil and steroids. After initial IV steroid treatment, patients were tapered from 20-25 mg/day prednisone to 2.5 mg/day by week 16.

Summary

Let's summarize this complicated part of this presentation where we took upon the task of reviewing treatments in nonrenal and renal lupus. I think, and I hope, that we have made very clear that the treatment goals in lupus should be remission and then, when that is not possible, low disease activity. And this is best achieved by minimizing steroid use. Think of adding immunosuppressants, adding biologics early in the course of the disease to minimize steroid exposure. You are now aware of the, of the good and the bad of steroids. Minimizing steroid exposure is part of our treatment goals.

In patients with longer disease activity our focus is on minimizing damage. Early on in the disease, decrease disease activity quickly and effectively using the least amount of steroids. Patients with longer disease, focus on controlling comorbidities, focus on minimizing and treating damage. And while we presented the treatment for nonrenal and renal lupus separately, the goal for both is minimizing disease activity, hopefully achieving remission which, for lupus nephritis, is the complete renal response and/or low disease activity for nonrenal lupus. For renal lupus, the community has not come together in defining a low disease activity equivalent and I think that, while partial renal response, it may be as good as it gets for some people. I don't think it is good enough to call that low disease activity.

OUTLOOK ON FUTURE SLE TREATMENTS

Anti-CD19 CAR T Cell Therapy for Refractory Systemic Lupus Erythematosus

Anca Askanase, MD: Let's look at what's coming in terms of future lupus treatments. I think that the excitement about using cell therapy is palpable in the world of lupus and that was sparked by this publication by Schett and colleagues that looked at using anti-CD9 CAR T cell therapy for refractory lupus. And the reason why this is so extraordinary is because it actually, in the patients where it was used—and the numbers are small and we can't get overly excited about this—is that it offers the promise of drug-free remission. These patients were

taken off immunosuppressants and treated with CAR T therapy and, at the end of 6 months, they were in drug-free remission. Several clinical trials are embarking on better understanding the role of this therapy in people with renal and nonrenal lupus.

Efficacy and Safety of Deucravacitinb, an Oral, Selective, Allosteric TYK2 Inhibitor, in Patients With Active Systemic Lupus Erythematosus: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study

This is another exciting new therapeutic. These are the data from the phase 2 trial of deucravacitinib, a TYK2 inhibitor, so part of the JAK-STAT family of signal transduction, use in the treatment of people with active lupus. A phase 3 trial is currently ongoing and these data from the phase 2 suggest a high efficacy associated with an acceptable safety profile for use of this medication in the treatment of lupus.

Trial of Anti-BDCA2 Antibody Litifilimab for Cutaneous Lupus Erythematosus

Another drug in development: these are the data from the phase 2 study of an anti-BDCA antibody called litifilimab. A phase 3 trial of this particular medication is ongoing, so more to come.

MULTIDISCIPLINARY MANAGEMENT

Diane Kamen, MD: As we know, with all of its complexities and the systemic nature, patients are often already seeing multiple specialties, including rheumatology. How can we really make this work best for the patient? When it's working, it can be a beautiful collaboration between a large care team that the patient trusts and communication is optimal and that can sometimes be challenging, everyone being busy and stressed. But I think it's super-important, I know it's super-important, that it's one of the priorities of the patient to make sure that they have the right team, that people are focused on the best outcomes for them and that we're all communicating well.

Clinical Trial with SLE Patients

Minorities Are Underrepresented in Clinical Trials

	Percent of Prevalent Cases	Representation in Clinical Trials
White/Caucasian	~33%	51%
Black	43%	14%
Hispanic/LatinX	16%	21%
Asian	13%	10%

Falasinnu T, et al. *Curr Rheumatol Rep*. 2018;20:20

Patient Barriers to Clinical Trial Participation

Barrier	Examples
Access	• No rheumatologists who know about clinical trials • Difficult transportation to clinic
Opportunity	• Lack awareness of clinical trials • Lack of referral
Mistrust	• History of exploitation • Fear of deportation
Health literacy	• Lack of disease education • Dislike and misunderstanding of clinical trial protocols • Beliefs about clinical trial value and benefits
Cultural	• Lack of friendly patient-provider relationship

Sheikh SZ, et al. *J Clin Med.* 2019;8:1245. doi:10.3390/jcm8081245

Summary

We do find, in our clinical trials, when referrals come from their own rheumatologist, patients are much more engaged with the process than if they're just hearing about it from a flyer or from an ad or something and they're calling in. They tend to be more hesitant. We always try to have a conversation with their rheumatologist, but when the actual idea comes from their rheumatologist, that makes a world of difference.

I think that we've learned from oncology that clinical trials are not only the way to make progress and bring new medications, but they're also part of the treatment. I'm hoping that our patients suffering from lupus will start thinking about clinical trials as part of their clinical care. And you've made the point that outcomes for people that are participating in clinical trials where they take drug or placebo and were a lot better than for lupus people in general. I could not advocate more strongly, using clinical trials as part of care. The barriers to clinical trials are multifaceted and they ultimately boil down to patient barriers, provider barriers and system barriers. We've done a

lot of work in improving patients' understanding of clinical trials. We've done a lot of work in having buy-in from the providers. There's a lot of work being done at the system levels. It takes a lot of work and effort.

CASE STUDIES

Case 1 - 25-year-old African American woman

Anca Askanase, MD: This is a case of 25-year-old African American woman that came to clinic complaining of shortness of breath, chest pain and lower extremity edema.

On examination, she has evidence of alopecia. She has bilateral knee arthritis and she has a malar rash. The astute ER physician also notes that her blood pressure is 150/90 and thinks about the possibility of a systemic disease. It's somebody that seems to have fluid overload, arthritis, alopecia and a rash. Makes sense to think of a systemic illness. Work-up is sent, ANA is positive, double-stranded DNA is positive, complements are low and urinalysis show proteinuria, red cell and red blood cell casts. This is coming together as a possible case of lupus nephritis.

The point is to have index of suspicion, send that ANA but also send the routine work-up with urinalysis, the metabolic panel, the CBC with differential and work up the chest pain and shortness of breath just because, well, this happened to be a lupus patient with fluid overload, but you want to make sure you're not missing a cardiac event and you're not missing a pulmonary embolism. Maintain suspicion for lupus, but rule out other more common causes for fluid overload, for chest pain, for elevated blood pressure.

Once the diagnosis of lupus with the possibility of lupus nephritis is made, the next step, the next logical step here is to actually involve the nephrologist and get a kidney biopsy.

We won't get into all the details of lupus nephritis classification, but please know that every person with lupus presenting with proteinuria greater than 500 mg should have a kidney biopsy as part of the work-up.

The backbone of treatment for lupus nephritis and this is true for class 3, 4, and 5, is that there's a time of induction treatment where we're attempting to decrease proteinuria, preserve renal function and do that with the least amount of side effects. And that treatment includes steroids, cyclophosphamide or mycophenolate mofetil, and based on the data, we looked at the possibility of including voclosporin and belimumab. Induction and maintenance, minimizing the dose of steroids, possibly using lower doses of the immunosuppression medications that were used for induction and possibly continuing the advanced therapies, voclosporin and belimumab. Now, you will note that these are 2012 guidelines. The voclosporin and belimumab were added here only as proposed, so this is our opinion of where belimumab and voclosporin could fit.

People with lupus are more likely to be women and are more likely to be women of reproductive age, so the issue of pregnancy in lupus is front stage and center for a lot of people with lupus and thinking about pregnancy planning and making sure that things are stable and in the best possible situation for the pregnancy to be successful is critical.

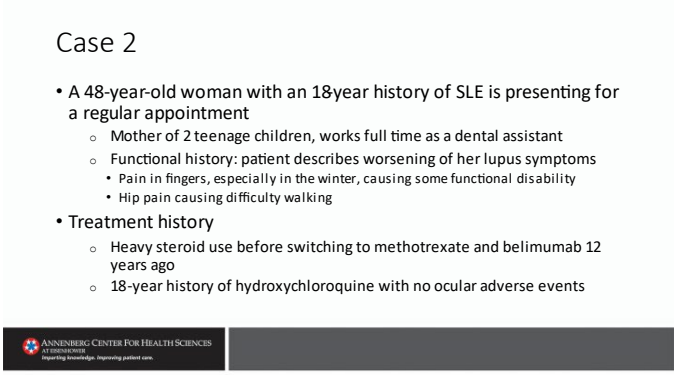
How would this new diagnosis of lupus and lupus nephritis impact her plans? This is a situation where this is very active lupus with an organ-threatening involvement of the kidneys. This is a situation where we would recommend that the patient puts the plans to start a family on hold until lupus nephritis is controlled. Why? Because trying to have a baby in the middle of very active lupus is associated with very high risk of pregnancy failure. The wisdom is that you wait until the disease is inactive for 6 to 12 months, and when that's not possible, make sure that the disease is well-controlled before embarking on plans to conceive.

Dr. Kamen, does that sound reasonable to you and would you advise your patient in the same way?

Diane Kamen, MD: I agree with all of your wisdom. Helping a patient with lupus have a healthy baby and get through a pregnancy without major complications is one of my very, very favorite things to do. But patience for the patients and the rheumatologist and the OB and family is critical because you want it to be the right time.

I definitely utilize these 2 websites, LupusPregnancy.org and ReproRheum.duke.edu. Both of those sites have worksheets that patients can print and bring to their different providers and kind of know the right timing of things. It goes into not just pregnancy, pregnancy planning, but also effective contraception, even things like egg harvesting and planning in the future for pregnancies.

Case 2 - 48-year-old woman



Diane Kamen, MD: Stepping back and thinking about what is going on with this patient, we want to definitely differentiate disease activity which a lot of patients know when they're experiencing symptoms that are resulting from disease damage. They think of it as their lupus. Rightly so, but it might actually be damage already done, irreversible compared to what we would call activity which would be something that would respond hopefully to treatments, whether immunosuppression or immunomodulatory agents. Or, you know, it might be something totally unrelated to the lupus that's just confusing things. Thinking about her, we know, because of her treatment history, there's going to be certain screenings that she needs. You know, is she still having periods? Is she postmenopausal? In which case, we would want to make sure she's up to date with things like bone density screening. She definitely needs cardiovascular screening and given her history of what sounds like cold-induced pain in her fingers, we want to … could this be something that we see in a lot of patients with lupus, may or may not be actually lupus activity, but something like Raynaud's phenomenon which is vasospasm that's cold-induced in the capillaries, particularly in the fingers and toes? It'd be unusual to develop that later in a course, but sometimes it does happen.

Thinking about the treatment goals, we want to definitely distinguish activity from damage because that will be treated very differently. If, on further history-taking and exam, we decide that this is indeed Raynaud's phenomenon, there can be conservative managements like keeping gloves handy. If you're going to be reaching into the ice box of the grocery store, making sure you put on the gloves or getting away from air conditioning blowing on you or whatever the case might be, there can be some conservative hand-warming measures that patients can use. A baby aspirin a day can be helpful as well and things like calcium channel blockers to help prevent flare-ups and attacks of the Raynaud's. Making sure also that they're aware to contact you if things progress. If they start to get even digital pitting or certainly ulceration, that needs to be addressed right away and not wait until the next appointment.

For her hip pain, let's say imaging shows early avascular necrosis. That would be managed very different than if it was truly like an inflammatory hip pain which would be unusual for lupus to involve just 1 hip. You think about too, someone on immunosuppression, could it be a septic arthritis and so that exam, that imaging, is going to be very important, kind of distinguishing the different causes of hip pain. It may be trochanteric bursitis which is my favorite thing because then you can do a steroid injection in the office, teach them some stretches and hopefully that'll be the quickest to resolve. But oftentimes, what's called hip pain is actually, unfortunately, a complication of having been on those high-dose steroids in the past. For avascular necrosis, the pain management and bone health issues, seeing ortho, early intervention for that is going to be, is going to make a big difference. And then monitoring or managing toxicity from any future steroid use.

I think this case illustrates very well the concept of making sure that the symptoms that a lupus patient is complaining of are related to lupus or comorbidities. Here, the story is made clear that the finger pain is not due to arthritis, but is due to active Raynaud's and vasospasm. It's also clear that the hip pain is due to avascular necrosis, but keep in mind when you're evaluating a patient that these are the management decisions you'll need to make. Is this continued lupus activity? Do I propose a change in treatment, more immunosuppression or is this an unrelated, a nonlupus comorbidity or, I mean it's not that it's not lupus-related because ultimately Raynaud's are part of lupus, but not something that we would use immunosuppressants for. And obviously, avascular necrosis, other than conservative measures and when it's too far-gone, referral to the orthopedic surgeon, we can't do much.

You, as the rheumatologist, can play such a huge role with this. You think about how you would manage this vs if the patient didn't have the rheumatologist and was going to the emergency room and said, oh, I have lupus and I have these pains, 99% of the time they're going to get probably a Medrol dose pack or some form of steroid which would be not the right treatment.