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:

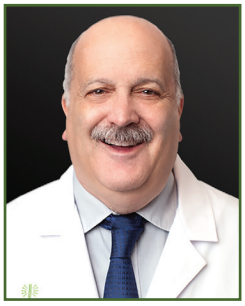
- Apply the ACR diagnostic criteria to recognize patients who may have SLE
- Utilize and interpret laboratory findings to investigate possible SLE
- Develop SLE treatment plans based on individual patients' disease characteristics, treatment goals, and consensus recommendations
- Identify a validated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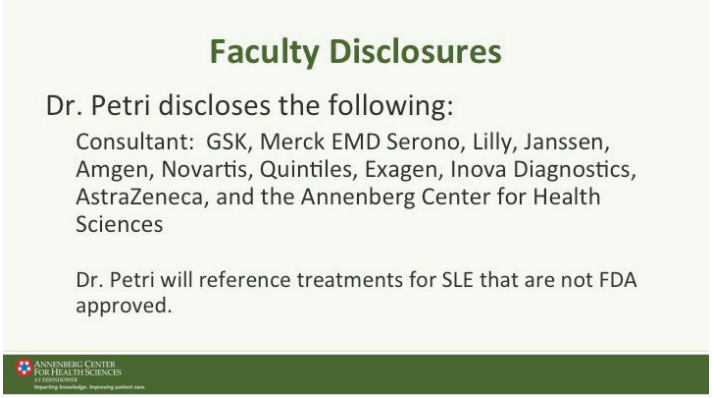
Editor's Note

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."

Michelle Petri, MD, MPH

Hello, my name is Michelle Petri. I'm the director of the Lupus Center at John's Hopkins University School of Medicine. I want to discuss some advanced topics in treatment outcomes. The studies in this section look at prognosis and predictors of organ damage. Here are my disclosures.



Treatment Goals

I want to start with a problem we currently have that the outcome measures in randomized clinical trials aren't used in clinical practice, and they really don't reflect the goals we have in clinical practice. The most common one you'll see used is the SRI or the Systemic Lupus Responder Index. That usually is a 4-point reduction in the SLE disease activity index. Of course, we all want the manifestations of lupus to be less active, but that's insufficient in the clinic, where we also want patients to be able to reduce their prednisone.

BICLA is just a variation on the SRI where the major focus is on the reduction of BILAG disease activity index. We're moving to organ specific measures. 90% of lupus is skin or joints, so it won't surprise you that the CLASI, which measures skin involvement, and the tender and joint count are important.

I want to emphasize that we have to reduce prednisone if we're going to have our patients do well. This is a longitudinal study that we did that showed if the maintenance dose of prednisone is above 6 mg, there is a 50% increase in permanent organ damage, and you can see over a 2-fold increase in permanent organ damage when doses are above 18 mg. So, our goal in clinical trials should be the very same goal that we have in our clinical practice, which is to keep the maintenance prednisone dose below 6 mg.

Effect of Prednisone on Organ Damage

Adjusting for Confounding by Indication
Due to SLE Disease Activity

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

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Thamer M, et al. *J Rheumatol.* 2009;36:560–564.

When we talk about organ damage, the most common organ damage is going to be osteoporotic fractures, followed by cataracts, and of course people don't die usually of osteoporotic fractures, but yes, with hip fractures sometimes. And people don't die from cataracts. The major cause of death in lupus turns out to be cardiovascular events, and it turns out that prednisone is a direct factor in cardiovascular events as well. And here, on this slide, you see the very strong dose response. So, if the prednisone dose is 10-19 mg, there is a 2-fold increase in cardiovascular events, and if it's 20 or above, there is over a 5-fold increase.

Prednisone Itself Increases the Risk of Cardiovascular Events

Prednisone Use	Observed Number of CVEs	Rate of Events/1000 Person-Years	Age-Adjusted Rate Ratios (95% CI)	*P* Value
Never taken	22	13.3	1.0 (reference group)	
Currently taking				
1-9 mg/d	32	12.3	1.3 (0.8, 2.0)	0.31
10-19 mg/d	**31**	**20.2**	**2.4 (1.5, 3.8)**	**0.0002**
20+mg/d	**25**	**35.4**	**5.1 (3.1,8.4)**	**<0.0001**

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

In modeling, we adjusted for all the traditional cardiovascular risk factors, and we also adjusted for the disease activity for which the prednisone was prescribed. So, this shows you how all-pervasive the damage from prednisone really is and it is contributing to the major cause of death.

Now where should we go? In a perfect world we would want to have our outcome measure in both clinical trials, and in our practice, be remission. And, in fact, a DORIS group has come up with definitions for remission. And there can be a remission or there can be a remission on treatment.

Regardless, it requires that the prednisone dose either be zero or 5 mg or less. Immunosuppressant drugs are allowed and hydroxychloroquine is allowed. Serologies do not have to normalize, because I think everyone recognizes it's almost impossible to correct low complement anti-DNA in everyone.

Our problem is that the remission, even though it's (on) our wish list, is not actually achievable, and I wanted to show you how hard it is to get to remission if your patient starts at a baseline requiring a lot of treatment. We're talking about years to try to achieve a remission. That's not practical in clinical trials, is it, where the clinical trial will only last for 12 months. But it's also unrealistic in our practice, where we and the patient want to have a realistic goal.

Results: Median Time to Remission in Years

Baseline Activity	Baseline Treatment	Clinical Remission	Complete Remission	Clinical ROT	Complete ROT
All	All	8.7	11.0	1.8	3.1
High	High	15.0	>16.0	3.0	5.6
Low	High	10.5	>16.0	1.6	2.1
High	Low	3.3	6.0	1.5	2.7
Low	Low	1.4	1.5	0.8	1.0

Low activity: PGA < 1 and SLEDAI < 3
High activity: PGA > 1 or SLEDAI > 3

Low treatment: Prednisone < 5 mg/d and no Immunosuppressant use
High treatment: Prednisone > 5 mg/d or Immunosuppressant use

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Wilhelm TR, et al. *Ann Rheum Dis.* 2017;76:547-553.

Lupus Low Disease Activity State

We do know the patients who are highly unlikely to ever achieve a remission. In my practice it is my African American patients, but it's also patients who start out with active serologies or patients who start out with hematologic lupus like hemolytic anemia or thrombocytic anemia. So those are patients who are going to be much more difficult to treat and much more difficult to achieve remission.

Predictors of Remission (Relative Risk)

	Clinical Remission	Complete Remission	Clinical ROT	Complete ROT
African American	0.6 *p< 0.0001*	0.6 *p* < 0.0001	0.7 *p* < 0.0001	0.7 *p* < 0.0001
Baseline Low C3	0.6 *p<0.0001*	0.4 *p* < 0.0019	0.7 *p* < 0.0005	0.4 *p* < 0.0001
Baseline Low C4	0.7 *p* < 0.015	0.4 *p* < 0.0001		0.5 *p* < 0.0001
Baseline Anti-dsDNA		0.7 *p* = 0.0019		0.6 *p* < 0.0001
Baseline Hematologic Activity	0.6 *p* = 0.0002	0.6 *p* = 0.0002	0.6 *p* < 0.0001	0.5 *p* < 0.0001

Predictors in multivariable models controlling for all the characteristics in the table, baseline disease activity and treatment, based on univariable models checking further for sex, age, use of hydroxychloroquine and disease activity in different organ systems

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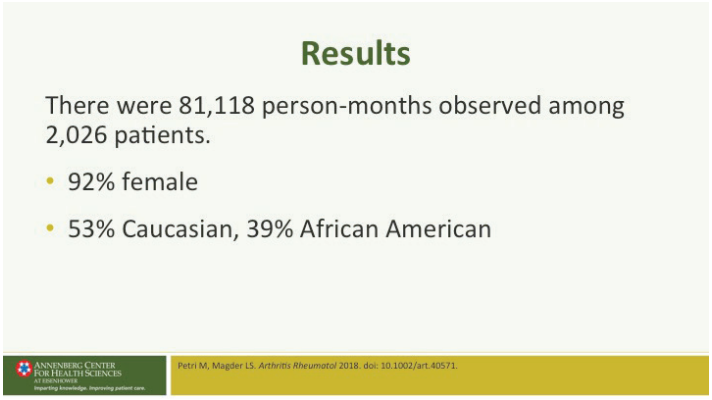
Wilhelm TR, et al. *Ann Rheum Dis.* 2017;76:547-553.

If remission is a wonderful wish list, but isn't really achievable by today's treatment standards, where should we go? And I think the place we should go in both our clinical trials and in our practice is a treat-to-target where the target is lupus low disease activity state, or LLDAS for short. Now in this, we use 2 activity measures. The SLE disease activity index should be less than or equal to 4, and the physician global assessment on a zero to 3 scale should be less than or equal to 1, meaning mild. There can be no major organ involvement, so no renal, no CNS, no new activity, meaning no flare, and it allows for a very low dose of prednisone and immunosuppressive drugs and hydroxychloroquine.

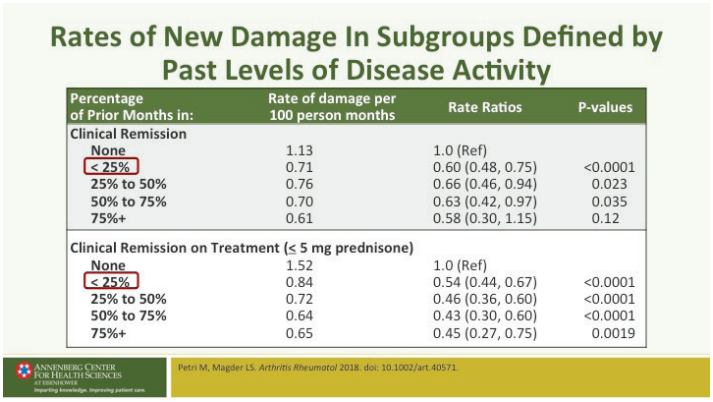
LLDAS is achievable, but now I want to prove to you that it's going to lead to very good long-term outcomes as well. So how did I show this? I run the Hopkins Lupus Cohort study. This is a study of over 2,000 lupus patients who are seen every 3 months, and we do all these activity indexes and laboratory tests necessary to complete them at every visit. So, I'll be telling you about 2,000 patients followed for over 80,000 person-months. As in most lupus studies, most of the patients will be female, and my cohort is pretty much balanced between African Americans and Caucasians.

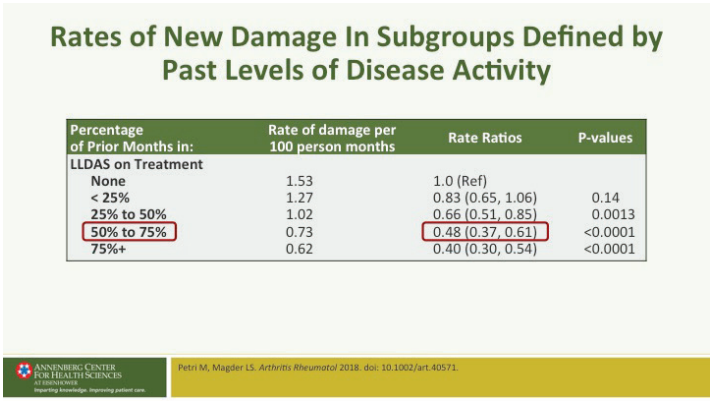


First of all, when someone achieves remission, remember, our most wonderful goal, but the impractical one, even less than 25% of their visits, they have a significant reduction in later organ damage so I'm never going to dismiss remission. People who achieve remission do very well, even if it's not at every visit. So, it's still some day going to be our goal—it's just not practical yet.

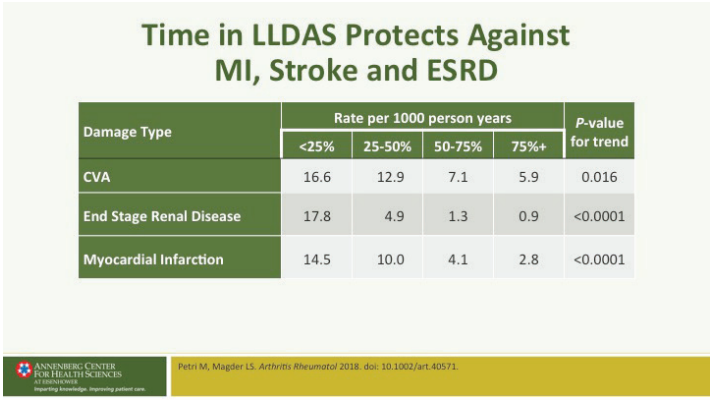
What about LLDAS? What do we have to achieve on LLDAS to reduce later organ damage? The patient needs to achieve LLDAS at 50% of her visits, and then she will have a 50% reduction in later organ damage.

So very easy to remember. Achieve at 50% of the time, you will have a 50% reduction in later organ damage.





What kinds of organ damage will be reduced? Well, I think the most important ones. So, the cardiovascular and white stroke and myocardial infarction. And also end-stage renal disease. You know that in large population studies, the frequency of end-stage renal disease from lupus has not decreased in the last couple of decades, so I think this shows us what we need to achieve as clinicians so we can avoid this bad outcome.



Achieving LLDAS is not perfect, so I always want to be honest and show both sides of the story. So, when we achieve LLDAS, we get rid of those bad outcomes, but we don't get rid of these. So, on this slide you see the problems that will be yet unsolved. We will not reduce cognitive impairment. One of the problems here is that cognitive impairment is actually present at the time of diagnosis. It's already there. We can't prevent something that's already present. It won't prevent deep vein thrombosis, but that's probably because that's mediated by antiphospholipid antibodies, not so much active lupus. It won't prevent malignancy and it doesn't prevent our bad pulmonary outcomes, pulmonary fibrosis or pulmonary hypertension, telling us there's something about pulmonary lupus that we don't have a handle on, at least, not yet. Now, it does not protect against cataract, but you're aware. Cataracts are increased by even very low doses of prednisone.

Time in LLDAS Does NOT Protect Against Pulmonary Fibrosis, Pulmonary Hypertension, Cognitive Impairment and Malignancy

Damage Type	Rate per 1000 person years				*P*-value for trend
	<25%	25-50%	50-75%	75%+	
Cognitive Impairment	7.8	9.4	3.7	10.9	0.94
DVT	2.7	3.9	0.7	0.9	0.31
Malignancy	28.7	22.4	18.0	19.2	0.12
Pulmonary Fibrosis	16.9	12.7	9.9	14.5	0.31
Pulmonary Hypertension	10.9	14.6	8.9	8.6	0.41

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Petri M, Magder LS. *Arthritis Rheumatol* 2018. doi: 10.1002/art.40571.

My conclusion from studying this treat-to-target issue is that the DORIS remission definitions are important, and remember, if someone achieves that (at) even less than 25% of her visits, she's going to have a significant reduction in later organ damage. But LLDAS is much more practical. It's achieved 3 times more frequently than the remission definition, and (a) very simple take home message achieved—LLDAS 50% of the time—you will have a 50% reduction in later organ damage.

I favor LLDAS. I think it can be an immediate treat-to-target in our clinical practice as well as convincing pharmaceutical companies that this is a good outcome in randomized clinical trials.

Cardiovascular Risk

Remember that 1 of the points I've already made is that lupus patients don't die of active lupus. The major cause of death in the Western world is cardiovascular events and of course there is also, unfortunately, deaths still from infection.

In rheumatoid arthritis, there is already a handle on how to use cardiovascular risk formulas and they have a very simple method of just multiplying the existing risk formula and using that to tell the patient what is your risk of cardiovascular events. Lupus is so heterogeneous, I don't think we can have a simple multiplication factor. I think if we're going to do better at identifying and treating patients at greatest risk, we're going to have to individualize it with all the different risk factors, so nothing is as simple as let's multiply Framingham by 1.5.

How bad is the risk? We believe at least in Baltimore that our lupus patients have a 2.66-fold increased risk at cardiovascular events over the general female population. This is often forgotten, that lupus should be right up there with diabetes, in terms of understanding the risks of cardiovascular disease.

If we do a cardiac CT to measure a coronary calcium score, lupus patients have a 2-fold increase in these noninvasive measures, of very early preclinical atherosclerosis.

I've already shown you this slide, that it's not just lupus. It's not just traditional cardiovascular risk factors that are causing this problem. Prednisone is right in there as

Time in LLDAS Does NOT Protect Against Cataract (Which is Associated With Low Doses of Prednisone)

Damage Type	Rate per 1000 person years				*P*-value for trend
	<25%	25-50%	50-75%	75%+	
Cataract	47.6	31.0	42.1	40.7	0.49

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

well. So, you can see how multifactorial it is and how difficult it's going to be for us to improve this, or hopefully someday completely eradicate this accelerated atherosclerosis risk.

When we did a study of statins, we did look to see what are the risk factors for progression of atherosclerosis that's already there? And it turned out that there were a lot of risks that we see in the general population as well, and depending on what vessel we looked at, the risks were slightly different. So, for coronary artery calcium, age, smoking, and of all things, a low high-sensitivity CRP, not a high. For the carotid intimate media thickness, it was age and hypertension, and for carotid plaque, it was age and hypertension. So, you get an idea here, we can't escape being general internists when we are treating our lupus patients. We have to treat these traditional cardiovascular risk factors to target.

The HSCRP story in lupus is very interesting. Remember that in the general population in women, HSCRP may be just as important as LDL cholesterol as a risk factor. Turns out, it doesn't work well in lupus patients where the HSCRP is affected by a lot of things, including weight. It's not just a cardiovascular risk factor, and when we studied it, it doesn't predict which lupus patient is going to have a myocardial infarction or angina.

We looked at 100 cardiovascular events in my lupus cohort and asked what were the predictors. So, in other words, let's start from scratch and build a lupus Framingham risk formula for cardiovascular events in lupus patients. And these were our model results. Now, the things that we can never change, of course, are patient age and patient gender, and then you see that there are a lot of the traditional cardiovascular risk factors like hypertension, cholesterol, smoking, diabetes. I want to draw your attention to the last 3 on the list. Here we see some lupus-specific risk factors for cardiovascular events. Overall disease activity, that's that SLE disease activity index, the lupus anticoagulant, so the most important antiphospholipid antibody, and then a low C3, so a serology. So already you see the complexity of this risk formula. It's going to include traditional cardiovascular risk factors, but it's also going to include lupus-specific factors.

Estimating Cardiovascular Risk

What do we do next? We want to find out what is the risk of a cardiovascular event in 10 years, and so we're going to use a risk formula. To do that, we need to know the patient's history. I'm going to give you an example. This is a 50-year-old man. He has the lupus anticoagulant. So here we're going to circle

Calculation of 10-year Risk Using Model

RISK of a CVE in 10 years is:

$1 - 0.975^{(\text{Hazard Ratio})}$

Where the Hazard Ratio is defined relative to someone age 40, female, SBP=120, Cholesterol=150, SLEDAI=0, and no other risk factors

the hazard ratios, age per decade, because he's 10 years older than 40, and he'll have a hazard ratio of 1.5 because he's a man, and he's going to have a hazard ratio because he has the lupus anticoagulant. The way risk formulas work is we are now going to multiply these different hazards and put them in the exponent, and now you can calculate what his own risk is over the next 10 years. Remember, we're not going to accept the rheumatoid arthritis way of just multiplying by 1.5. We're going to individualize each patient.

Model Results

	Hazard Ratio (95% CI)	*P*-value
Age (per decade)	1.3 (1.1, 1.5)	0.0050
Male (vs female)	1.5 (0.8, 2.8)	0.17
Systolic Blood Pressure (per 10 mmHg)[1]	1.3 (1.1, 1.6)	0.0010
Cholesterol (per 25 mg/dl)[1]	1.1 (1.0, 1.2)	0.11
Current Smoking	1.6 (1.0, 2.6)	0.055
Diabetes	1.5 (0.9, 2.6)	0.12
SLEDAI (per unit increase)[1]	1.1 (1.0, 1.2)	0.028
History of Lupus Anticoagulant	2.2 (1.4, 3.3)	0.0003
Low Mean C3[1]	1.8 (1.1, 2.9)	0.027

Example
50 yr-old Male, hx of Lupus Anticoagulant:
Total Hazard Ratio = 1.3 x 1.5 x 2.2 = 4.29

	Hazard Ratio (95% CI)
Age (per decade)	1.3
Male (vs female)	1.5
SBP (per 10 mmHg)	1.3
Cholesterol (per 25 mg/dl)	1.1
Current Smoking	1.6
Diabetes	1.5
SLEDAI (per unit increase)	1.1
History of Lupus Anticoagulant	2.2
Low Mean C3	1.8

Calculation of 10-year Risk Using Model for 50-year Old Male With Lupus Anticoagulant

Hazard Ratio = 1.5 x 1.3 x 2.2 = 4.29

RISK = $1-0.975^{(4.29)}$ = 10.3%

Cardiovascular Risk: SLE cohort

If the patient with lupus just has traditional cardiovascular risk factors, the answer we get will be about the same as if we just used the Framingham formula. But look what happens when we start to add lupus-specific risk factors, or 2 lupus-specific risk factors. You can see now that the lupus-specific formula gives you that much higher risk, the real high risk that we know from our longitudinal data.

Comparison With Framingham Formula

Risk Profile	Estimated 10-year risk, SLE formula	Estimated 10-year risk, Framingham formula
Woman, age 50, BMI 23, SBP=150, Chol=150	4.3%	4.7%
Woman, age 50, BMI 23, SBP=150, Chol=220	8.8%	7.8%
Woman, age 50, BMI 23, SBP=150, Chol=220, Lupus Anticoagulant	15.0%	7.8%
Woman, age 50, BMI 23, SBP=150, Chol=220, High disease activity	15.5%	7.8%
Woman, age 50, BMI 23, SBP=150, Chol=220, Low complement	17.8%	7.8%

I think this is what's going to happen in the future, and then we're going to have to decide, once we know that we have a patient that has a particularly high risk, what are we going to do. Is it going to be low-dose aspirin? Are we going to add statins, or are we going to have some practice guidelines to help? It's not enough to know that the person's at high risk, we have to decide together how we're going to treat high risk patients.

I want again to show you the example of comparing risk factors and the different formulas. You know there's more than just a Framingham formula right now. The American College of Cardiology and the American Heart Association have a formula as well.

Comparison of Estimated 10 Year Risk With ACC/AHA

Risk Factors						Estimated 10-year risk based on various formulae	
Race/Sex	Age	SBP	Chol	HDL	SLE-related	Hopkins Lupus Cohort†	ACC/AHA†
W/F	40	120	150	40	none	2.5%	0.7%
W/F	60	120	150	40	none	4.2%	3.9%

†Risk of Stroke or MI

Here's an example of looking at different risk factors and our cohort data and the American College of Cardiology answer. So again, remember when you have multiple SLE-related risk factors, you'll be able to show, with the lupus specific risk formula, that the patient's at much higher risk.

Comparison of Estimated 10 Year Risk With ACC/AHA

Risk Factors						Estimated 10-year risk based on various formulae	
Race/Sex	Age	SBP	Chol	HDL	SLE-related	Hopkins Lupus Cohort†	ACC/AHA†
W/F	60	120	150	40	Mean SLEDAI=3	5.7%	3.9%
W/F	60	120	150	40	Low C3	7.2%	3.9%
W/F	60	120	150	40	Hx of LAC	8.8%	3.9%
W/F	60	120	150	40	SLEDAI=3, Low C3	9.8%	3.9%
W/F	60	120	150	40	Hx of LAC, Low C3	15.0%	3.9%
W/F	60	120	150	40	SLEDAI=3, Hx of LAC, Low C3	20.1%	3.9%

†Risk of Stroke or MI

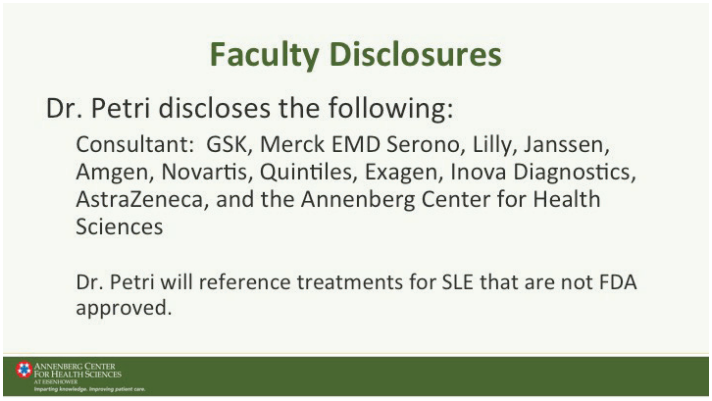
There are limitations on one center. Baltimore. One rheumatologist. These kinds of risk formulas have to be independently validated and they might be slightly different in different centers, and of course this reflects the follow-up that occurred in my cohort, and you could argue that perhaps a patient seen right now might have slightly different follow-up over the next 10 years.

To conclude, a data-driven cardiovascular risk formula included 3 lupus-specific factors. You remember, that was the overall disease activity, the lupus anticoagulant and the low C3. Things that we all know how to measure. They're available to all of us in practice. It also included 5 traditional cardiovascular risk factors. I think it's so important to think about lupus cardiovascular risks in this way. It's multifactorial. The traditional cardiovascular risk factors and lupus-specific risk factors go into that formula and as you know, remember, while it's not part of the formula because treatment isn't in these formulas, but prednisone increases the risk as well.

Introduction: Advanced Treatment Topics

This is an in-depth look at some treatment topics. We're going to look at hydroxychloroquine including data on retinopathy. We'll look at vitamin D, we'll look at immunosuppressive drugs, and we'll look at the belimumab clinical trials and some brand new data as well.

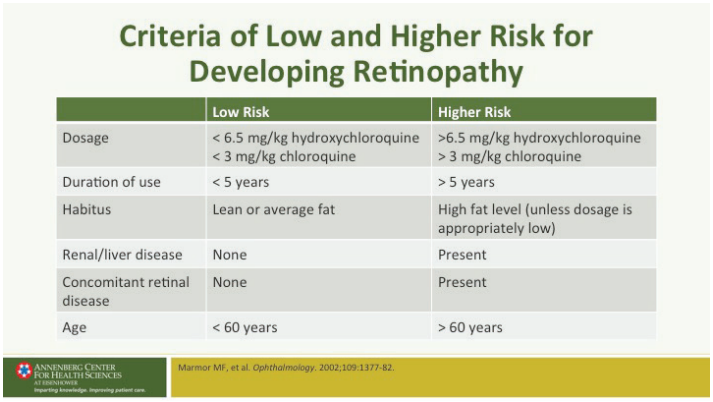
Here are my disclosures. I wanted to start with immunomodulators. Immunomodulators means something that changes the immune system, but without suppressing the immune system. I always want to emphasize these in our practice because these do not cause infection, and they don't increase the later risk of malignancy. There are at least 3 of these available to all of us. The one we all know about is hydroxychloroquine, but there's also vitamin D and DHEA, or prasterone.



Hydroxychloroquine and Retinopathy

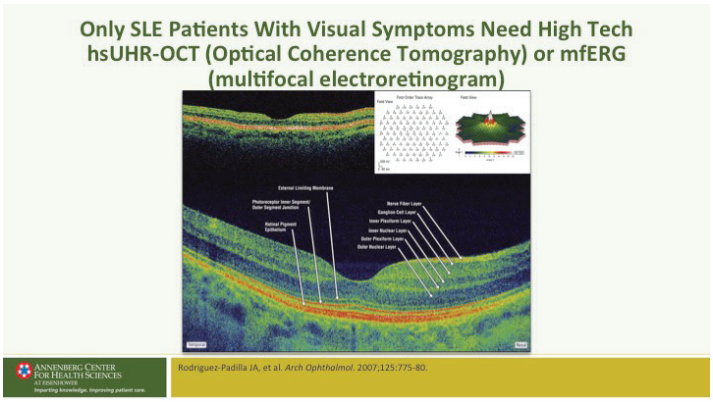
I would argue that hydroxychloroquine should be background therapy in nearly all lupus patients. Yes, there are a few who have allergic skin reactions to it, for example. There are some very rare patients that have a lot of GI toxicity, but the great majority of lupus patients should be on this medication from the time of diagnosis onwards, for so many reasons. So yes, it does help disease activity. In particular, it helps skin and joints. But it has a role as a long-term medication to prevent the long-term complications of lupus. We know, for example, that it can help to prevent organ damage, including renal damage. It has a very beneficial profile for cardiovascular risk factors, so it actually reduces LDL cholesterol. It can reduce the incidence of diabetes. Half of our lupus patients have antiphospholipid antibodies, and hydroxychloroquine reduces the risk of thrombosis. For our patients with renal lupus, it triples the complete remission rate on mycophenolate, and there are several studies that show improvement in survival. And I want to reiterate that. Hydroxychloroquine is our only medication that has been proven to extend survival.

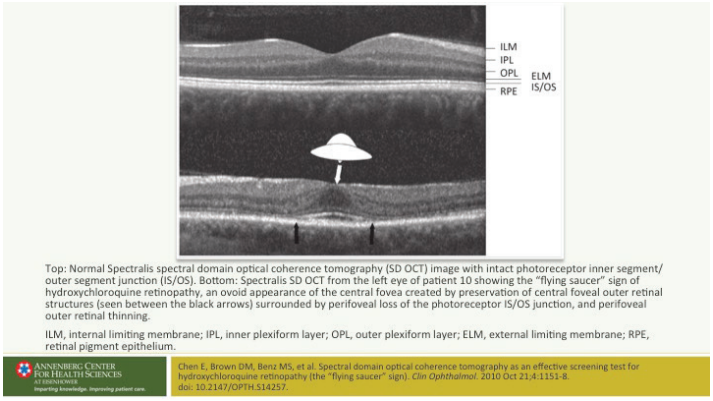
There has been concern about retinopathy and how we should monitor for retinopathy. We have used older guidelines, as shown on this slide, for some time. It is now recognized that retinopathy is more common after years of use than was recognized earlier. So, for example, in my cohort, after 16 years of use, 9% of my patients have retinopathy. The controversy is whether or not we should be reducing our dosing guidelines,



which currently are 6.5 mg per kg, although we always have to reduce the dose if there's renal insufficiency or hepatic problems, and we also reduce the dose in the elderly. It's not clear whether we should go with a 6.5 or 5 mg per kg. I, in fact, feel that in the future we will base our dosing on hydroxychloroquine blood levels. In other words, we will personalize it.

We do have good rules now on when and how to monitor. Here is an example of the monitoring tasks that's recommended. It's called the OCT or the Optical Coherence Tomogram, and it basically gives you a nice cross-section of the retina. In the parafoveal





Top: Normal Spectralis spectral domain optical coherence tomography (SD OCT) image with intact photoreceptor inner segment/outer segment junction (IS/OS). Bottom: Spectralis SD OCT from the left eye of patient 10 showing the "flying saucer" sign of hydroxychloroquine retinopathy, an ovoid appearance of the central fovea created by preservation of central foveal outer retinal structures (seen between the black arrows) surrounded by perifoveal loss of the photoreceptor IS/OS junction, and perifoveal outer retinal thinning.

ILM, internal limiting membrane; IPL, inner plexiform layer; OPL, outer plexiform layer; ELM, external limiting membrane; RPE, retinal pigment epithelium.

Chen E, Brown DM, Benz MS, et al. Spectral domain optical coherence tomography as an effective screening test for hydroxychloroquine retinopathy (the "flying saucer" sign). *Clin Ophthalmol*. 2010 Oct 21;4:1151-8. doi: 10.2147/OPTH.S14257.

region there should that nice dip that you see on the top. Now, with hydroxychloroquine retinopathy, the dip is gone. Instead of the dip you see what looks like a flying saucer in the retina. I've always thought this part was fun, that ophthalmologists have a sense of humor. But of course, it's not good if you have the flying saucer sign.

How often do we need to check? We should check it at baseline, and then the guidelines say to check it at 5 years, and then after 5 years we should check yearly. Now our problem is it's not always easy to interpret these retina studies, and so, for example, in the OCT, if the patient had lupus nephritis and was on high-dosed prednisone, they might have had a retinal problem called central serous retinopathy, or CSR for short. When this is very bad, by the way, the patient loses vision, and we have to reduce the prednisone to regain their vision. This changes the OCT forever, and so we need the ophthalmologist and the rheumatologist to be very careful before we ascribe all OCT abnormalities to hydroxychloroquine.

And there are more sensitive tests than OCT, such as the ERG, but the problem with that one is that it's abnormal in anybody who has a cataract. And of course, some of our patients are getting older, they will have macular degeneration that's going to affect these tests. So, the ophthalmologist needs to be an expert in hydroxychloroquine retinopathy.

I want you to know that patients do not go blind from hydroxychloroquine. I think as rheumatologists, we need to stop the fear of hydroxychloroquine. This is a medication that's been around since World War II. Nothing has changed. I don't have any blind patients from hydroxychloroquine. So, I think we need to follow the guidelines for the amount of monitoring, but let's be very careful and not be so afraid of this medication that our patient begins to fear the only medication that's going to extend her survival.

Vitamin D

I've been very interested in vitamin D as an immunomodulator. There are so many studies now of vitamin D and lupus. I did the very large cohort study, but there's also now a randomized clinical trial proving that vitamin D supplementation reduces lupus disease activity.

Low Vitamin D in SLE

Author & Year	Design	N	Location	Regimen	Outcome	Result
Ruiz-Irastorza 2010	Longitudinal Observational	80	Spain	600-800iu/day 24 months	SLEDAI SDI Fatigue (VAS)	Fatigue: VAS, 4.1 vs 3.3 P=0.015. SLEDAI: No effect SDI: No effect
Terrier 2012	Open-label	20	France	100,000iu/week 4/52 then 100,000/ month for x 6/12	Safety SLEDAI B cells T cells Cytokines	SLEDAI: non-significant. Anti dsDNA: Decreased at 2 and 6 months. CD4: Non significant increase CD*: Decreased in frequency but not in number. T regs: Increased
Petri 2013	Longitudinal cohort	1006	USA (37% AA)	50,000 iu/week + 400iu calcium/ vitamin D/day	SLEDAI Physician global (0-3) UPCR	SLEDAI: Significant decrease. Physician global: Improved significantly UPCR: 20 ng/ml increase in the 25(OH)D value was associated with a 4% decrease in UPCR
Abou-Raya 2013	Randomized Placebo-controlled	267	Egypt	2000iu daily/ placebo	SLEDAI	SLEDAI: Correlated negatively with vitamin D.
Andreoli 2015 Piantoni 2015	Randomized Unblinded	34	Italy	300,000 bolus, 50,000iu/month Vs 25,000iu/month	T cell and B cell populations SLE serology	Promotion of regulatory T cells Production of Th2 cytokines Serology: Unchanged
Arnow 2015	Randomized Double blind Placebo controlled	54	USA (54%AA)	2000iu, 4000iu / placebo	Interferon signature	No effect on interferon gene signature
Lima 2015	Randomized Double blind Placebo controlled	50	Brazil (Juvenile)	50,000iu/week Vs placebo	K-FSS SLEDAI ECLAM	SLEDAI: Improved (*P*=0.01) ECLAM: Improved (*P*=0.006)

What I've showed was that our goal for supplementing vitamin D should be to achieve a 25-hydroxy vitamin D level of 40 ng per mL. Just pay attention to the left-hand part of this slide. The right-hand part of the slide shows that getting higher than 40 ng per mL does not increase the benefit. So we can do this very safely and my cohorts study showed that achieving that 40 ng per mL goal meant a reduction in disease activity, and in particular a reduction in the urine protein.

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

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

Disease Measure	Slope over range of 0-40 ng/mL (95% CI)	*P*-value	Slope over range of ≥40 ng/mL (95% CI)	*P*-value
Physician's Global Assessment	–0.04 (–0.08, –0.01)	**0.026**	0.01 (–0.02, 0.04)	0.50
SELENA-SLEDAI	–0.22 (–0.41, –0.02)	**0.032**	0.12 (–0.01, 0.24)	0.065
Log Urinary Protein/Creatinine	–0.03 (–0.05, –0.02)	**0.0004**	–0.01 (–0.01, 0.00)	0.24

SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index.

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

How do we achieve this? I usually give 50,000 IU once a week, but in an overweight patient you're likely going to need 50,000 units twice a week. I do frequently check for adherence. If the patient stops taking it, her vitamin D level will plummet very quickly.

I've gotten interested in vitamin D not just as an immunomodulator. It turns out that vitamin D might

be antifibrotic. Antifibrotic in the lung, but also in the kidney. I think there's going to be greater interest in vitamin D as the years go by for many reasons (other) than lupus.

In addition to its antifibrotic role, vitamin D likely has cardiovascular hematologic benefits as well. For example, in our lupus cohort, we've been able to show that vitamin D helps to lower blood pressure, systolic blood pressure. But there's so many studies of the benefit of vitamin D in reducing thrombosis, and this actually includes a randomized clinical trial that was done in cancer.

Any Thrombotic Event

	Any Thrombotic Event		No Thrombotic Event		
	Mean (SD)	N (%)	Mean (SD)	N (%)	*P*-value
Vitamin D (ng/ml) (Mean/SD)	27.6 (15.1)		30.6 (14.6)		0.0008
Vitamin D < 40 ng/ml (N/ %)		299 (80.4)		759 (75.4)	0.064

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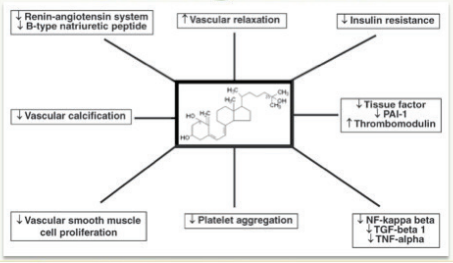
Vitamin D May Have Cardiovascular and Hematologic Benefits



Targher G, et al. *Semin Thromb Hemostasis*. 2012;38:114-124.

Annenberg Center for Health Sciences at Eisenhower

Low Vitamin D Is NOT Associated With Arterial Events

	Arterial Thrombosis		No Arterial Thrombosis		
	Mean (SD)	N (%)	Mean (SD)	N (%)	*P*-value
Stroke					
Vitamin D (ng/ml) (Mean/SD)	28.9 (15.2)		29.9 (14.7)		0.5408
Vitamin D < 40 ng/ml (N/ %)		79 (75.2)		988 (76.9)	0.7914
Myocardial Infarction (MI)					
	Mean (SD)	N (%)	Mean (SD)	N (%)	
Vitamin D (ng/ml) (Mean/SD)	30.2 (16.9)		29.8 (14.7)		0.883
Vitamin D < 40 ng/ml (N/ %)		35 (70)		1032 (77)	0.3258

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We know that vitamin D likely has a benefit in patients with antiphospholipid antibodies. It actually reduces tissue factor expression. Tissue factor, as you remember from medical school, starts out the coagulation cascade. Vitamin D tends to be lower in patients with antiphospholipid antibodies, and lower in those who have had a thrombotic event. But this is something easy we can do. Now, remember, hydroxychloroquine also reduces thrombosis. So here, if we have our lupus patient on both hydroxychloroquine and vitamin D, we have her on 2 very safe therapies that will help to prevent thrombosis.

We asked whether low vitamin D was associated with thrombosis in my lupus patients and we adjusted for the lupus anticoagulant, that antiphospholipid antibody that is so strongly associated. And again, you know, these are always very large studies when you're involved with my cohorts, so in this study we had over 1,300 patients. And what we were able to show is that having a low vitamin D was associated with having more thrombotic events.

What's very interesting (is) the difference. It's not going to be that helpful for arterial events. It's going to be helpful in preventing venous thrombosis. I don't want you ever to think that lupus is simple, and that's why

Low Vitamin D Is NOT Associated With Venous Thrombosis

	Venous Thrombosis		No Venous Thrombosis		
	Mean (SD)	N (%)	Mean (SD)	N (%)	*P*-value
Deep Vein Thrombosis					
Vitamin D (ng/ml) (Mean/SD)	25.9 (13.4)		30.4 (14.9)		<0.0001
Vitamin D < 40 ng/ml (N/ %)		171 (87.2)		895 (75)	0.0002

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we do these detailed analyses. We still need low-dose aspirin to prevent arterial events. Vitamin D is going to help on the venous side.

We adjusted for everything and still found that having a low vitamin D was associated with deep vein thrombosis. Remember, it's not associated with arterial. And then we looked prospectively. Now this is harder to do because most of my patients are on hydroxychloroquine. I don't see a lot of prospective thrombotic events. But even given the low numbers, we were still able to show an association. Low vitamin D predicts future thrombotic events.

After Adjustment (Race, Age, Sex, LAC) Low Vitamin D Is Still Associated with DVT

Dependent Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Any Thrombosis	1.33 (0.99,1.79)	1.36 (0.99,1.86)
Stroke	0.91 (0.58,1.45)	0.92 (0.57,1.48)
Myocardial Infarction	0.7 (0.38,1.29)	0.8 (0.42,1.53)
Deep Vein Thrombosis	2.28 (1.47,3.54)	2.31 (1.47,3.65)

So to conclude this part, low vitamin D was associated with deep vein thrombosis but not arterial. What we're thinking about in the future is that to prevent thrombosis we'll want vitamin D, we'll want hydroxychloroquine, but if we're going to prevent arterial thrombosis, I think we're still going to need low-dose aspirin on board.

Prospective Analysis
(Excluding Thrombosis Before the First Vitamin D Measure)

Hazard Ratio (Any Thrombosis) =

1.75 (1.04, 3.92)

after adjustment for race, age, sex

Introduction: Clinical Trials in SLE

Now we are going to review clinical trials for several lupus treatments. We have several compounds that are in late stage testing, but we have some that are in earlier stages of testing, and I'll go over the results and also the mechanisms involved.

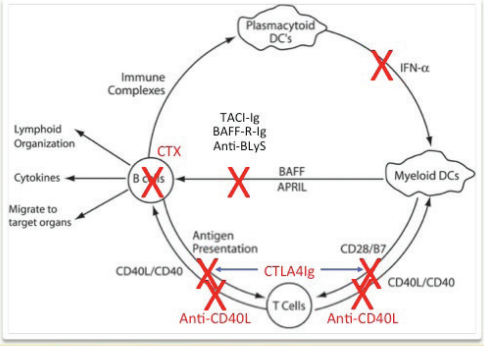
Here are my faculty disclosures. Lupus is complex, but don't panic. I call this Immunology 101. Let's start at the top. In lupus patients the plasmacytoid dendritic cells are making too much interferon and this happens in about 50% of our patients. It's called the interferon gene signature and it has consequences. When there is more interferon there is going to be more activation of the myeloid dendritic cells and these are important for 2 reasons. They make BLyS, the B-lymphocyte stimulator factor or BAFF is its other name, and this is what keeps B cells alive. It's sort of a survival factor, but also myeloid dendritic cells present self-antigen into the T cells and of course we know in lupus there's too much T helper,

Faculty Disclosures

Dr. Petri discloses the following:

Consultant: GSK, Merck EMD Serono, Lilly, Janssen, Amgen, Novartis, Quintiles, Exagen, Inova Diagnostics, AstraZeneca, and the Annenberg Center for Health Sciences

Dr. Petri will reference treatments for SLE that are not FDA approved.



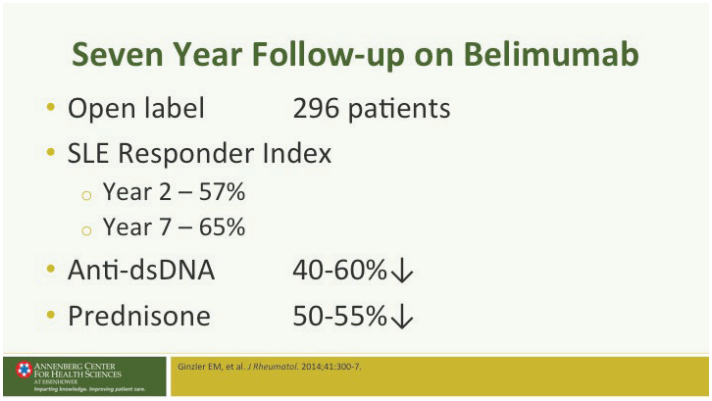
Ramanujam M, Davidson A. *Arthritis Res Ther*. 2004. 6:197-202.

there's not enough T regs and so now the T cells are going to activate the B cells, and the B cells, by making autoantibodies, will end up with a formation of immune complexes that can now activate the plasmacytoid dendritic cells. We put this circle around and this circle is a feed-forward loop so it's going to keep going around.

I like to think of this as an equal opportunity slide. There's so many different places where we could break this cycle, and perhaps we need to personalize it. Perhaps in some patients, breaking the cycle at one point is more important or more effective than breaking it at another. So I think someday, before we start any new treatment, we'll have some simple genetic/proteomic test that will tell us which biologic or which small oral molecule to pick.

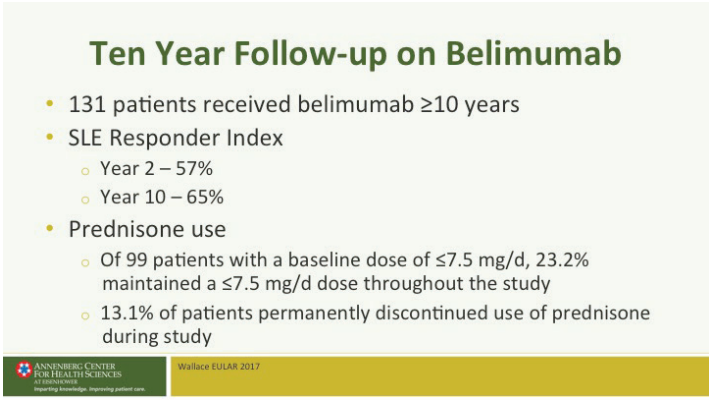
Belimumab: Long-term Follow-up

We have 1 approved biologic for lupus, belimumab. What belimumab does is it blocks BLyS or BAFF. We do have wonderful long-term safety studies, but the safety studies are also instructive, in that they tell us something about durability and efficacy. The first long-term safety study published was the open label follow-up after the



phase 2 and phase 3 clinical trials. And in this 7-year, follow-up study, it showed great durability, and in terms of the SLE responder index, the durability was incredibly good. It wasn't that there was any tachyphylaxis. There was reduction in serologies and reduction in prednisone use, and no new safety signals.

We can go even further than that because we now have the 10-year follow-up study of the patients who were in the phase 2 and phase 3 trials. And again, almost identical data on the durability in terms of the SLE responder index, and even more information on being able to taper prednisone.

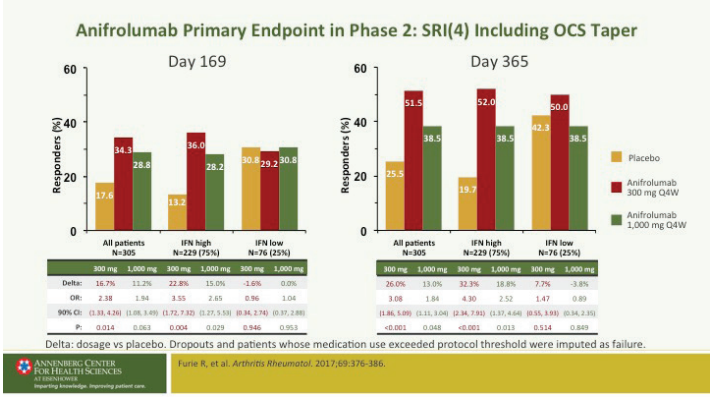


When the belimumab studies were first published—the phase 3 trials—there weren't a lot of African American patients in the 2 phase 3 trials, and there was some question about whether it had benefit in African Americans. Actually, in the phase 2 trial, African Americans did particularly well. But we now have many more data from both investigator-initiated and GSK-initiated studies that show benefit in African Americans.

In particular, we know from an investigator-initiated study from the Toronto cohort that comparing patients from the belimumab trial from similar patients from the Toronto cohort, the patients in the belimumab trials had less accrual of organ damage. Ultimately, we want many things from new treatments for lupus. We want a reduction in disease activity, but we want a reduction in prednisone and a reduction in organ damage as well. So, I think this Toronto study is particularly informative for that reason.

Targeting IFN-a

Another potential target are those patients that have the interferon gene signature. In clinical practice it's probably about 50%, but here in the ILLUMINATE trial you can see it's even higher, I think, of course, because our randomized clinical trials are enrolling sicker patients than we see in our clinical practice.



In the anifrolumab phase 2 trial, there was great efficacy of the anti-interferon alpha receptor blocker, and in fact, you see that this efficacy, the delta, was shown in those patients that had the interferon gene signature. As expected, there wasn't a delta vs standard of care in patients who did not have the interferon alpha gene signature. This was a very strong phase 2 trial because it required not just a reduction in the SRI, but a reduction in the steroid dose for the patient to be considered a responder. Unfortunately, there's been a major shock in that the first of the 2 phase 3 trials of anifrolumab has been reported to be negative. We'll have to wait for the second trial and for subanalyses to try to figure out how, when there was such a positive phase 2, the phase 3 was negative.

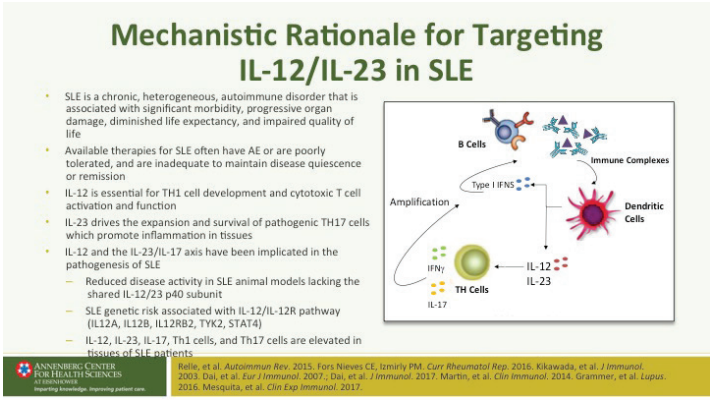
Other Investigational Treatments

We have many other targets, so what produces the majority of our antibodies in our lupus patients are the plasma cells. And of course, we do know how to target plasma cells. That's what we do in multiple myeloma.

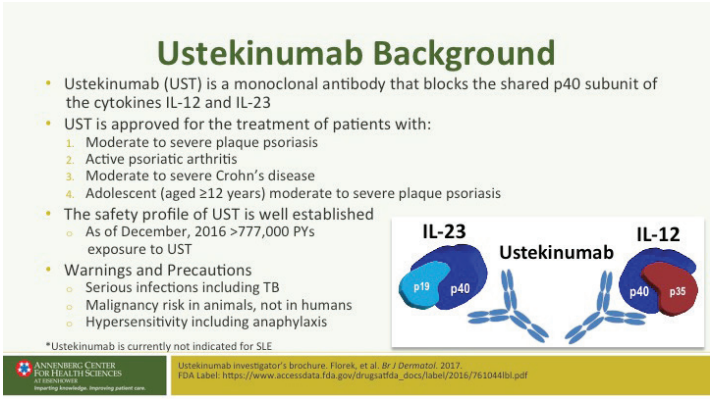
Investigators in Europe have been brave enough to study bortezomib in lupus and did find efficacy. Now there are newer generation drugs that target plasma cells. The reason that we haven't all jumped on board to do this is because bortezomib, for example, has major toxicity, including things like neuropathy.

Targeting Interleukin

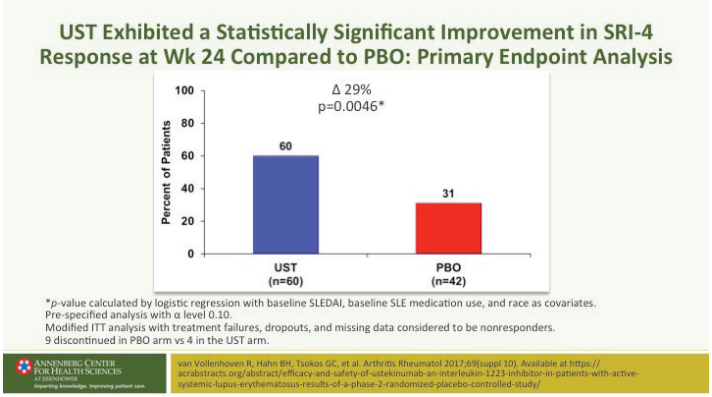
There are some brand new studies that I think you'll find fascinating, because we wouldn't have normally thought about these for lupus. And the first one we are going to talk about is interleukin-12/interleukin-23 as targets in lupus, and these are important because these are T cell targets. And you'll remember from my Immunology 101, there's absolutely no doubt that T cells are very important in lupus for many reasons and many subtypes of T cells.



How do we target interleukin-12/interleukin-23 with a drug that's already available? We can do that with ustekinumab. Most rheumatologists have a comfort level with ustekinumab because our psoriasis patients, our inflammatory bowel disease patients, have been on it. We understand it, we know it's safe, we know its profile, we know its dosing.



It turns out that ustekinumab worked in a phase 2 trial for lupus and it worked quite well. It's really quite a dramatic effect over standard of care with a very large delta. Now remember we've gotten a little scared about phase 2 trials in lupus. They don't always translate into successful phase 3s but our hope is, of course, that ustekinumab will.



Ustekinumab also prevented lupus flares. What's particularly important also, is that it's not enough to just control disease activity. You and I want to prevent flares as well. And it also improves serologies. Now we would never pick a treatment just to improve serologies, but if it also improves serologies, it may also help to prevent cardiovascular lupus where accelerated arthrosclerosis is highly associated with low C3.

There's a JAK inhibitor that's been successfully tested for lupus in a phase 2, and that's baricitimib. Baricitimib of course is also FDA approved for rheumatoid arthritis. We understand its mechanism of action, and in the phase 2 trial of lupus it helped joints. There may not have been enough very severe skin patients to identify benefit for skin.

There are some studies that are being done of new treatments for lupus that haven't reached the level of a randomized clinical trial, or not yet. And one that I think is quite interesting is mesenchymal stem cells. This is predominantly been studied in China, but there's now going to be a clinical trial in the US as well. Mesenchymal stem cells may actually help T regs. So, there may be many reasons why they could have benefit in lupus.

Another fascinating approach to lupus, which again, is not to immunosuppress, is the idea of using low-dose interleukin-2. Low-dose interleukin-2 increases T regs. I love this idea because it would allow the immune system to police itself. Now of course there's a narrow

window here. You don't want too much interleukin-2, so you have to be within that window, but this has been tested in investigator-initiated studies in Europe and in China. Seems to have worked well with very little toxicity, so this is now going to be a focus of several pharmaceutical companies.

El Greco – *Saint Sebastian* (©Museo Nacional del Prado)

Conclusion

I wanted to end this presentation with this photograph of a painting by El Greco of St. Sebastian. I want you to pay attention to all these arrows because our problem in lupus is that our patients usually don't die of active lupus. One of those arrows is active lupus but the patient is going to die from all the other comorbidities. The accelerated atherosclerosis is to be increased by the prednisone. The infections, the end stage renal disease, all the prednisone complications. So, our goal with new treatments is that they must reduce lupus activity, but they must also allow us to reduce prednisone, and they'd better not significantly increase infections because that would be a trade-off that would be unacceptable in clinical care. So, a very high barrier, right? We're very demanding of randomized clinical trials in lupus, but for good reason, because every single lupus patient is a precious human being.