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Sjögren's Myth Busters: Can You Detect Fact from Fiction on Emerging Therapies?

Announcer:
Welcome to CME on ReachMD. This activity, titled "Sjögren's Myth Busters: Can You Detect Fact from Fiction on Emerging Therapies?" is provided by Clinical Care Options, LLC dba Decera Clinical Education in partnership with Smart Patients.

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Dr. Johr:
We are learning more and more about what causes Sjögren's. One thing that seems clear is the salivary gland epithelium, which you see in the bottom left-hand corner there, those two healthy-looking cells, if you look to the right, there is a lot of cells that look haggard and unhappy. We know the salivary gland epithelial cells are not the victims here, but also part of the whole crime scene. They are contributing to the problems as well as being part of what is being damaged.

It is thought that there is a microbial trigger, as you can see on the left side there. As you go left to right, you can see there is type 1 interferon production from the epithelial cells. There is also release of autoantigens and nucleic acids. There is also upregulation of MHC, which we would not normally see in this type of cell. It is upregulated as these cells are more immunologically active.

All of this contributes to auto-reactivity with B and T cells. As you see up here, B cells get activated, releasing autoantibodies. We have autoantibodies like SSA, we have B cells, plasma cells, T cells invading the epithelium, causing inflammation. That is what we will see in lip biopsy samples.

We have damage and release of different materials, which together can form immune complexes between the antibodies and antigens. Dendritic cells can then release interferon, sensing these immune complexes, which continues the whole cascade around and around and around.

Myth 1: Sjögren's Disease Is Just Dryness

A lot of patients are told this by their providers. They get very upset by this because we know Sjögren's is so much more than dryness. Of course, Sjögren's is an autoimmune disorder. It affects the exocrine glands, but it can affect so much more. The main symptoms are dry mouth and dry eye. Common symptoms also include fatigue, aches and pains, amongst others.

We know that Sjögren's can occur alone, but it can also be seen with other autoimmune conditions. About a third of lupus patients may have Sjögren's. Maybe about a tenth of rheumatoid arthritis patients have Sjögren's. You can see it in scleroderma, primary biliary cholangitis, and others.

Systemic Symptoms of Sjögren's Disease

Sjögren's is so much more than dryness, as you can see here with this next slide. Many different organ systems can be involved. You can have musculoskeletal system. About two-thirds of patients can have joint and muscle involvement. Then you see the skin. People can have Raynaud's, various types of vasculitis or other rashes.

Next, you can see neurologic. About two-thirds of patients with Sjögren's have symptoms suggesting neuropathy. Many patients have numbness, tingling, other symptoms. Up to 50% of patients, according to some studies, have symptoms suggestive of autonomic neuropathy. I certainly believe that. I see that in a large percentage of my patients.

Next, you see renal. Patients with Sjögren's can have type 1 renal tubular acidosis. You can look for patients with hypokalemia or low bicarbonate level, can also have glomerulonephritis in some cases.

Hematologic, a lot of patients with Sjögren's have cytopenias or other abnormalities in the blood, like with complement and others.

Pulmonary, airways disease is seen in about half of patients with Sjögren's. ILD is seen in about 20% of patients with Sjögren's. Cysts are commonly seen on CAT scan of patients with Sjögren's.

The GI system is very commonly affected in Sjögren's. Autoimmune stuff in the GI tract includes autoimmune hepatitis in a small percentage. Primary biliary cholangitis in about 5% or less. You can also see dysautonomia and problems with motility as pretty widespread in my Sjögren's patients.

Cardiovascularly, people with Sjögren's are at increased risk of coronary artery disease. More recent studies show their increased risk for arrhythmias and other cardiac issues. I used to think that Sjögren's pretty much spared the heart, but now it seems pretty clear it does affect the heart as well.

Myth 2: Sjögren's Disease Is a Mild "Syndrome"

Sjögren's is not just dryness; it really affects every organ system. It is also not just some mild syndrome. A lot of people think of it as something like fibromyalgia syndrome, Sjögren's syndrome, no big deal. It has really profound effects on patients, as you can see here.

Mental health, 80% of patients say their disease causes significant emotional burden.

For home life, 76% report stopping or cutting back on housework.

Cognition, 80% report experiencing brain fog as a symptom. I see this all day long.

Financial health, about two-thirds say their disease imposes significant financial burden.

Work life, 64% said they have to make changes at work.

Then 33% report that their disease affects their ability to enjoy food. Really not fun.

Risk Factors for Lymphoma in Sjögren's Disease

Patients with Sjögren's are at increased risk of developing lymphoma. About 1 in 10 to 1 in 20 patients with Sjögren's eventually develop lymphoma. This is a 20-fold increased risk compared to the general population. This slide shows a predictive score for non-Hodgkin's lymphoma, which was published about 10 years ago. The takeaway here is if you have three or more of the risk factors you see in the bottom left, the risk for non-Hodgkin's lymphoma goes up significantly between having a positive SSA, positive rheumatoid factor, salivary gland enlargement, lymphadenopathy, Raynaud's, monoclonal gammopathy, and C4 hypocomplementemia.

Risk Factors for Mortality

Mainly the lymphoma - again, 5 to 10% lifetime risk, and ILD. ILD affects about 20% of patients with Sjögren's. Almost 60% of deaths are attributable to comorbidities.

Smart Patients Focus Group: Patient Insights

If you ask patients, they know what is going on here, and they feel sometimes providers are in the dark. If we look at the key takeaways here on the right in red, patients frequently described long diagnostic journeys accompanied by uncertainty, dismissal of symptoms, emotional distress. Patients reported difficulty with having their non-dryness-related symptoms recognized and validated. A lot of times, people feel like their symptoms are not taken seriously. Patients express variable levels of trust that depended on whether their healthcare providers acknowledged their uncertainty and invited questions about care options.

Myth 3: Sjögren's Disease Only Affects Middle-Aged Women

Myth number three is that Sjögren's disease only affects middle-aged women. We know Sjögren's affects 1 to 4 million people in the United States. Women are at least nine times more likely than men to have Sjögren's. I do have men with Sjögren's in my panel, but far more women. Men may be more likely to have higher disease activity, higher constitutional symptoms, lymphadenopathy, pulmonary, and liver involvement. ILD is something we really need to look for in the men with Sjögren's.

Average age at diagnosis for Sjögren's is mainly people in their 50s. It is often misdiagnosed and underdiagnosed. I see this all day long. In part, this is because it requires multiple specialists to diagnose. I do not know about you, but I cannot use a slit lamp, so I cannot do an ocular staining score. I can do a Schirmer test, but ocular staining score is actually more sensitive. Schirmer can be totally normal, ocular staining score can be very abnormal, indicating dryness.

Also, I do not do lip biopsies. There are some rheumatologists who do this here in the United States, but they are few and far between. Most of us have to rely on an ENT specialist or some other oral specialist to obtain a minor salivary gland biopsy.

The average time to diagnosis is about three years. Men and children may experience longer delays due to misconceptions and missed symptoms.

Atypical Presentations of Sjögren's Disease

There are atypical presentations and some heterogeneity in racial minority populations. People with African ancestry demonstrate more hypergammaglobulinemia, increased Erythrocyte Sedimentation Rate, and parotid enlargement. Native Americans show lower rates of abnormal tear and saliva production and greater disease activity.

Comorbid Autoimmune Conditions

There is comorbid conditions, some of which are autoimmune. In the survey of over 3000 patients by a Harris Poll that was shepherded by the Sjögren's Foundation, more than 80% had at least one ocular, oral, or nervous system-related comorbidity. Seventy percent had more than one other comorbid autoimmune condition.

They did not talk to us when they put this together. Most of us do not consider fibromyalgia an autoimmune condition per se, but it is a comorbid condition. It is common in our Sjögren's patients as well as rheumatoid, Hashimoto's, and others.

When I see people with fibromyalgia with a positive rheumatoid factor or fibromyalgia with a positive ANA, I think Sjögren's. Certainly, if someone has Hashimoto's or a family history of autoimmune disease, I am concerned for Sjögren's.

Posttest 1

A 52-year-old woman with Sjögren's disease reports persistent fatigue, widespread pain, difficulty concentrating despite stable sicca symptoms. She is concerned that her disease is worsening. Which statement best reflects the burden the patient is experiencing?

A. Sjögren's disease is primarily limited to the salivary and lacrimal gland dysfunction;

B. Impacts on daily living and cognitive symptoms may reflect systemic Sjögren's;

C. These symptoms indicate a coexisting autoimmune condition; or

D. Extraglandular manifestations occur infrequently and usually late in the disease course.

Announcer:
Voting is open. Please vote. We will give a few more seconds for incoming replies. Thank you. We will close that poll and share the results.

Dr. Johr:
Very good. You guys know the answer. We are going to move on here. Impacts on daily living, cognitive symptoms may reflect systemic Sjögren's.

Posttest 1: Rationale

The rationale here is fatigue, chronic pain, and cognitive impairment are common, impactful features of Sjögren's disease. Fatigue is really the number one symptom that Sjögren's patients have that affects their quality of life. These symptoms reflect systemic immune dysregulation, significantly affect quality of life. Acknowledging this burden is important for patients, patient education, and validation. Totally true.

Screening and Diagnosis

Early diagnosis of Sjögren's is critical for symptom management and prevention of oral complications and lymphoma.

Wide spectrum of clinical presentations and high prevalence of atypical symptoms make the diagnosis challenging. This is so true. Sjögren's can present in so many different ways. If you see somebody with rheumatoid arthritis and they have fibromyalgia, strange numbness and tingling that does not make any sense, I think of Sjögren's. If you see someone with lupus who has some mild dryness,

but they have maybe some gland swelling, definitely think of Sjögren's. If you get a consult for somebody with strange neuropathy symptoms, the neurologist found a positive rheumatoid factor ANA, I think of Sjögren's, even without the SSA.

Healthcare providers may not inquire about dryness as a symptom. This is what throws a lot of people off. We know in the literature that subjective dryness and objective findings of dryness often do not correlate. I have had patients tell me that they have no dryness at all, and then I do a Schirmer test, and they literally did not make any tears. There is no wetness of the paper at all. I stick this Schirmer paper in your eye. If you have normal glands, that will get wet very quickly. Five minutes in this person's eye and there is no moisture at all. They did not complain of dry eye at all. The symptoms and the objective measures often do not go together, which is why it is really important to do objective testing on patients, even if they're not complaining, if you suspect the diagnosis. Patients may not know to mention dryness as a concern, they might not think it is relevant.

Salivary gland biopsy is often important for diagnosis. It is not always needed in clinical practice, but often needed for a definitive diagnosis. If you ask me, when do you order? When do you do a salivary gland biopsy? My simple answer is, if my suspicions for Sjögren's is high enough and the SSA is negative. That is my basic answer. There is a lot more nuance to it, but I imagine we will talk more about this later if people have more questions.

ACR/EULAR 2016 Classification Criteria for Sjögren's Disease

Of course, this is classification criteria. It is meant for trials. In the absence of diagnostic criteria, this is often used as, at least, a guidepost to help people with diagnosis. It is useful for that purpose. I may not use it strictly this way, but it is helpful. What you see here is to be classified as a Sjögren's patient. You need a score of at least four. The bottom three criteria are all about dryness.

I explain to patients that having dryness alone does not mean you have Sjögren's. There is so many reasons why you might have dry eye or dry mouth. It does not mean that it is an autoimmune disease. We need evidence of autoimmunity. In terms of classification criteria, the strict evidence of autoimmunity is a positive SSA or a lip biopsy with a focus score of one or more. If you have one of those two pieces at the top and one of the pieces at the bottom, then you meet classification for Sjögren's, and the diagnosis is pretty sound.

EULAR Sjögren's Syndrome Patient-Reported Index

How do we tell how active someone's Sjögren's is or how bad their Sjögren's is? This is very difficult to do. For studies, we look at the Sjögren's Syndrome Patient-Reported Index, which basically reports symptoms. How bad are your symptoms? This looks at the main symptoms of dryness, joint and muscle pain, and fatigue. Essentially, patients are asked on a scale of 1 to 10 for each of those, and then you come up with an average. If you have five dryness, ten joint pain, and zero fatigue, the score overall will be five. Greater than five, as you can see here, for the ESSPRI, is a high symptom activity, less than five is low symptoms, less than three is minimal. A change of one is considered statistically significant. What you want to see in studies, which we will look at later, is that the ESSPRI change at least by one point, which would indicate that the subjects or the participants in the study, their symptoms had some significant improvement.

EULAR Sjögren's Syndrome Disease Activity Index

Here we have the ESSDAI, which is the Sjögren's Syndrome Disease Activity Index. What this is trying to measure is systemic activity. The reason why there is two different measurements is because we know patients may have lots of symptoms, but may not have a lot of organ or systemic involvement. We are measuring both of these things concurrently. This is measuring the systemic involvement.

You can see there is a bunch of different domains here. Constitutional — that is basically asking people, have you lost weight? Do you have night sweats, any unexplained fevers? Lymphadenopathy, which you'll find on exam or imaging. Glandular abnormalities like parotid swelling. Articular involvement, like synovitis or significant arthralgias with significant stiffness. Cutaneous — it is hard to find this, but these are significant rashes like purpura or subacute cutaneous lupus. Pulmonary — do you have any PFT findings or imaging findings consistent with ILD? Renal — do you have any findings consistent with tubulo-interstitial nephritis, etc.? Muscular — do you have elevated CK or EMG that is positive? Peripheral nervous system — do you have EMG findings consistent with neuropathy and others? Central nervous system, which is rare to score, that is for people who have optic neuritis, transverse myelitis, or something of that nature. Hematologic is common for my patients to score here. People who have anemia, chronic disease, for instance, or mild thrombocytopenia. Biological domain is essentially looking at low complement scores, hypergammaglobulinemia, cryoglobulins.

If we look here at the bottom, an ESSDAI score of less than five is considered low disease activity. We have maybe something like 2000-plus patients in our cohort here at Pennsylvania. Our average ESSDAI score is two or something like that. Low disease activity is pretty much the norm. If you look at the average ESSPRI, I do not know what it is, but I imagine it is above five. Patients may have lots of symptoms, but they may not have systemic involvement. It is all that significant. A score between 5 and 13 is moderate, and a score above 13-14 is high disease activity.

What is important is a change of at least three points is minimal response to treatment from a clinical standpoint. Later, when we look at some of these trials, you want to keep this in mind. Do they have an improvement of the ESSDAI of at least three points? That would be considered clinically significant improvement. That is quite a bit because if your score is six, then you have moderate disease activity, and it improves by three, now you are down at low disease activity, and that is pretty good.

Systemic Domains Outside of ESSDAI Domains

This is basically showing you that patients with Sjögren's have a whole lot potentially going on. Not everything is measured in the ESSDAI. There is a lot of patients online who are really mad about this. I am not quite sure exactly how accurate this is. It depends on how you measure it. For instance, in the bottom right here, you see dysautonomia. Dysautonomia is hard to measure. According to some studies, patients with Sjögren's, if you ask them a dysautonomia questionnaire, like a compass with 40 questions, about half of patients with Sjögren's qualify for dysautonomia, at least, based on the subjective questions. Dysautonomia is a lot more common in Sjögren's than this. That is why a lot of patients get mad at me because I tell them that, according to their ESSDAI, their disease activity is low, but they feel very terrible, and they're dizzy, and they're passing out, and all kinds of problems. Same with small-fiber neuropathy in the corner there; 0.8% is really an underestimation. It is probably more like 10%+ of patients with Sjögren's have small-fiber neuropathy. It is just not measured here by the ESSDAI. We move on.

Diagnostic Ultrasound

People are often curious about ultrasound. A lot of folks use ultrasound in lieu of a minor salivary gland biopsy for diagnosis, especially when the SSA is negative, SSB is negative. So, ultrasound can be helpful. It is useful to have the radiologist report OMERACT score. We have asked this of our radiologists over the past few years, and now they have trained themselves to do this and do this routinely. It is quite helpful.

Essentially, looking at the parenchyma, you can see the parenchyma here has some of these black circles in it. These are anechoic areas. This is what we are looking for in Sjögren's. This is what we see. A score of zero is normal parenchyma. Everything looks smooth and homogeneous. A score of one is some inhomogeneity, but there is no anechoic areas. There is none of these pockmarks. A score of two is you have some of these. A score of three is that these are widespread and diffuse. Two and three is associated. It can be helpful for the diagnosis of Sjögren's.

For instance, I saw someone just yesterday who's had over 10 years of dryness, dry eye, dry mouth, SSA is negative. She is convinced she has Sjögren's. I had her go for an ultrasound, and the score was zero. Hard for me to imagine that her dryness after so long is from Sjögren's. There is really no changes in the anatomy that we typically see in Sjögren's if she's really that severely dry. I do not know if a lip biopsy would be all that helpful in that patient. On the flip side, it could be. I have seen patients who have a normal ultrasound and do have a positive lip biopsy. Of course, for that patient having dryness for that long, I would not expect it. Certainly, people who have symptoms for just a year or two. Having a negative ultrasound in my mind does not rule out Sjögren's. Maybe just has not had enough time to have significant changes. I have at least 10 or 20 patients with zero and one changes on ultrasound, but a lip biopsy that is positive.

Round 2: Emerging Therapies for Sjögren's Disease.

Myth Busters 3

Which statement is true regarding symptom-based management of Sjögren's disease in clinical practice?

A. Symptom-directed therapies may improve dryness but may have limited impact on other systemic complaints;

B. Persistent symptoms are more often related to comorbid conditions than to ongoing Sjögren's disease activity;

C. Optimizing topical and supportive measures leads to sustained improvement across most symptom domains.

Announcer:
Polling is open. Please vote. We will give a few more seconds for incoming replies. Thank you. We will go ahead and close that poll and share the results.

Dr. Johr:
We got a mix here. Symptom-directed therapies may improve dryness, but may have limited impact on other systemic complaints. That is how I see it there.

Myth Busters 4

Which statement is true regarding emerging therapies for Sjögren's disease?

A. Quality of life benefits observed with emerging therapies are driven by improvement of sicca symptoms.

B. Persistent symptoms are more often related to comorbid conditions than to ongoing Sjögren's disease activity; or

C. Improvements in objective disease activity translate into parallel improvements in quality of life.

Speaker:
Polling is open. Please vote. We will give a few more seconds for incoming replies. We will go ahead and close that poll and share.

Dr. Johr:
Improvements in objective disease activity translate into parallel improvements in quality of life. Okay. A lot of you were with me there.

2020 EULAR Recommendations for Sjögren's Disease Management

Let us move on. Now we have the EULAR Recommendations for Sjögren's Disease Management. I like this paper. There is a lot of nice figures in there that are useful. They mentioned that patients with Sjögren's should be managed using a multidisciplinary approach. That is certainly very true. Patients have lots of problems with lots of different organ systems involved. It is helpful to have different specialists assist in caring for the patient.

In blue here, first therapeutic approach for dryness is symptomatic relief: artificial tears, ocular gels and ointments, saliva production stimulators or artificial saliva. Severe ocular dryness can be managed with immunosuppressive drops or autologous serum eye drops. I wonder how many of you have patients who have serum eye drops made from their own serum. Analgesics/pain management agents for musculoskeletal pain.

In black here, we see systemic therapies may be considered for treatment of active systemic disease. Steroids should be kept at the minimum, which is pretty common for us in our diseases. Immunosuppressive agents, there is no evidence to support one over the other. That may have been true in 2020. There might be some evidence to suggest one might be better than another, but overall, that is still pretty true.

B-cell targeted therapies can be considered for severe refractory systemic disease. We know that the B cells play a huge role in Sjögren's with antibodies, etc., and lymphocyte infiltration in different tissues. It makes sense that B-cell targeted therapies should be helpful for Sjögren's.

Myth 4: Symptom Management Is the Only Approach for Sjögren's Disease.

This slide is showing how things perhaps were in the past or have been using biologics early on is rarely done, at least back here in 2017. Perhaps that is going to change.

Hydroxychloroquine for Primary Sjögren's Disease

Let us look at other therapies for Sjögren's. Hydroxychloroquine is prescribed for nearly 50% of patients. Certainly, I offer it for majority of my patients. Even though the JOQUER trial - many of you may know JOQUER trial is a randomized controlled trial that showed no improvement in Sjögren's symptoms. The endpoint was a little funny. They looked at 30% increase from week 0 to 24 in two of three scores of dryness, pain, and fatigue. They looked at a really breadth of different Sjögren's patients, part of the literature that is complicated, as patients with Sjögren's in some of these studies really, really broad. There was a sub-study looking at just patients who had a high symptom burden, and they seem to improve from hydroxychloroquine. Maybe some patients that improve, others that do not. Here, we just looked at such a large group of patients that it did not come out in the wash here.

Then they mentioned the RepurpSS-I trial in 2020 which, as far as I know, is the first randomized controlled trial in Sjögren's to have a positive outcome - found a significant clinical response when hydroxychloroquine was combined with leflunomide, which is why I say what I said in the previous slide that there is no data to show why one medication may be better than another. You could argue here leflunomide, along with hydroxychloroquine, showed some improvement, so perhaps you might add leflunomide to hydroxychloroquine if hydroxychloroquine alone is not working. You could argue that here, based on this data.

New disease-modifying agents are still needed, which is very true.

Posttest 2

A 46-year-old woman with Sjögren's disease presents with a history of dry eye and dry mouth despite regular use of artificial tears. Over the past three months, she has also noted swelling of the parotid glands, fatigue, and arthralgias. What can you tell the patient to explain her symptoms?

A. Symptom-directed therapies may improve dryness but often do not address systemic disease burdens;

B. Supportive care resolves both glandular and extraglandular symptoms when used consistently;

C. That fatigue and arthralgias may indicate an associated autoimmune condition; and

D. Systemic symptoms will dissipate once glandular dryness is stabilized.

Announcer:
Polling is open. Please vote. We will give a few more seconds for incoming replies. We will go ahead and close that poll and share.

Dr. Johr:
Looks like you know the answer. Very good.

Posttest 2: Rationale

Topical supportive therapies can relieve sicca symptoms. Many patients continue to experience fatigue, pain. Systemic manifestations significantly affect quality of life. This highlights the unmet treatment need beyond dryness-focused management. Broader therapeutic strategies are needed to address systemic disease burden. True.

Myth 5: Disease-Modifying Therapies for Sjögren's Disease Have Failed in Clinical Trials

We are going to talk about those in red here. You can see in the upper left corner, telitacicept and ianalumab both affecting the B cell, affecting BAFF-R and APRIL. In the middle here, dazodalibep affecting the interaction between B cells and T cells. At the bottom here, deucravacitinib, a JAK inhibitor, inhibiting TYK2. In the bottom right, the FcRn inhibitor, nipocalimab, which affects IgG recycling, lowering IgG levels.

NEPTUNUS-1/2: Ianalumab (BAFF-R Inhibitor) in Patients with Primary Sjögren's Disease

We are going to look at these trials, starting with NEPTUNUS-1 and 2. This is looking at ianalumab, which is essentially blocking the BAFF receptor. Most of us are familiar with belimumab, which blocks BAFF, and rituximab which ends up destroying B cells. Interestingly, the ianalumab attacks the BAFF receptor, which blocks BAFF and winds up killing the B cells. I think of it as a combination of these two drugs. Pretty interesting, at least in theory.

This is an international double-blind, placebo-controlled, randomized phase III trials, NEPTUNUS-1 and 2, where they took patients with Sjögren's who had a positive SSA, who had some salivary flow, and who had an ESSDAI score. Remember, the ESSDAI is systemic involvement of greater than or equal to five across eight domains. You had to have at least moderate active disease and a positive SSA to be in this trial. You could have concurrent stable doses of hydroxychloroquine, methotrexate, etc.

What they did was they took the patients and looked at them. They gave them ianalumab 300mg subcutaneous monthly for 52 weeks or placebo monthly for 52 weeks. That was NEPTUNUS-1. In NEPTUNUS-2, they just had more patients, and they had a third arm, which was ianalumab every three months. There is a third arm. They looked at them, followed them up at weeks 48 and 52.

The primary endpoint was a change in the ESSDAI score at week 48. There was a bunch of other endpoints there, as you see, including Physician Global Assessment, Patient Global Assessment, and other safety, etc.

NEPTUNUS-1/2: Change in ESSDAI Score Over 52 Weeks

What we see here in these images, in NEPTUNUS-1, you can see ianalumab versus placebo, both had a significant improvement in ESSDAI score. Remember we want to see the ESSDAI change by at least three. Here you can see placebo improved by 5.1, and then ianalumab improved by 6.4. There was a significant difference between the least square mean of the two. You can see here in NEPTUNUS-2, on the right side, a significant difference between ianalumab monthly and placebo.

They also want to point out that, in both trials, quality of life according to patient and physician global assessments in NEPTUNUS-1 versus placebo was also significantly improved. What is this telling us? That means that not only did we have an improvement in this obscure score that most of you may not be testing and measuring, but also the patient global, the patients felt better. In the physician global, the physicians thought the patients were doing better. There is improvement from the patient's standpoint and the physician's standpoint on this drug.

NEPTUNUS-1/2: Safety

In terms of safety, if we look at serious adverse events, ianalumab 3.6% versus placebo 8.7% in NEPTUNUS-1, 9.5% compared to 10.7%. Overall, this seems to be a safe medication. If you look at serious infections, 2.2% in ianalumab versus placebo, 0.7 in NEPTUNUS-2, which had more patients, 3% versus 4.7% in placebo. Really seems to be a safe drug.

Telitacicept (BLyS/APRIL Inhibitor) in Patients with Primary Sjögren's Disease

We are going to look at the other B-cell-directed therapy, telitacicept. This affects BLyS but also affects APRIL, which is a similar type of molecule also affecting B cells in patients with primary Sjögren's. A multicenter, double-blind, placebo-controlled, randomized phase III trial.

Again, they looked at patients who met the classification criteria we reviewed who had a positive SSA. A lot of these trials really want to make sure that patients do better. They got the people who had a very active immune system. Having positive SSA patients was a plus. An ESSDAI score of greater than five. You had to have at least moderate disease activity.

They had them in three different groups. The telitacicept subcutaneous weekly at 80mg - low dose in red, higher dose in blue, 160mg, and then placebo. They followed them up at weeks 24 and 48. The primary endpoint was a change in ESSDAI score at week 24. They had a bunch of different secondary endpoints which you see listed here.

Telitacicept: Change in ESSDAI Score Over 48 Weeks

Telitacicept significantly improved ESSDAI scores at week 24 in both treatment arms versus placebo, as you could see. Again, red is the low dose, blue is the higher dose. You could see the change in ESSDAI score up here between placebo. Again, you want to change ESSDAI of at least three to be clinically significant. People here did not respond to placebo in this trial, but they certainly responded here to the telitacicept. You can see the same thing over here. What you see here is the placebo folks were offered the drug, and the dotted line is after they got the drug at the different doses, what happened over time. You see that they catch up with the two groups that were treated.

Certainly, looks like telitacicept is doing something there in terms of the ESSDAI up here. Then the bottom, this is looking at the ESSPRI. Symptoms were improving significantly here, and symptoms were improving significantly in the treatment group. It looks pretty nice.

Telitacicept: Safety

Most adverse events were mild to moderate in severity. No deaths were reported.

Dazodalibep (CD40 Ligand Antagonist) in Patients with Sjögren's Disease

Let us look at dazodalibep. This is a CD40 ligand antagonist. It inhibits the interaction between B cells and T cells. They cannot interact properly. That is how it works. This is an international double-blind, placebo-controlled, randomized phase II trial. I like this trial. What they did is they looked at two different populations. Population 1 was patients who had an ESSDAI score of greater than five. That is what we are looking at with all these other trials today. Population 2 was those who had an ESSDAI of less than five. I told you the average ESSDAI score in my population here is two point something. A lot of the patients do not qualify for these trials because they just do not have a high enough ESSDAI. Population 2 pretty much all comers. They just had to have symptoms, which is pretty much like 90% of my patients have an ESSPRI that is elevated, but maybe an ESSDAI that is not so high. This would literally apply to 90%+ of our patients here, so they could enter this trial if they wanted to.

In Population 1 or 2 was the same. They gave patients dazodalibep 1,500mg IV essentially every two weeks at first and then monthly versus a similar placebo. Halfway through, they switched. Those who were on dazodalibep got placebo, and those were on placebo got dazodalibep, and then they looked at the data. The primary endpoint was a change in the ESSDAI score for those who had a high ESSDAI or a change in the ESSPRI, again, the symptoms, in those who had lots of symptoms. I like the study, pretty nice.

Dazodalibep: Change in ESSDAI and ESSPRI Scores by Population

What they saw was significant improvement. On the left here, Population 1, again, these are people who had at least moderate systemic involvement, you can see the improvement in ESSDAI score. The placebo effect was pretty significant, was around four. The placebo group seemed to improve quite a bit. The dazodalibep group improved even more. The difference between the two was statistically significant. The dazodalibep group improved by six points. It was quite a bit. That is a lot. Again, zero to five is low disease activity, 5 to 13 is moderate, and they improve by six. It is a lot. Very good.

On the right side, you see the population that has lots of symptom burden but do not have a lot of systemic involvement. You could see, again, the change in ESSPRI of one or more is clinically significant. You can see the grey line there, they are not improving by one. People who got placebo did not have a significant improvement in their symptoms. Population 2, dazodalibep improved by -1.8. Significant improvement in symptoms and statistically significant compared to placebo as well.

DAHLIAS: Nipocalimab (FcRn Antagonist) in Patients with Moderate to Severe Primary Sjögren's Disease

Next, we look at nipocalimab. This is a FcRn antagonist. Essentially, this is going to lead to lower IgG immunoglobulin in patients, including immunoglobulin that is causing trouble. That is how it is going to help in patients with moderate to severe primary Sjögren's disease. Multicenter, double-blind, placebo-controlled, randomized phase II trial.

Again, this one is looking at patients with a high ESSDAI, but they have an even higher bar. ESSDAI score of six or more as opposed to five or more, had to be positive SSA. What they measured was not just the normal ESSDAI but a ClinESSDAI. Essentially, this gets rid of the biologic domain. If you remember biologic domain, you can get points for hypocomplementemia, hypogammaglobulinemia. It would not make sense to measure that here because we know that nipocalimab is going to lower IgG levels. If you get points in your ESSDAI for hypogammaglobulinemia, this is going to show that that improves every time just because of the mechanism of action, like tocilizumab lowering CRP. They removed that from the scoring system to make the data make more sense and be cleaner.

You needed a change in the ClinESSDAI at week 24. They had five milligrams. Red is the lower dose, blue 15mg per kilo is a higher dose, and then placebo. You see the secondary endpoints there were ESSPRI and others.

DAHLIAS: Change in ESSDAI Score at Week 24

What you see here is with the higher dose group, on the left, a change in ESSDAI scores over time. The nipocalimab in blue, the higher dose group has a statistically significant improvement in ESSDAI compared to the placebo group. We see that nipocalimab may be helpful according to the DAHLIAS study. We will see if we see this drug. Very interesting.

DAHLIAS: Response Rate by ClinESSDAI Domain

This shows you some of the different domains, like which domains were improved the most by nipocalimab. Maybe these are the people for whom the drug may be most helpful. Patients with constitutional, glandular, articular, cutaneous, hematological involvement. It might be that these patients are the ones most likely to improve with this drug.

DAHLIAS: Safety

DAHLIAS was well tolerated. There were no deaths or opportunistic infections. Most common adverse events were hypersensitivity reactions, COVID-19 infection, and headache. Much of this trial was done during the pandemic.

Deucravacitinib: Modulation of IFN Inflammatory Pathways

Our last we have deucravacitinib. This is a JAK inhibitor blocking T2, which leads to diminished interferon. This is modulation of interferon inflammatory pathways. In a phase II clinical trial for lupus, deucravacitinib demonstrated significant reduction in interferon gene expression. Results suggested deucravacitinib could be effective for managing Sjögren's. The pathogenesis of Sjögren's and lupus, both tied to interferon pathways. Phase III trials are ongoing.

Disease-Modifying Candidates in Later-Stage Development

You can see here that there is trials that are ongoing here in development of recruiting. We are recruiting folks for at least one trial and hopefully a second one soon.

How can these newer therapies be used in practice? We are going to see. It is going to be a very interesting time. Talking about this a lot with my patients. They are very interested in this. They are interested in trying to feel better and trying to make their disease better. It is not always so easy. It does take a village. You can see here.

Interdisciplinary Management of Sjögren's Disease

Interdisciplinary management of Sjögren's disease really takes a lot of different specialists. I have sent my patients to lots of different providers to help with their various manifestations. Hopefully, all together we make a difference for our patients.

Posttest 3

During her appointment, a 49-year-old woman with Sjögren's disease shares that she recently heard about ianalumab from an advocacy group. Based on emerging data, which of the following best summarizes what she can expect?

A. Improvement in glandular symptoms only;

B. Improvement in extraglandular symptoms only;

C. Improvement ESSDAI score;

D. Improvement in Physician Global Assessment and Patient Global Assessment scores but no change in ESSDAI score.

Announcer:
Polling is open. Please vote. We have a few more seconds for incoming replies. Thank you. We will close that poll and share.

Dr. Johr:
Great. Exactly. Improvement in ESSDAI score.

Posttest 3: Rationale

In phase III, NEPTUNUS-1 trial, ianalumab showed improvement in ESSDAI, Physician Global Assessment, Patient Global Assessment.

Key Clinical Takeaways and Q&A

Key Takeaways

Disease burden extends well beyond sicca symptoms. Sjögren's is so much more than dryness. Fatigue, chronic pain, cognitive dysfunction, psychological distress, significantly affecting patients' quality of life, daily functioning. These patients really suffer.

Current management strategies for Sjögren's disease are largely symptom-directed; however, emerging targeted therapies may reshape this landscape. Very exciting time.

Early recognition and patient education on Sjögren's disease are critical. Helps patients understand the systemic nature of their disease and rationale for multidisciplinary care.

Q&A Session

Poll 3

Do you plan to make any changes in your clinical practice based on what you learned in today's program?

Announcer:
Polling is open. Please vote. I will give it a few more seconds here. Thank you. We will close that poll.

Dr. Johr:
Good. I am glad.

Poll 4

Please take a moment to enter one key change you plan to make in your clinical practice based on this education. Scan the QR code. I am happy to answer any questions that you may have. I do not even know how many of you there are. I really like giving presentations in-person. It is always strange to do it virtually. I do not know if I am talking to five people or 5000. It is Texas, so maybe it is 5000. I do not know.

Announcer:
Yes. Thank you so much, Dr. Johr. We are now taking any questions that you may have for Dr. Johr. Please use the Q&A function in Zoom to submit them. While you do so, there are links in the chat panel. We will also put in a few QR codes momentarily. One will lead to the downloadable slide deck from today's presentation, and the other will lead to the program evaluation link to complete and claim your credit for attending. You will need to log in to or create a DCE account. We would encourage you to claim your credit within 30 days, as credit for today's program will expire after this time frame.

We do have one final opportunity for any questions. I do see a few that have come in, Dr. Johr. I'll go ahead and read those out to you.

The first is, how should fatigue and cognitive symptoms be interpreted when sicca findings are stable?

Dr. Johr:
I do not think of these things as necessarily going hand-in-hand. A lot of patients can have any number of different symptoms and manifestations changing at different times. It is like somebody who has spondyloarthritis and IBD; their gut might be stable, but their joints might get worse or vice versa. They do not necessarily have to go together. Regardless of someone's sicca manifestations, if their fatigue is worse, I am going to look for treatable causes and try to address that. I may try addressing it in any number of ways.

To talk about fatigue in Sjögren's, I could probably spend an entire hour talking about that. It is difficult. Definitely look at their thyroid. A lot of patients with Sjögren's have concurrent autoimmune thyroid disease. I check a TSH in my patients yearly who do not have known thyroid disease. I look at their hemoglobin, I look at their ferritin a lot of times, look at their B12. A lot of patients have concurrent B12 deficiency due to atrophic gastritis and other things. That is a long answer. I hope I answered that well enough for now.

Announcer:
I do see a comment in the chat asking if the slides will be shared after the meeting. There is a link in the chat panel to lead you to the slide deck. You will need to log in to or create a DCE account in order to access those.

The next question, Dr. Johr, is what metrics best reflect disease control.

Dr. Johr:
I am sorry. Read that again, please.

Announcer:
What metrics best reflect disease control?

Dr. Johr:
I am not sure how to answer that question beyond stating what we reviewed today. We measure patients' ESSDAI. Certainly, having an improvement in ESSDAI reflects disease improvement and control. If someone's ESSDAI is low, then they have low disease activity. I also pointed out that this does not cover everything; it does not cover symptoms, it does not cover some of the manifestations that are just not reflected in the ESSDAI. My patients who have very severe autonomic dysfunction, for instance, their ESSDAI might be zero, but their disease is very poorly controlled and out of control. They are passing out. They are having all kinds of issues. It is a very heterogeneous disease. It totally depends on the patient. We look at symptoms, we look at organ manifestations, and whatever that patient happens to have. The answer varies based on that.

Announcer:
The last question that I see now is - this could maybe fold into what you just mentioned. It says, how do ESSPRI and ESSDAI complement each other in assessing disease burden?

Dr. Johr:
ESSDAI is looking at the systemic nature of the disease, and the ESSPRI is looking at some of the patient's symptoms that may or may not reflect the systemic disease. That is why we have both of those things. A lot of patients may have a low ESSDAI, but still feel terrible. We want to record that. That is why we have both of these.

I challenge us all to come up with something better. It is not ideal. There is certainly a lot of patients who are unhappy with this and feel like we can do better. I bet we can, and I bet we will, but that is what we have for now. We have been using the literature for a while. It is certainly helpful to measure some of those different activities.

It is really useful to look at the ESSDAI because it does force you to go over all the different manifestations of Sjögren's. When I started using ESSDAI in my regular clinical practice through Epic, my EMR, I started asking different questions and asking certain questions more regularly because I was looking for the answers to the ESSDAI, and finding that patients really are having a lot of these symptoms and a lot of these problems that I may not have been asking about before.

Announcer:
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