Transcript Details
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Implementing Biologics into Treatment for your Lupus Patients

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature, titled “Implementing Biologics into Treatment for your Lupus Patients” is sponsored by GSK. This program is intended for physicians. Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
Biologics may impact the way we treat systemic lupus erythematous, or SLE. But where do they fit in the treatment landscape? And how do we implement them into our standard of care?

This is ReachMD, and I’m your host, Dr. Jennifer Caudle. This program is sponsored by GSK. And joining me today is Dr. Alvin Wells, a Board-Certified Rheumatologist practicing in Franklin, Wisconsin, who is compensated by GSK.

Dr. Wells, thank you so much for being here today.

Dr. Wells:
Thank you. I’m glad to be here.

Dr. Caudle:
So, let's begin with a look at the treatment landscape. Dr. Wells, can you tell us about some of the most recent advances in the treatment of systemic lupus erythematosus?

Dr. Wells:
Well, first of all, I have to say it’s – it’s exciting to be a rheumatologist. If you think about diseases that we treat on a daily basis – rheumatoid arthritis, psoriasis, and psoriatic arthritis – we always talk about treat to target, meaning there’s a predefined goal, whether the remission of low disease activity, and the goal is to get as close to that as possible, and we’re having those same discussions as we talk about treating patients with lupus and lupus nephritis. We know, for example, that the B cell is one of the primary drivers of the pathophysiology of patients who have lupus and lupus nephritis, and we want to kind of target those cells when we think about treating our patients who are active disease.

Dr. Caudle:
And how much experience do you have treating SLE?

Dr. Wells:
As a rheumatologist, one of our most common diseases that we see is lupus. I do have quite a few patients in my practice, and I think part of that is because I have a Ph.D. in immunology and really, really delve into the science behind the cause of lupus and lupus nephritis. We don’t know what triggers the disease, but we know that the B cells become activated and then those B cells differentiating the plasma cells, and that makes some of the autoantibodies that we use to make the diagnosis of lupus – things like a double-stranded DNA, things like a antinuclear antibody – and also we see other laboratory parameters that can help us make the diagnosis of a patient who has a disease.

So, remember when lupus is not just the clinical symptoms that they present in the clinic – it’s also the laboratory parameters, and those together help me to come up with the ideal treatment target for individual patients.

Dr. Caudle:
Now, when do you consider biologics in your treatment of SLE and why?

Dr. Wells:
I always tell my colleagues, when a patient with lupus comes into the practice, my job as a board-certified rheumatologist is give the best evidence-based medicine for treating our patients.

We start with what I call some standard therapies, and that could be hydroxychloroquine, it could be other agents that we use, but from the beginning, if a patient has a diagnosis of lupus, and we have the codes that we use – M32 – that patient then demands that they get aggressive treatment. And when I say aggressive treatments, I want to use drugs that have been vetted in randomized control clinical trials, data that has been published in peer-reviewed journals, and drugs that have been approved by the FDA, and all of those together help us to make a targeted approach for treating our patient with lupus. At our meetings, we always talk about what's the best outcome and what is remission where there's low disease activity, but all those different things we individualize because at the end of the day, keep in mind, it's the patient that we're treating and not the laboratory parameters, but the goal is to get their disease under control as quickly and as soon as possible.

Dr. Caudle:
Now, before we continue, I'd like to take a moment to share the indication for a biologic we'll be taking a look at today, BENLYSTA, also known as belimumab.

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BENLYSTA is indicated for patients aged 5 years and older with active systemic lupus erythematosus, SLE, or active lupus nephritis who are receiving standard therapy. BENLYSTA is not recommended in patients with severe active central nervous system lupus.

Important Safety Information.

BENLYSTA should not be administered to patients with a history of previous anaphylaxis with BENLYSTA.

Serious and sometimes fatal infections have been reported and occurred more frequently with BENLYSTA. Use caution in patients with severe or chronic infections, and consider interrupting therapy in patients with a new infection.

We'll continue to share additional important safety information throughout our program.

Dr. Caudle:
So, Dr. Wells, do you see a difference in your patients when you choose to use biologics prior to an immunosuppressant versus after an immunosuppressant?

Dr. Wells:
Well, I always say that my patients come to me for my best advice, and that includes the scientific data, and I need data that's been peer-reviewed, that's been published, I need data that's been vetted. So, randomized control clinical trials – that's the data that we use the most, and that's what the data the FDA relies on because the FDA gives the drugs that show that they're efficacious in treating disease, but they also evaluate the safety. So, if you have a young lady, for example, who has lupus – guess what?

We're not waiting. We're starting aggressive therapy and then we tailor the therapy based on her response. If she continues to have active disease, we can add other therapies. If her disease improves, we can decrease some of these therapies. And one of the therapy we like to stop or decrease altogether is corticosteroids. So, now we have newer options that show a reduction on long-term steroid use, which we know plays a significant role in organ damage.

Well, as we've been discussing my patients are expecting my scientific input, my evaluation of evidence-based medicine, and to me, that means using drugs that have been vetted in clinical trials. The drugs of the past – these are drugs that were used from other specialties – so, like oncology some things like mycophenolate, azathioprine, and methotrexate. Indeed, we have very few randomized control clinical trials that use those drugs to show that they are better than placebo.

Fast forward to where we are today – we know the patient with lupus, that the B cell is one of the primary drivers of the disease, and now we have drugs like BENLYSTA that targets the B cells. Remember, B cell binds to BLyS and on those autoreactive B cells that they need that to survive, and by blocking BLyS, those cells slowly undergo what we call normal cell death – apoptosis – and now we can see the down stream effects from blocking that process.

ReachMD Announcer:
BENLYSTA binds to soluble B-lymphocyte stimulator (also know as B-cell-activating factor), preventing its binding to B-cells, thus inhibiting the survival of B-cells, including auto-reactive B-cells. The clinical relevance of these effects on B-cells has not been established. Treatment results may vary.

Dr. Wells:

One of the things I like about BENLYSTA data is not only to show some of the clinical response, but it show me some of the things by using what we call the Lupus Responding Index 4 data looking at from the three pivotal trials. It shows me the immunologic responses as well, so I like to see things in patients who have active disease. So, we have evidence from the BLISS-52 and the BLISS-76 trials that the double-stranded DNA levels go down, that immunoglobulin levels go down, and that the complement levels go up, and those are things that we measure on a routine base in our patient who have active lupus.

ReachMD Announcer:
Please stay tuned for more information on the study designs.

Dr. Caudle:
And what are the long-term outcomes you expect your patients to have when you use biologics?

Dr. Wells:
In my clinical experience, if a patient has alopecia, oral ulcers, arthritis, things that drive the patient to the clinic, I say it's going to take a while if we get those things under control, and in my experience, some patients it can take up to 6 to 12 months to notice improvement. One of the things I tell them is – hey, if you start a drug like BENLYSTA, I can see when it starts to have an effect. We know that clinically, but we also know the effect it has on the immune system as well, but also that patients respond differently. I know that one patient is not going to respond like another, and each patient is different. We always have to keep the patient in mind. How do I know that? Again, because I know the baseline labs, and at 4 to 8 weeks, I'm looking for changes like increase in the their complement levels, decreases in their immunoglobulin levels, and decrease in their double-stranded DNA level, and then I'm also looking for the clinical features as well. They come in with joint complaints – I'm looking for the joints to improve. If they come in with a rash, I want their skin to improve. If they have other mucocutaneous and musculoskeletal symptoms, all of those things need to improve, and that happens pretty quickly. If I don't get the patients better, they're going to present to the emergency room where it's going to cost more. They're also going to be exposed to other treatments like corticosteroids, which I don't like to use long-term on my patient who have active lupus. We have other things that we can do.

So, to help determine if a patient has lupus nephritis, I get them to a nephrologist for a kidney biopsy, but if I can't get them sooner rather than later to a nephrologist, I work with interventional radiology to help me get a kidney biopsy because I need to know what type of kidney disease they have. I can't treat in the dark. Is it type 3, 4, or 5 kidney disease? At the end of the day, I am the hub of the care of a patient's wheel and they are like the spokes all around me. I have the nephrologist, I have the nutritionist, I have the primary care doctor.

All of us work together to get the patient under control, and when the disease is under control, we know that this significantly lowers the chance of regressing to end-stage renal disease. I believe that the best chance to achieve this is by getting them on aggressive therapy sooner rather than later.

ReachMD Announcer:
Treatment results may vary.

Before we continue, here's some additional Important Safety Information we need to be aware of.

Cases of JC virus-associated Progressive Multifocal Leukoencephalopathy, or PML, resulting in neurological deficits, including fatal cases, have been reported. If PML is confirmed, stop immunosuppressant therapy, including BENLYSTA.

Acute hypersensitivity reactions, including anaphylaxis and death, and infusion-related reactions have been reported. Generally, reactions occurred within hours of the infusion but may occur later, including in patients who have previously tolerated BENLYSTA. Non-acute hypersensitivity reactions, such as rash, nausea, fatigue, myalgia, headache, and facial edema, typically occurred up to a week after infusion. Monitor patients during and after treatment and be prepared to manage anaphylaxis and infusion-related reactions. Be aware of the risk of hypersensitivity reactions, which may present as infusion-related reactions. Discontinue immediately in the event of a serious reaction. With intravenous administration, if an infusion reaction develops, slow or interrupt the infusion.

Depression and suicidality were reported in patients receiving BENLYSTA. Before adding BENLYSTA, assess patients' risk of depression and suicide and monitor them during treatment. Instruct patients or caregivers to contact their HCP if they experience new or worsening depression, suicidal thoughts or behavior, or other mood changes.

There is an increased risk of malignancies with the use of immunosuppressants. The impact of BENLYSTA on the development of malignancies is unknown.

Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established.

Available data do not support the safety and efficacy of concomitant use of BENLYSTA with rituximab in patients with SLE. An increased incidence of serious infections and post-injection systemic reactions in patients receiving BENLYSTA concomitantly with rituximab compared to patients receiving BENLYSTA alone has been observed. The safety and efficacy of BENLYSTA concomitantly with other biologic therapies, including B-cell-targeted therapies, have not been established. Caution should be exercised if BENLYSTA is administered in combination with other biologic therapies.

Dr. Caudle:
Dr. Wells, did you encounter any obstacles when starting patients on biologics? And how have you overcome them?

Dr. Wells:
Well, some of my colleagues talk about the obstacles they have when starting patients on biologics. I'm in a unique position. I'm director of the department of rheumatology here at Advocate Aurora Medical Group, and I have a pharmacist and a pharmacy tech in the clinic, and they serve a vital role. So, example, if I have a patient with lupus, and we make that diagnosis, I'm already talking with the team – hey, I want to start this patient on a biologic drug, and we use, for example, a drug like BENLYSTA. And then their goal is to help make sure to get the prior authorization done. If the drug is denied, they write the letters of denial. So, we do all of those things to get my patient on the drugs sooner rather than later. Now, many of my colleagues say they don't have the luxury of hiring a pharmacist and a pharmacy tech – you don't have to. You can partner with other companies – that way they can provide these services for you because at the end of the day, treating your patient who have lupus and lupus nephritis, you want to get those patients under control. You want to have not only my target but have the patient's target in mind to get a best outcome possible.

Dr. Caudle:
Are there any thoughts you'd like to share with other rheumatologists who either don't feel comfortable using biologics in their patients or choose to use biologics only after immunosuppressants?

Dr. Wells:
One thing I tell my colleagues is that in this day and age, you need to take a step back and evaluate if you're really doing evidence-based medicine. The reason that physicians, our patient, and pharmaceutical companies invest so much in doing clinical trials is so that we can know where we are now. We can see drugs that are FDA-approved. They're drugs that work and they work better than standard of care alone. So, they go to the target of the disease, and we have post hoc data that show the pool analyses of the 5 lupus trials with BENLYSTA, that they can help with the mucocutaneous disease, the musculoskeletal disease, and even their renal disease. We also have evidence around the long-term organ damage and the progression of organ damage from the 2019 Toronto Lupus Cohort.

ReachMD Announcer:
Please stay tuned for more information on the study designs.

Dr. Wells:
I think that's where I tell my colleagues – you need to do evidence-based medicine. I'm very fortunate to have two healthy kids – my young daughter who is African-American, she just turned 30 years old – and, indeed, if she developed lupus and lupus nephritis, I'm not going to sit back and hoping these other drugs are going to work. I'm not going to wait till she gets kidney disease damage before I start her on the drug.

I ask all my colleagues to do the same thing – to treat your patients as if they were somebody in your family, if you were on the other side of the exam table, what would you expect and what would you demand from your treating physician? And at the end of the day, we expect peer-to-peer reviewed data, drugs that have been approved by the FDA and showing the long-term evidence, both efficacy and safety that we need, and that's where I am in my practice, and that's the message I would give to my colleagues.

ReachMD Announcer:
Before we continue, here's some additional Important Safety Information we need to be aware of.

The most common serious adverse reactions in adult SLE clinical trials were serious infections; some were fatal. The most common adverse reactions (greater than or equal to 5 percent) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, and injection site reactions (with the subcutaneous injection).

Adverse reactions reported in clinical trials with SLE pediatric patients (age 5 years and older) and adult patients with lupus nephritis were consistent with those observed in adult SLE trials.

There are insufficient data in pregnant women to establish whether there is drug-associated risk for major birth defects or miscarriage. After a risk/benefit assessment, if prevention is warranted, women of childbearing potential should use contraception during treatment and for at least 4 months after the final treatment.

HCPs are encouraged to refer patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972 or visiting mothertobaby.org/ongoing-study/benlysta-belimumab.

BENLYSTA, Belimumab, can be given as an I.V. infusion 120 milligrams per vial in patients aged 5 and older, or by subcutaneous injection 200 milligrams per milliliter in adults.

I would like to remind our audience that to report SUSPECTED ADVERSE REACTIONS, contact GSK at 1-888-825-5249 or the FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see full Prescribing Information and Medication Guide for BENLYSTA.

Dr. Caudle:
Well, with those final considerations in mind, I'd like to thank my guest, Dr. Alvin Wells, for joining us to discuss implementing BENLYSTA for the treatment of systemic lupus erythematosus. Dr. Wells, it was great speaking with you today.

Dr. Wells:
Thank you very much.

ReachMD Announcer:

Lupus Study Design and Results

Study Design:
In three Phase III, double-blind, multicenter studies, 2,520 SLE patients were randomized to BENLYSTA plus standard therapy or placebo plus standard therapy. In two of the trials, BENLYSTA 10 mg/kg, BENLYSTA 1 mg/kg, or placebo was administered by intravenous (IV) infusion over one hour on Days 0, 14, and 28, and at 4-week intervals thereafter through Week 52 (BLISS 52)or Week 76 (BLISS 76). In BLISS-SC patients received weekly doses of subcutaneous (SC) BENLYSTA 200 mg or placebo for 52 weeks. BENLYSTA 1mg/kg is not an approved dose and is not included in data shown. Response rate, as assessed by SRI 4, at week 52 was the primary endpoint in all trials.

Results:
The SRI 4 response rate at Week 52 for BENLYSTA plus standard therapy vs placebo plus standard therapy was 61% (n=554) vs 48% (n=279) for BLISS-SC, 58% (n=290) vs 44% (n=287) for BLISS-52, and 43% (n=273) vs 34% (n=275) for BLISS 76, $P<0.05$ for each.

Lupus Nephritis Study Design and Results

Study Design:
In a phase III study, 448 adult patients with active lupus nephritis were randomized to BENLYSTA plus standard therapy or placebo plus standard therapy. BENLYSTA 10 mg/kg or placebo was administered by IV infusion on Days 0, 14, and 28, and at 4 week intervals thereafter through week 104. Treatment failures were defined as patients who received prohibited medications.

Outcomes are defined as achieving renal response at Week 104 (primary endpoint), complete renal response at Week 104 (secondary endpoint), and time to renal related events or death (secondary endpoint).

Renal Response defined as eGFR $\geq$ 60 mL/min/1.73m^2 or no more than 20% below preflare value, uPCR $\leq$0.7 and not a treatment failure at Week 104. Significantly more patients on BENLYSTA (n=223) achieved renal response vs placebo (n=223); 43% vs 32%, respectively (P=0.0311).

Be-SLE:

A pooled, post hoc analysis of five double blind, placebo-controlled studies found that treatment with BENLYSTA plus standard therapy, in patients who had organ involvement at baseline, resulted in improvements in skin, joint and kidney domains, as defined by SELENA-SLEDAI when compared to standard therapy alone at Week 52. The five studies included in the post hoc analysis were BLISS-52, BLISS-76, Northeast Asia, BLISS-SC and EMBRACE. The primary endpoint – SRI-4 at Week 52 – was not met in EMBRACE. Patients were treated with BENLYSTA plus standard therapy, 10 milligrams per kilogram or 200 milligrams subcutaneously, n=1869 or placebo plus standard therapy, either intravenously or subcutaneously, n=1217. The analysis included SRI-4 by visit. These results are descriptive, as individual studies were not designed to evaluate efficacy in specific organ domains.

Study Design Evaluating Long Term Organ Damage Progression:

A post hoc, propensity score matching comparative analysis (or PSM) was performed to assess the difference in organ damage progression between patients from the BLISS-76 long term extension trial (or LTE) and from the Toronto Lupus Cohort (or TLC). The primary endpoint of organ damage progression was measured by the SLICC/ACR Damage Index (or SDI) in patients with at least 5 years of follow up.

The BLISS-76 LTE was an extension of a 76 week, phase III, randomized, double-blind, placebo-controlled study comparing BENLYSTA to placebo both with Standard therapy. The primary endpoint was the response rate at week 52, as assessed by SRI-4. From the LTE, only patients from the US on BENLYSTA IV 10 mg/kg plus Standard therapy were evaluated in the PSM study.

The TLC was chosen based on its size, the extent of organ damage in patients, and the severity of disease activity. Regimen was standard therapy alone and did not include BENLYSTA.

The eligibility criteria from the BLISS-76 LTE study were applied to the patients in the TLC. Then the eligible patients from both cohorts were matched based on 17 different variables.

Results are descriptive. Real-world studies cannot definitively establish causality and are designed to evaluate association. Limitations important to interpret results: patients matched only on known variables; unmatched variables exist (eg., year of entry, patient populations, and data collection vs randomized controlled trials).

This program was sponsored by GSK. If you missed any part of this discussion, visit ReachMD.com/Industryfeature. This is ReachMD. Be Part of the Knowledge.

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