Transcript Details
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Go Beyond the Symptoms: Redefining Treatment Goals for Lupus

ReachMD Announcer:
Welcome to ReachMD.

This medical industry feature, titled “Go Beyond the Symptoms: Redefining Treatment Goals for Lupus,” is sponsored by GSK.

Here’s your host, Dr. Paul Doghramji.

Dr. Doghramji:
Lupus can be difficult to identify and challenging to treat, but an approved treatment option may improve outcomes for patients. This is ReachMD, and I’m Dr. Paul Doghramji. This program is sponsored by GSK, and joining me to discuss lupus and BENLYSTA, also known as belimumab, is Dr. Kristi Mizelle, a board-certified rheumatologist also sponsored by GSK, practicing in Newport News, Virginia.

Dr. Mizelle, welcome to the program.

Dr. Mizelle:
Thank you so much. I’m very happy and excited to be here today.

Dr. Doghramji:
We’re thrilled to be here in Philadelphia, which has been an amazing opportunity to once again discuss lupus and BENLYSTA.

ReachMD Announcer:
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. Doghramji:
As we know, lupus has a heterogenous presentation that can make it difficult to detect. Dr. Mizelle, can you start by helping us better understand the underlying disease process, and what causes this heterogeneity?

Dr. Mizelle:
Sure. This disease process underlying systemic lupus erythematosus (SLE or lupus), includes abnormal activation of B cells. Autoreactive B cells produce autoantibodies. These autoantibodies bind to self-antigens to form immune complexes which may move through the circulatory system, leading to inflammation and tissue damage in multiple organs.

B cells need B lymphocyte stimulator, or BLyS, for survival and activation. BENLYSTA selectively binds to soluble BLyS which prevents BLyS from activating and stimulating B cells. Over time, this causes more B cells to undergo apoptosis, and reduces their differentiation into antibody-producing plasma cells. Unlike other medications that affect B cells, BENLYSTA does not directly bind to B cells or directly

deplete B-cell populations. The clinical relevance of these effects on B cells has not been established.

Dr. Doghramji:
And what do we typically see as the disease progresses in patients with lupus?

Dr. Mizelle:
As time goes on, the combination of disease activity including flares, and drug toxicities from standard therapies like steroids and immunosuppressants, may lead to irreversible organ damage. The European Alliance of Associations for Rheumatology, or EULAR, treatment recommendations highlight the importance of controlling disease activity and flares, while also limiting steroid dose. Treatment goals also include improving long-term outcomes. We should aim at remission of disease, prevention of damage progression, and minimization of drug side effects. In addition, as the disease progresses, many patients with lupus will develop lupus nephritis within a few years of their lupus diagnosis. A substantial number of patients with lupus nephritis will experience kidney failure, and lupus nephritis contributes to overall morbidity and mortality regardless of treatment.

ReachMD Announcer:
Before we continue, here is 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.

Dr. Doghramji:
Dr. Mizelle, before we dive in, what do you want us to remember about BENLYSTA after our conversation?

Dr. Mizelle:
I would love it if everyone watching and listening could remember these three key points: disease activity, steroids and kidney.

Dr. Doghramji:
All right. Let's keep those in mind as we talk about the data. Can you take us through the design of the pivotal trials?

Dr. Mizelle:
BENLYSTA was studied in three phase 3, double blind, multicenter studies, in which 2,520 adult SLE patients were randomized to BENLYSTA plus standard therapy or placebo plus standard therapy. In two belimumab international SLE studies, also known as BLISS, BENLYSTA 10 milligrams per kilogram, BENLYSTA 1 milligram per kilogram, or placebo was administered by IV infusion, over one hour on days 0, 14, and 28, and at 4-week intervals thereafter through Week 52 for BLISS-52, or Week 76 for BLISS-76. In BLISS-SC, patients received weekly doses of subcutaneous BENLYSTA 200 milligrams, or placebo, for 52 weeks. BENLYSTA 1 milligram per kilogram is not an approved dose and will not be discussed today. Disease activity reduction, as assessed by systemic lupus erythematosus responder index 4, or SRI-4, at Week 52 was the primary endpoint in all trials.

To be considered a responder for SRI-4, patients must meet all three of the following components: Number one – reduced safety of estrogen in lupus erythematosus, national assessment version of a systemic lupus erythematosus disease activity index or SELENA-SLEDAI score by at least four points; Number two – no new British Isles Lupus Assessment Group or BILAG-A, or no more than one new BILAG-B domain score and; Number three – no worsening from baseline in the Physician's Global Assessment by greater than or equal to 0.3 points.

Dr. Doghramji:
And what were the results for the primary endpoint from the pivotal trials?

Dr. Mizelle:
Yes, let's bring it back to point number one- symptoms. Patients achieved significant reduction in disease activity across all 3 trials.

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.

Dr. Doghramji:
Okay, and what about point number two? How can BENLYSTA help patients with lupus lower their steroid burden?

Dr. Mizelle:
So, steroid-sparing effects were observed in clinical trials and in a real-world setting.

In our three pivotal trials, steroid reduction was defined as at least a 25% reduction in steroid dose, to 7.5 milligrams per day or less, at Week 52. There was a numerical difference in favor of BENLYSTA.

There were more individuals who experienced steroid dose reduction, but the results were not statistically significant. In our real-world data, the OBSErve US cohort study assessed the effectiveness of BENLYSTA 10 milligrams per kilogram plus standard therapy, in adult patients with SLE over 24 months, in U.S. clinical practices across 27 states, and included 92 rheumatologists. To qualify for enrollment, patients were required to have at least eight infusions of BENLYSTA. The baseline was the date of first infusion. Physician-assessed clinical response was reviewed at six-month intervals, using medical charts and data collected using case report forms.

Of the patients prescribed steroids at baseline, n=386, 86% reduced their steroid dose or discontinued steroids at Week 26, compared to their use at baseline.

This trend was similar at each six-month interval, up to 24 months versus baseline, using last observation carried forward. At Week 26, the mean reduction in daily steroid dose reduced by 58% versus baseline, 19.9 milligrams per day versus 8.4 milligrams per day, respectively. During the two-year observation, 45% of participants were lost to follow up or discontinued the use of Benlysta. This data is from an observational study, therefore changes in steroid doses were not captured and may be unrelated to disease improvement or worsening. Results are descriptive.

The primary objective of OBSErve US was a physician-assessed clinical response to BENLYSTA at six months. Between baseline and month six, greater than or equal to 50% improvement in overall clinical response was reported for 48.7% of participants. During the two-year observation, 45% of participants were lost to follow up, or discontinued the use of BENLYSTA.

The key data limitations were lack of control group, risk of selection bias, validated disease assessment tool not consistently used, patient attrition, potential measurement error based on nonuniform categorization or interpretation of disease severity and treatment response, and reasons for change in steroid dose were not captured and may be unrelated to disease improvement or worsening.

ReachMD Announcer:
Before we continue, here's some additional important safety information we need to be aware of.

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 and 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. Doghramji:
Well, that brings to point number three. Dr. Mizelle, can you talk to us about the BENLYSTA lupus nephritis trial?

Dr. Mizelle:
That's right, point number three – kidney. BLISS Lupus Nephritis, or BLISS-LN, was a phase 3 study of 448 adult patients with active lupus nephritis, who were randomized to either BENLYSTA plus standard therapy or placebo plus standard therapy. Standard therapy included induction with either cyclophosphamide or mycophenolate mofetil with high-dose steroids, plus either BENLYSTA or placebo.

Maintenance therapy included azathioprine plus low-dose steroids for those patients who received cyclophosphamide at induction, or mycophenolate mofetil plus low-dose steroids, plus either BENLYSTA or placebo.

BENLYSTA 10 milligrams per kilogram, 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.

An aspect of BLISS-LN is that BENLYSTA was studied as an add-on to mycophenolate mofetil, or cyclophosphamide, during both the induction and maintenance phases of treatment. The primary endpoint in this trial was renal response, which was measured at Week 104. Renal response was defined as eGFR greater than or equal to 60 milliliters per minute, per 1.73 meters-squared, or eGFR no worse than 20% below pre-flare value, urine protein-to-creatinine less than or equal to 0.7, and not a treatment failure at Week 104. Significantly more BENLYSTA patients achieved renal response versus placebo – 43% versus 32%, respectively.

Dr. Doghramji:
Now let's dig into the data further. Can you tell us about the secondary endpoint, complete renal response?

Dr. Mizelle:
Absolutely. Complete renal response, or CRR, at Week 104 was defined as eGFR greater than or equal to 90 milliliters per minute, per 1.73 meters-squared, or eGFR no worse than 10% below the pre-flare value, and urine protein-to-creatinine ratio less than 0.5, and not a treatment failure.

Significantly more patients treated with BENLYSTA achieved complete renal response at Week 104, with 30% of patients in BENLYSTA achieving CRR, while only 20% of patients on placebo achieving the endpoint at Week 104.

For patients on BENLYSTA, this translates to 74% greater odds of achieving a CRR at Week 104, compared with those who received placebo.

Dr. Doghramji:
And how did patients from the trial fare in terms of kidney function?

Dr. Mizelle:
In a post hoc analysis, kidney function was assessed via two endpoints. First, we have the percentage of patients experiencing one or more renal flares, between Weeks 24 and 104. During this time, 26% of patients on placebo had at least one flare, while only 14% of patients on BENLYSTA had at least one flare. This represents a 55% reduced risk of renal flares for the patients treated with BENLYSTA.

The other post hoc endpoint used to assess kidney function is the eGFR slope. This endpoint is defined as the change in eGFR from Week 24 to Week 104. For patients on placebo, the slope was a decline of 5.72 milliliters per minute per 1.73 meters-squared per year, indicating eGFR loss. For patients on BENLYSTA, the slope was a decline of 2.12. The difference in the two slopes is 3.61, representing 63% less eGFR loss over time for the patients treated with BENLYSTA.

ReachMD Announcer:
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%, 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 four 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. Doghramji:
And finally, Dr. Mizelle, when do you add BENLYSTA for patients with lupus?

Dr. Mizelle:
That is a great question, and one that I hear often. My advice is that BENLYSTA can be added as early as after hydroxychloroquine, to as late as diagnosis of severe lupus nephritis. Wherever your patient is in their journey, you can probably add it now, keeping in mind that every patient is different, and their results may vary.

Dr. Doghramji:
That's a great comment for us to think on, as we come to the end of today's program.

I want to thank my guest, Dr. Kristi Mizelle, for helping us better understand lupus and BENLYSTA. Dr. Mizelle, it was great speaking with you today.

Dr. Mizelle:
Thanks so much for having me. It has been an absolute pleasure.

Dr. Doghramji:
I'm Dr. Paul Doghramji

ReachMD Announcer:
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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