Transcript Details

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The First Biologic Approved to Treat PMR: A Clinical Deep Dive

ReachMD Announcer:
You're listening to ReachMD. This medical industry feature, titled "The First Biologic Therapy Approved to Treat Polymyalgia Rheumatica (PMR): A Clinical Deep Dive," is brought to you by Sanofi and Regeneron.

Today, we'll be taking a look at KEVZARA® (sarilumab), indicated for treatment of adult patients with:

- moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).
- polymyalgia rheumatica (PMR) who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper.

Here's your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD, and I'm Dr. Charles Turck. Joining us to dive into the clinical data of KEVZARA is an expert from the medical team who conducted the SAPHYR trial, studying KEVZARA in PMR, Dr. Robert Spiera. Dr Spiera is a Professor of clinical medicine at Weill Cornell Medical College and Director of the Scleroderma, Vasculitis, and Myositis Center at the Hospital for Special Surgery in New York City. Dr Spiera has also been compensated by Sanofi and Regeneron for this program, as well as for his role as an investigator in SAPHYR. Dr Spiera, thanks for joining us!

Dr. Spiera:
Thank you for having me.

Dr. Turck:
Starting with some background, Dr Spiera, what is KEVZARA and why is it important for PMR?

Dr. Spiera:
Well, KEVZARA, or sarilumab, is a human monoclonal antibody that binds with high affinity to both soluble and membrane-bound IL-6 receptors.[1]

Upon binding to these receptors, KEVZARA can inhibit classic cis-signaling through membrane-bound IL-6 receptors or trans-signaling through soluble IL-6 receptors.[2]

In PMR, IL-6 is known to be an important driver of the systemic and local inflammatory response and it plays an important role in PMR pathogenesis,[3] so our rationale was to inhibit IL-6 signaling in PMR patients using KEVZARA, or sarilumab, to see whether that strategy would be safe and associated with improved outcomes. KEVZARA was tested in a Phase 3 clinical trial in a group of patients with refractory PMR. It demonstrated disease control in these patients, along with a known safety profile, which was generally consistent with the known safety profile of KEVZARA demonstrated in the rheumatoid arthritis, or RA clinical trials.[1]

Dr. Turck:
Thank you for that background, Dr Spiera. So, what type of PMR patient is appropriate for treatment with KEVZARA?

Dr. Spiera:

KEVZARA is indicated for the treatment of adult patients with PMR who've had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper.[1] Patients who cannot tolerate corticosteroid taper may include those whose disease worsens during tapering.[4]

Dr. Turck:
We look forward to hearing more about clinical data for KEVZARA, Dr Spiera. But before getting into that, there is a boxed warning associated with KEVZARA use.

ReachMD Announcer:
IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS
Patients treated with KEVZARA are at increased risk for developing serious infections that may lead to hospitalization or death. Opportunistic infections have also been reported in patients receiving KEVZARA. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Avoid use of KEVZARA in patients with an active infection.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before KEVZARA use and during therapy. Treatment for latent infection should be initiated prior to KEVZARA use.
- Invasive fungal infections, such as candidiasis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral and other infections due to opportunistic pathogens.

Closely monitor patients for signs and symptoms of infection during treatment with KEVZARA. If a serious infection develops, interrupt KEVZARA until the infection is controlled.

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection.

Dr. Turck:
Let's turn our attention to the SAPHYR clinical trial, which assessed the efficacy and safety of KEVZARA, or sarilumab. Dr. Spiera, can you give us an overview of the trial and the patient population that was studied?

Dr. Spiera:
Before we discuss the details of the SAPHYR trial, I want to provide some context on how important this study and this approval is. While corticosteroids have been effective in treating PMR, clinicians have been waiting for a proven, effective therapy that controls PMR along with a known safety profile for patients who are not responding to corticosteroids or who are having trouble with tapering. Keep in mind that corticosteroid treatment can pose certain challenges, especially in an older patient population, so there is an unmet need in the treatment of PMR.

Now let's talk about the SAPHYR trial: The efficacy and safety of KEVZARA in PMR were assessed in a randomized, double-blind, placebo-controlled, 52-week, multi-center study in adults with PMR diagnosed according to the American College of Rheumatology/European Union League against Rheumatism (ACR/EULAR) classification criteria. Patients had at least one episode of unequivocal PMR flare while attempting to taper corticosteroids.[1] The patients recruited for this trial were difficult-to-treat patients with refractory PMR. They were over 50 years old, with a median age of 69 for the KEVZARA group and 70 for the placebo group. The median duration of PMR was 292 days in the KEVZARA group and 310 days in the placebo group. These patients were also not treatment naïve for PMR. They had a history of being treated for at least 8 weeks with prednisone, at least 10 milligrams per day. In addition, patients enrolled had to have experienced a flare of PMR despite receiving 7.5 mg or more of daily prednisone in the 12 weeks preceding randomization, meaning that they were steroid-refractory patients.[5]

Dr. Turck:
And what can you tell us about the trial's design?

Dr. Spiera:
In the SAPHYR trial, patients were randomized to one of two treatment strategies. The placebo group received a standard 52-week steroid taper with placebo injections every other week, while the active treatment group received KEVZARA 200 mg every other week and a 14-week steroid taper,[1] and I want to emphasize how important this is — a 14-week taper is much quicker than what refractory or

even treatment-naïve PMR patients are generally offered in standard practice.[6] Meaning it would be surprising for those patients to do well with such a rapid taper, unless they were receiving another agent to control PMR.

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr Charles Turck, and I'm speaking with Dr Robert Spiera about KEVZARA (sarilumab), for patients with polymyalgia rheumatica.

Dr Spiera, turning to the results, can you tell us about the primary endpoints involved in the SAPHYR trial?

Dr. Spiera:
The primary endpoint was the percentage of patients achieving sustained remission at Week 52. The definition of sustained remission in this trial was a very stringent one — a composite endpoint, defined as meeting four criteria. One, patients had to be in disease remission at 12 weeks, defined as absence of signs and symptoms and CRP < 10 mg/L, suggesting that KEVZARA was already having an effect by then to control PMR signs and symptoms. Two, absence of disease flare sustained through Week 52. Flare was defined as recurrence of signs and symptoms attributable to active PMR requiring an increase in corticosteroid dose, or elevation of ESR attributable to active PMR plus an increase in corticosteroid dose. Three, adherence to the protocol-defined steroid taper sustained through week 52 and four, have sustained reduction of C-reactive protein to less than 10 milligrams per liter sustained through week 52. So to summarize, what I mean by stringent composite endpoint is that in order to meet the primary endpoint, a patient had to meet all four criteria.[1]

In terms of results, we saw that a greater proportion of patients achieved sustained remission in the KEVZARA arm compared to the placebo-controlled arm at Week 52.[1] More specifically, about 28% of patients treated with KEVZARA, along with the 14-week taper, met the primary endpoint compared to 10.3% of patients treated with placebo plus a 52-week taper,[1] which means almost 3 times as many patients met the primary endpoint when treated with KEVZARA compared to placebo, that in the context of the chronically relapsing patient cohort enrolled in the study is of particular clinical significance. I would like to add that, to further ascertain the robustness of the primary endpoint results, we conducted a sensitivity analysis for the primary endpoint, in which the acute phase reactants criteria—CRP and ESR—were removed from the definition of sustained remission.[1]
The reason why we did this sensitivity analysis was because we know that KEVZARA, or sarilumab, can suppress CRP and ESR, so we wanted to make sure that the differences between groups was not driven by the suppression of the acute phase reactants. We found that it was not, and the difference between the placebo and KEVZARA arms was indeed a clinical effect. The effect at Week 52, when excluding the acute-phase reactants, continued to be greater in the KEVZARA plus 14-week taper group compared to the placebo plus 52-week GC taper group: 31.7% of patients treated with KEVZARA versus 13.8% of patients treated with placebo.[1]

The results of the sensitivity analysis suggest that the sustained remission observed in patients treated with KEVZARA was not driven primarily due to the reduction of ESR/CRP by IL-6 inhibition.

Dr. Turck:
That's very interesting, thank you. What about other endpoints?

Dr. Spiera:
Treatment with KEVZARA showed improvement across all four components of sustained remission. More patients in the KEVZARA arm achieved disease remission by Week 12 compared to the placebo arm. In addition, from Week 12 to Week 52, 55% of patients treated with KEVZARA did not experience disease flares (compared to 32.8% of patients treated with placebo), 66.7% had sustained reduction of CRP (compared to 44.8% of patients treated with placebo), and 50% were able to adhere to prednisone taper (compared to 24.1% of patients treated with placebo). In other words, not only did the patients achieve disease remission in the first 12 weeks, but the clinical benefits (reduction of flares, reduction of CRP and adherence to the prednisone taper) extended longer than the end of the tapering schedule, up to 52 weeks.

The cumulative corticosteroid dose during the 52-week study for the patients treated with KEVZARA was about a third of the dose taken by patients in the placebo-controlled arm; that is, 777 milligrams vs 2044 milligrams.[1]

Dr. Turck:
So it looks like the cumulative corticosteroid dose was much lower in the KEVZARA arm.

Dr. Spiera:
Yes, it was. And it's important to note here that the difference in steroid exposure is not only due to the corticosteroid exposure per protocol, but also because fewer rescue therapies were used in the KEVZARA arm of the study.[5]

Dr. Turck:
And what about safety? What were the results there?

Dr. Spiera:
Common adverse reactions occurring in ≥5% of patients treated with KEVZARA were neutropenia (15.3%), leukopenia (6.8%), constipation (6.8%), rash pruritic (5.1%), myalgia (6.8%), fatigue (5.1%), and injection site reaction pruritus (5.1%). Injection site reactions were mild in severity. The proportion of patients with serious infections was similar in the KEVZARA group (5.1%) compared to the placebo group (5.2%) but no cases of serious opportunistic infections occurred in this trial. Neutropenia was the most common adverse event that led to treatment discontinuation, and it was observed in three patients (5.1%) in the KEVZARA group.[1]

During the 12 months of this Phase 3 SAPHYR trial, the total patient years duration in the KEVZARA PMR population was 47.37.[1]

Dr. Turck:
So, what is the dosage for KEVZARA and how is it administered?

Dr. Spiera:
The recommended dosage of KEVZARA for patients with PMR is 200 milligrams once every 2 weeks, given as a subcutaneous injection. This is in combination with a tapering course of systemic corticosteroids or as a monotherapy following discontinuation of corticosteroids. And no dosage adjustments are recommended based on age, gender, race, or weight.[1]

In summary, KEVZARA, or sarilumab, is an option for the treatment of PMR and should be considered for steroid-refractory patients, meaning those who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper.[1]

Overall, in the clinical trial, the proportion of patients with PMR achieving sustained remission at Week 52 was higher in the KEVZARA arm compared to the placebo-controlled arm. In addition, the patients treated with KEVZARA received less corticosteroids overall, some of this difference is because the KEVZARA arm received less corticosteroids due to the shorter tapering schedule per-protocol.[1]

Also, the overall safety profile observed in patients treated with KEVZARA was generally consistent with the known safety profile of KEVZARA in RA, which is something that many of us already have experience with.[1]

Dr. Turck:
And before we close, let's take a moment to review some additional Important Safety Information.

ReachMD Announcer:
CONTRAINDICATION
Do not use KEVZARA in patients with known hypersensitivity to sarilumab or any of the inactive ingredients.

WARNINGS AND PRECAUTIONS
Infections. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including KEVZARA. The most frequently observed serious infections with KEVZARA included pneumonia and cellulitis. Among opportunistic infections, TB, candidiasis, and pneumocystis were reported with KEVZARA.

- Hold treatment with KEVZARA if a patient develops a serious infection or an opportunistic infection.
- Patients with latent TB should be treated with standard antimycobacterial therapy before initiating KEVZARA.
- Consider anti-TB therapy prior to initiation of KEVZARA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but having risk factors for TB infection.
- Consider the risks and benefits of treatment prior to initiating KEVZARA in patients who have: chronic or recurrent infection, a history of serious or opportunistic infections, underlying conditions that may predispose them to infection, been exposed to TB, or lived in or traveled to areas of endemic TB or endemic mycoses.
- Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with KEVZARA.

Laboratory Abnormalities. Treatment with KEVZARA was associated with decreases in absolute neutrophil counts (including neutropenia), and platelet counts; and increases in transaminase levels and lipid parameters (LDL, HDL cholesterol, and/or triglycerides). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with KEVZARA. Assess neutrophil count, platelet count, and ALT/AST levels prior to initiation with KEVZARA.

Monitor these parameters 4 to 8 weeks after start of therapy and every 3 months thereafter. Assess lipid parameters 4 to 8 weeks after start of therapy, then at 6 month intervals.

Gastrointestinal Perforation. GI perforation risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Gastrointestinal perforations have been reported in clinical studies, primarily as complications of diverticulitis. Promptly evaluate patients presenting with new onset abdominal symptoms.
Immunosuppression. Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with KEVZARA on the development of malignancies is not known but malignancies have been reported in clinical studies.

Hypersensitivity Reactions. Hypersensitivity reactions have been reported in association with KEVZARA. Hypersensitivity reactions that required treatment discontinuation were reported in 0.3% of patients in controlled RA trials. Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of KEVZARA immediately. Do not administer KEVZARA to patients with known hypersensitivity to sarilumab.

Active Hepatic Disease and Hepatic Impairment. Treatment with KEVZARA is not recommended in patients with active hepatic disease or hepatic impairment, as treatment with KEVZARA was associated with transaminase elevations.

Live Vaccines. Avoid concurrent use of live vaccines during treatment with KEVZARA due to potentially increased risk of infections. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving KEVZARA.

ADVERSE REACTIONS
For Rheumatoid Arthritis: The most common serious adverse reactions were infections. The most frequently observed serious infections included pneumonia and cellulitis. The most common adverse reactions (occurred in at least 3% of patients treated with KEVZARA + DMARDs) are neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections.

For Polymyalgia Rheumatica: Serious adverse reactions of neutropenia occurred in 2 patients (3.4%) in the KEVZARA group compared to none in the placebo group. The proportion of patients with serious infections was similar in the KEVZARA group (5.1%) compared to the placebo group (5.2%). The common adverse reactions occurring in ≥5% of patients treated with KEVZARA were neutropenia, leukopenia, constipation, rash pruritic, myalgia, fatigue, and injection site pruritus.

DRUG INTERACTIONS
Exercise caution when KEVZARA is co-administered with CYP substrates with a narrow therapeutic index (e.g. warfarin or theophylline), or with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure which may reduce the activity of the CYP3A4 substrate.

Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity such as in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signaling by IL-6Rα antagonists such as KEVZARA might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug concentrations.

USE IN SPECIFIC POPULATIONS
KEVZARA should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Because monoclonal antibodies could be excreted in small amounts in human milk, the benefits of breastfeeding and the potential adverse effects on the breastfed child should be considered along with the mother's clinical need for KEVZARA.

Use caution when treating the elderly.

Please see full prescribing information including boxed warning at the link at the bottom of this page or at Kevzarahcp.com.

Dr. Turck:
So just to recap, KEVZARA, or sarilumab, helps some patients to achieve disease remission and a reduced steroid burden, and the safety profile is consistent with previous studies in RA.

Dr. Spiera:
These are interesting findings. I can also say it has been really rewarding to be part of the SAPHYR study. It is exciting as an investigator to identify a biological rationale for a strategy to help address an unmet clinical need and then to be able to test the

hypothesis in a clinical trial. And then to see the success of the strategy is of course enormously gratifying, especially as it is so clinically relevant to our patients. And as a rheumatologist, it is exciting to have FDA approval for a therapy that will finally help address such an unmet need for PMR patients.

Dr. Turck:
That's a great way for us to round out our discussion and I want to thank my guest for his time today. Dr Spiera, it was great speaking with you.

Dr. Spiera:
Thank you for having me. I enjoyed being here.

ReachMD Announcer:
This program was sponsored by Sanofi and Regeneron. If you missed any part of this discussion, visit ReachMD.com/IndustryFeature. This is ReachMD. Be Part of the Knowledge.

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