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Examining Clinical Data for a Therapeutic Treatment Option in PMR

ReachMD Announcer:
You're listening to ReachMD. This medical industry feature, entitled "Examining Clinical Data for a Therapeutic Treatment Option in PMR," is sponsored by Sanofi and Regeneron. Here's your host, Dr Charles Turck.

Dr. Turck:
Welcome to ReachMD. I'm Dr Charles Turck and today we will be talking about the treatment option KEVZARA® (sarilumab) for patients with polymyalgia rheumatica, or PMR for short, who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper. Here with me are two renowned experts Dr Grace Wright, independent consultant rheumatologist in New York City, and Dr Gordon Lam from Arthritis & Osteoporosis Consultants of the Carolinas. Dr Wright, Dr Lam, thanks for joining us!

Dr. Lam:
It's my pleasure.

Dr. Wright:
Thank you for having me.

Dr. Turck:
Before we get into the content, a few notes. This program is sponsored by Sanofi. Both speakers are being compensated by Sanofi in connection with this presentation. The content contained in this presentation was developed by Sanofi and is not eligible for continuing medical education credits.

So let's dive right in, starting with you, Dr Lam. How has PMR typically been managed up until now?

Dr. Lam:
Well, first, I think it's important to mention that PMR is the most common inflammatory rheumatic condition in people over the age of 50.[1] It presents with pain and stiffness localized to the neck, shoulders, and pelvic girdle, which can really affect patients' daily activities.[1]

Now, corticosteroids have been considered the standard treatment for PMR, with prednisone usually being the first treatment used. Symptoms typically improve dramatically within the first few days of prednisone use, and once patients are clinically stable, they'll be gradually tapered off.[2,3]

Dr. Wright:
That's right; however, not all patients have an adequate response to corticosteroids and may require long-term corticosteroid use,[4] which can result in corticosteroid-related toxicities, even at low doses.[5-7]

Dr. Turck:
Interesting. So the risk from long-term corticosteroid use is one reason why some patients might benefit from exploring alternative therapies?

Dr. Lam:
Yes, clinicians know that the prolonged use of corticosteroids in an older patient population, such as in patients with PMR, is associated with adverse events.[2,5-8]

And it's not just the burden of long-term corticosteroid use that can be the problem. In fact, some patients cannot take corticosteroids at all because of comorbidities.[2,8] That's why we have been waiting for the FDA to approve an additional treatment option for patients who may need something beyond corticosteroids. So the FDA's approval of KEVZARA in February 2023 for PMR patients was welcome news.

KEVZARA's approval in PMR was based on an interesting study that looked at endpoints such as sustained remission rates and cumulative steroid doses over 52 weeks.[9]

There's a boxed warning associated with KEVZARA. So before we move on, let's take a moment to review that.

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.[19]

Avoid use of KEVZARA in patients with an active infection.

Reported infections include:[19]

- 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.[19] Patients with invasive fungal infections may present with disseminated, rather than localized, disease.[19]
- Bacterial, viral and other infections due to opportunistic pathogens.[19]

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.[19]

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection.[19]

Dr. Lam:
Please continue listening to the podcast to hear additional Important Safety Information and how to obtain the Prescribing Information

Dr. Turck:
Now, before we get into the trial data, let's turn to you, Dr Wright. What's the significance of IL-6 in PMR pathophysiology, and how does KEVZARA work?

Dr. Wright:
Well, the pathophysiology of PMR is not completely understood, but what we do know is that interleukin 6, or IL-6, is a pleiotropic proinflammatory cytokine that plays a critical role in PMR because it's a major driver of acute-phase response and systemic inflammation.[11]

IL-6 stimulates increases in C-reactive protein, or CRP, and the erythrocyte sedimentation rate, also known as ESR or sed rate, and it plays a role in pain, stiffness and other articular and systemic effects. So the effects of elevated IL-6 may affect patients' general daily activities.[11-15]Additionally, IL-6 levels correlate with PMR disease activity,[16] and circulating levels of the soluble IL-6 receptor may predict future relapses.[17]

Now in terms of how KEVZARA works, it's a human monoclonal antibody that binds with high affinity to both soluble and membrane-bound IL-6 receptors, and it's been shown to inhibit IL-6–mediated signaling to help counteract the effects of chronically elevated IL-6 levels in PMR.[9,17]

Dr. Turck:
Coming back to you, Dr Lam, what type of patient with PMR is appropriate for treatment with KEVZARA?

Dr. Lam:
So KEVZARA is indicated for the treatment of adult patients with PMR who have had an inadequate response to corticosteroids or who

cannot tolerate corticosteroid taper.[9]

It was approved for PMR in 2023 and has been indicated for adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs) since 2017.[18]

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr Charles Turck, and I'm speaking with Dr Gordon Lam and Dr Grace Wright about KEVZARA for the treatment of polymyalgia rheumatica.

So, Dr Wright, can you tell us how KEVZARA was studied and what the significance is of the trial's primary endpoint?

Dr. Wright:
Yes, so the safety and efficacy of KEVZARA were evaluated in the SAPHYR trial, which was a double-blind, placebo-controlled, 52-week, multicenter trial that compared KEVZARA and a 14-week GC taper against placebo and a 52-week taper of glucocorticoids.[9]

In fact, the trial included a predefined corticosteroid tapering schedule, which was a 14-week taper for the KEVZARA group versus a longer 52-week taper for the placebo group.[9] This is an important point because usually, patients with PMR are on corticosteroids for 1 or 2 years. In this trial, patients received either placebo, or 200 mg of KEVZARA once every 2 weeks, given as a subcutaneous injection.[9]

The study population on this trial were patients with active PMR symptoms that had at least 1 episode of PMR flare while tapering to at least 7.5mg of prednisone per day in the 12 weeks preceding randomization. Additionally, they required 10 mg/day or more for 8 weeks prior to randomization.[10] Lastly, more than half of patients at baseline had comorbidities - these include hypertension, osteoporosis, glaucoma, congestive heart failure, diabetes, and infections to name a few. Comorbidities such as these may need additional considerations when treating PMR patients.[20]

Now, the primary endpoint in this trial was the percentage of patients achieving sustained remission at Week 52, which was a composite endpoint that had not been studied before in PMR.[9,21-23]

And in this case, "sustained remission" was defined as meeting four criteria:

1. Disease remission, defined as the absence of signs and symptoms and CRP <10 mg/L no later than week 12,
2. Absence of disease flare from Week 12 through week 52, where 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
3. Sustained reduction of CRP to less than 10 mg/L from week 12 through week 52, and
4. Adherence to prednisone taper from week 12 through week 52.[9]

Dr. Turck:
With that in mind, Dr Lam, what were the results for this composite primary endpoint in the SAPHYR trial?

Dr. Lam:
Well, it was very interesting because nearly three times as many patients achieved statistically significant, sustained remission at Week 52 with KEVZARA plus 14-week corticosteroid taper. In fact, 10.3% of patients receiving placebo plus corticosteroids, which is the standard of care, over a 52-week taper, achieved the primary endpoint versus 28.3% of patients receiving Kevzara plus a 14-week corticoid steroid taper, which means nearly three times as many patients achieved sustained remission.[9] And even when acute-phase reactants criteria were removed from the primary endpoint in a sensitivity analysis, results were consistent with the primary analysis.[9]

Dr. Turck:
Can you elaborate on that sensitivity analysis for us, Dr Lam?

Dr. Lam:
Of course. So we know that KEVZARA can reduce the levels of acute-phase reactants in patients, and as Dr Wright mentioned earlier, the sustained reduction of CRP was one of the criteria that we used to define sustained remission. The sensitivity analysis was conducted to make sure that the difference in response seen between the groups was not significantly influenced by the CRP reduction. In fact, in the sensitivity analysis, the acute phase reactants (CRP and ESR) criteria were removed from the definition of the sustained remission.[9]

And the data show that the proportion of participants achieving a sustained remission at Week 52, excluding the acute-phase reactants, was greater in the KEVZARA plus 14-week taper group compared to the placebo plus 52-week glucocorticoid taper group. 31.7% of patients in the KEVZARA arm achieved sustained remission versus 13.8% in the comparator arm.[9]

And this is very important, because results of the sensitivity analysis were consistent with the primary endpoint results at Week 52.[9]

Dr. Turck:
Coming back to you, Dr Wright, what other endpoints supported the approval of KEVZARA in PMR?

Dr. Wright:
So, in addition to what Dr Lam just discussed, treatment with KEVZARA showed improvement across all components of sustained remission, including: absence of signs and symptoms and CRP <10 mg/L (disease remission) no later than week 12, absence of disease flare from Week 12 through week 52, sustained reduction of CRP to less than 10 mg/L from week 12 through week 52, and adherence to prednisone taper from week 12 through week 52.[9]

Additionally, by week 12, 46.7% of patients in the KEVZARA arm achieved disease remission compared to 37.9% of patients in the comparator arm, and this was while taking lower doses of corticosteroids[9]: in fact, at week 12 the KEVZARA arm was taking 3mg of corticosteroid daily, versus 9mg of corticosteroid daily for the comparator arm, excluding rescue corticosteroid, per study protocol.[20] Patients in the KEVZARA arm received a lower cumulative corticosteroid dose during the 52-week treatment period vs the comparator arm.[9] The cumulative median corticosteroid dose over the 52-week study for the patients treated with KEVZARA was about a third of the dose for patients in the placebo-controlled arm, at 777 mg versus 2044 mg, and the mean cumulative corticosteroid dose was 1040 mg for the KEVZARA arm, with standard deviation of 612, and 2236 mg for the comparator arm, with standard deviation of 839.[9] And so if we convert these numbers to a mean daily dose, we find that over the course of the study, patients in the KEVZARA plus 14-week corticosteroid taper arm received 3.17 mg of corticosteroids per day versus a mean daily dose of 7.23 mg per day in the placebo plus 52-week corticosteroid taper arm.[20]

As for the other endpoints, which included signs and symptoms of PMR, in an intent to treat analysis at Week 52, 45% of patients in the KEVZARA arm had no PMR signs and symptoms and had not received rescue therapy compared to 14% of patients in the comparator arm. Let's remember that these results are descriptive, no definitive conclusions can be made as data were not multiplicity controlled.[10]

Finally, 55% of patients in the KEVZARA arm did not experience a PMR flare during week 12 through week 52 compared to 32.8% in the comparator arm and 50 percent of patients in the KEVZARA arm demonstrated successful adherence to the prednisone taper from Week 12 through Week 52, compared with 24.1% of patients in the placebo controlled arm.[9]

Dr. Turck:
Thank you, Dr Wright. Could you also tell us how KEVZARA is administered and its recommended dosage?

Dr. Wright:
Sure. The recommended dosage of KEVZARA in PMR is 200 mg once every 2 weeks, given as a subcutaneous injection, in combination with a tapering course of systemic corticosteroids. KEVZARA can also be used as monotherapy following discontinuation of corticosteroids.[9]

And no dose adjustments are recommended based on age, gender, race, or weight.[9]

Dr. Turck:
And what about the safety profile of KEVZARA, Dr Lam? What can you tell us about those findings?

Dr. Lam:
Well, KEVZARA has an established safety profile from RA trials. In fact, it has been studied for 10 years in clinical trials for RA, in addition to the recent PMR trial.[9,10,24-31]

In the SAPHYR trial, the common adverse reactions occurring in 5% or more of patients treated with KEVZARA were neutropenia (15.3%), leukopenia (6.8%), constipation (6.8%), myalgia (6.8%) rash pruritic (5.1%), fatigue (5.1%) and injection site pruritus (5.1%) while none of these events occurred in the comparator arm. A higher incidence of serious adverse events was observed in the comparator arm with 20.7% compared to the KEVZARA arm with 13.6%.

Additionally, serious adverse reactions of neutropenia occurred in 2 patients (3.4%) in the KEVZARA group compared to none in the placebo group. The most common adverse reactions that resulted in permanent discontinuation of therapy with KEVZARA were

neutropenia, which occurred in 3 patients, or 5.1%; infection (including COVID-19), which occurred in 3 patients 5.1%; intervertebral discitis which occurred in one patient, and pneumonia which occurred in one patient.[9]

The incidence of infections was lower in the KEVZARA group with 37.3%, compared to the placebo-controlled group with 50% and the incidence of serious infections was similar in the KEVZARA group, with 5.1% compared to the placebo-controlled group with 5.2%.[9]

Dr. Turck:
Thank you both for breaking all of these data down for us. And now, let's hear additional Important Safety Information for KEVZARA.

ReachMD Announcer:
CONTRAINDICATION
Do not use KEVZARA in patients with known hypersensitivity to sarilumab or any of the inactive ingredients.[19]

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.[19]

- Hold treatment with KEVZARA if a patient develops a serious infection or an opportunistic infection.[19]
- Patients with latent TB should be treated with standard antimycobacterial therapy before initiating KEVZARA.[19]
- 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.[19]
- 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.[19]
- Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with KEVZARA.[19]

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.[19]

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.[19]

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.[19]

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.[19]

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.[19]

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.[19]

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.[19]

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.[19]

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.[19]

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.[19]

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.[19]

Use caution when treating the elderly.[19]

Please see full Prescribing Information, including Boxed WARNING, at adjacent link or at kevzarahcp.com.

Dr. Turck:
Dr Wright, do you have any final thoughts on PMR management using KEVZARA?

Dr. Wright:
Yes, so as an approved option for the treatment of PMR, KEVZARA has an established safety profile with more than 10 years of studies between PMR and rheumatoid arthritis and it should be considered for adult patients with PMR who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper.[9,10,24-31]

Dr. Lam:
And KEVZARA was studied in the SAPHYR trial with a shorter 14 week tapering schedule, which is a very welcome change in rheumatology.

Dr. Turck:
That's a great comment to round out our program, and I want to thank my guests, Dr Grace Wright and Dr Gordon Lam, for sharing all of this key information on KEVZARA. Dr Wright, Dr Lam, it was great speaking with you both today.

Dr. Wright:
Thank you for having me.

Dr. Lam:
Yes, thank you so much; I really enjoyed it.

ReachMD Announcer:
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