Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/the-role-of-il-6-in-pmr-from-disease-pathogenesis-to-treatment/26711/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Role of IL-6 in PMR: From Disease Pathogenesis to Treatment

ReachMD Announcer:
You're listening to ReachMD. This medical industry feature, titled "The Role of IL-6 in PMR: From Disease Pathogenesis to Treatment," is sponsored by Sanofi. The speakers featured in this program are being compensated by Sanofi, and the content contained in this presentation was developed by Sanofi and is not eligible for continuing medical education credits. And now, here's your host, Dr Charles Turck.

Dr Turck:
Welcome to ReachMD. I'm Dr Charles Turck, and today, we'll be talking about the role of IL-6 in polymyalgia rheumatica, or PMR.

Joining me in this discussion are two rheumatology experts, Dr Adam Brown, a rheumatologist, and Dr Alexa Meara, an associate professor. Thank you both for joining us today!

Dr Brown:
It's a pleasure to be here.

Dr Meara:
Thank you for having me.

Dr Turck:
Let's dive right in.

Dr Brown, could you start by giving us an overview of what drives inflammation in PMR and how IL-6 plays a role in that process?

Dr Brown:
Absolutely. PMR is an inflammatory disorder that typically affects older adults, causing pain and stiffness primarily in the shoulders, neck, and hips.[1-4] While we don't fully understand the exact cause of PMR, we know that both innate and adaptive immune responses contribute to the disease.[5]

One of the key ways the immune system contribute to PMR is by releasing proinflammatory cytokines.[5] And a major player here is IL-6, a cytokine that drives much of the inflammation that we see in PMR.[5,6]

In fact, IL-6 has been the focus of recent studies in PMR because its levels correlate with disease activity. IL-6 is believed to play a significant role in PMR pathogenesis[5,6]

Dr Turck:
Thank you, Dr Brown, for the clear explanation.

Dr Meara, building on what Dr Brown mentioned, could you explain more about how IL-6 functions in the body and in PMR?

Dr Meara:
Of course. IL-6 is a cytokine that affects many different cell types and regulates a wide range of biological processes.[3,7]

In healthy individuals, IL-6 levels in the plasma are virtually undetectable. But in patients who are newly diagnosed with PMR, we consistently see a significant increase in IL-6 levels—often at least 4 times higher than in healthy controls before treatment starts.[6]

Both levels of IL-6 cytokine and its soluble IL-6 receptor (sIL-6R) have been linked to disease activity. Higher levels of sIL-6Rs correlate with more frequent relapses and may even predict future relapses.[8]

Dr Brown:
That's a great point. In fact, research has shown that some patients with a certain genetic make-up, which is linked to higher circulating IL-6 levels, are actually more likely to experience relapses.[9]

All this evidence points to IL-6 as an important factor in PMR pathogenesis. Its levels are not only potentially an indication of disease severity but also to the likelihood of relapse and symptom recurrence.[1,6,8-12]

Dr Turck:
That's intriguing, Dr Brown. Would you tell us how exactly does IL-6 contribute to the symptoms that patients with PMR experience?

Dr Brown:
IL-6 can drive both local and systemic inflammation, which is involved in several symptoms that PMR patients experience such as pain and stiffness, which may impact patients' daily activities and routines.[13,14]

Dr Meara:
Exactly. I also would like to add that, because IL-6 stimulates increases in CRP and ESR, it may also affect other biological functions in patients with PMR.[1,6,8-12]

Dr Turck:
Thank you both for this insightful discussion on the role of IL-6 in PMR.

And so that brings us to KEVZARA. Given the important role of IL-6 in PMR, Dr Brown, what are your thoughts about KEVZARA (sarilumab) as a treatment option for your patients with PMR?

Dr Brown:
KEVZARA is the first and only IL-6 receptor inhibitor approved for PMR. It is indicated for adult patients with PMR who have had an inadequate response to corticosteroids (CS) or can't tolerate CS taper.[16]

Besides PMR, KEVZARA is also approved for 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 and for patients who weigh 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA).[14]

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.[14]

While many cytokines are elevated in PMR, IL-6 is currently the only one with an approved therapy specifically designed to inhibit its activity.[5,16,18]

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

Voiceover:
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.[16]

Avoid use of KEVZARA in patients with an active infection.

Reported infections include[16]:

- 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[16]

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection[16]

Please continue listening to the podcast to hear additional Important Safety Information and how to obtain the Prescribing Information, including BOXED WARNING.

Dr Turck:
Thank you for the information. Dr Brown, would you walk us through the clinical trial for KEVZARA in PMR?

Dr Brown:
Absolutely. 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 glucocorticoid (GC) taper against placebo and a 52-week taper of GCs.[16,19]

In this trial, patients were randomized to receive KEVZARA 200 mg as a subcutaneous injection every 2 weeks with a predefined 14-week taper of prednisone or placebo every 2 weeks with a predefined 52-week taper of prednisone.[16]

The study included patients with active PMR symptoms who had at least 1 episode of a PMR flare, while tapering to at least 7.5 mg of prednisone per day in the 12 weeks prior to randomization. In addition, these patients required 10 mg/day or more for 8 weeks before randomization.[19]

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.[17]

Dr Turck:
Thank you, Dr Brown for the information about the study design. Dr Meara, would you tell us about the study's primary endpoint and its significance?

Dr Meara:
Certainly. The primary endpoint in this trial was the percentage of patients achieving sustained remission at Week 52, which was a composite endpoint.[16]

Sustained remission in this trial was defined as meeting all 4 components.[16]

1. Absence of signs and symptoms and CRP <10 mg/L (disease remission) no later than Week 12.
2. Absence of disease flare from Week 12 through Week 52. A flare was defined as a recurrence of signs and symptoms attributable to active PMR that require an increase in corticosteroid dose, or elevated SED rate, 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.
4. Successful adherence to prednisone taper from Week 12 through Week 52. Successful adherence to the prednisone taper from Week 12 through Week 52 was defined as patients who had not taken rescue therapy from Week 12 through Week 52 and might include the use of any excess prednisone (beyond the protocol CS-tapering regimen) with a cumulative dose of ≤100 mg (or equivalent) steroids, which could be used to manage AEs not related to PMR. The cumulative dose of excess prednisone use was counted from baseline to Week 52

It is worth noting that this composite endpoint had never been studied before in PMR.[20-22]

Dr Turck:
Thanks for breaking that down for us, Dr Meara.

Dr Brown, would you tell us about the results regarding this composite endpoint?

Dr Brown:
Yes, well, it looks like it's quite encouraging because nearly 3 times as many patients in the KEVZARA arm achieved statistically significant, sustained remission at Week 52 compared to patients on placebo. 10.3 percent of patients receiving placebo plus corticosteroids achieved the endpoint over a 52-week taper, whereas 28.3 percent of patients receiving KEVZARA with the 14-week CS

taper achieved this composite endpoint.[16]

Dr Turck:
That's a notable difference.

Dr Meara, would you take us through the data for each component of the composite endpoint?

Dr Meara:
Sure. KEVZARA showed improvement across all components of the sustained remission.[16]

46.7% of patients in the KEVZARA arm achieved disease remission by Week 12 vs 37.9% of patients in the placebo arm.[16]

By Week 12, patients in the KEVZARA arm were on 3 mg of daily CS, while patients in the placebo-controlled arm were receiving 9 mg of daily CS per protocol, excluding rescue CS.[16,23]

55% of patients in the KEVZARA arm achieved absence of disease flare from Weeks 12 through 52 vs 32.8% in the placebo group.[16]

66.7% of patients in the KEVZARA arm achieved sustained reduction of CRP from Weeks 12 through 52 vs 44.8% in the placebo group.[16]

50% of patients in the KEVZARA arm achieved successful adherence to the prednisone taper from Week 12 through 52 vs 24.1% in the placebo group.[16]

Additionally, the trial showed that KEVZARA had a steroid-sparing effect, with patients receiving a lower cumulative corticosteroid dose over the 52-week period compared to the placebo group.[16]

Dr Turck:
Thank you, Dr Meara, for the detailed breakdown of the results.

Dr Brown, would you tell us more about the steroid-sparing effects of KEVZARA observed in the SAPHYR trial?

Dr Brown:
Absolutely. Like Dr Meara just mentioned, one of the components of sustained remission was adherence to prednisone taper, in fact 30 of the 60 patients in the KEVZARA arm achieved successful adherence to prednisone taper from Week 12 through Week 52 compared with 14 out of the 58 in the placebo-controlled arm.

Successful adherence to the prednisone taper from Week 12 to Week 52 is defined as patients who did not take rescue therapy from Week 12 through Week 52 and may include the use of any excess prednisone (beyond the per protocol CS tapering regimen) with a cumulative dose of ≤100 mg (or equivalent), such as those employed to manage AEs not related to PMR. The cumulative dose of excess prednisone use was counted from baseline to Week 52.

Additionally, over the 52-week study, patients treated with KEVZARA received a median cumulative steroid dose of 777 mg vs 2044 mg in the placebo group.[16]

The mean cumulative corticosteroid dose was 1040 mg with a standard deviation of 612 mg for the KEVZARA arm and 2236 mg for the placebo arm with a standard deviation of 839 mg.[16]

And so, if we convert these numbers into a mean daily dose, patients in the KEVZARA plus 14-week steroid averaged at 3.17 mg per day compared to 7.23 mg per day in the placebo plus 52-week steroid taper arm.[16,23]

Dr Turck:
What about the safety profile of KEVZARA, Dr Meara?

Dr Meara:
KEVZARA has an established safety profile, spanning over 10 years of combined studies across RA, PMR and pJIA.[19,24-31]

In the SAPHYR trial, common adverse reactions occurring in 5 percent or more of patients treated with KEVZARA were neutropenia (15.3 percent), leukopenia (6.8 percent), constipation (6.8 percent), myalgia (6.8 percent), pruritic rash (5.1 percent), fatigue (5.1 percent), and injection site pruritus (5.1 percent), whereas none of these events occurred in the placebo group. A higher incidence of serious adverse events was observed in the comparator arm with 20.7% compared to the KEVZARA arm with 13.6%. Serious adverse reactions of neutropenia occurred in 2 patients (3.4 percent) in the KEVZARA group versus 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 (5.1%), infections, which also occurred in 3 patients (5.1%), including one patient who had COVID-19, one patient who had intervertebral discitis, and one patient who had pneumonia.[16,17]

The incidence of infections was lower in the KEVZARA group at 37.3 percent compared to the placebo group at 50 percent. The incidence of serious infections, however, was similar in the KEVZARA and placebo-controlled groups, at 5.1 percent and 5.2 percent, respectively.[16]

Dr Turck:
Thank you both for breaking down these data for us. And now, let's hear additional Important Safety Information for KEVZARA and how to obtain the full Prescribing Information, including BOXED WARNING.

Voiceover:
CONTRAINDICATION
Do not use KEVZARA in patients with known hypersensitivity to sarilumab or any of the inactive ingredients.[32]

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. Among opportunistic infections, TB, candidiasis, and pneumocystis were reported with KEVZARA. The most frequently observed serious infections with KEVZARA in RA patients included pneumonia and cellulitis.[32]
  - 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.[32]
- ***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.[30]
- ***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.[32]
- ***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.[32]
- ***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.[32]
- ***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.[32] Prior to initiating treatment, it is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines.

ADVERSE REACTIONS

- **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.[32]

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.[32]
- 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.[32]

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.[32]
- Use caution when treating the elderly.[32]

Advise patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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

Dr Turck:
Before we wrap up, do you have any final thoughts you'd like to share with our audience?

Dr Brown:
Absolutely. When treating patients with PMR, remember that IL-6 is a key inflammatory cytokine in PMR, and its levels are not only a potential indicator of disease severity but also associated with the risk of relapse and recurrence of symptoms.[1,6,8-12] This makes inhibiting IL-6 receptors a compelling strategy to potentially impact PMR symptoms.[16]

Dr Meara:
Exactly, and in the SAPHYR trial, KEVZARA, an IL-6 receptor inhibitor, demonstrated sustained, steroid-free remission for patients after 52 weeks of treatment with a predefined 14 week CS taper.[16]

So a treatment option like KEVZARA should be considered as an option for appropriate adult patients with PMR who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid tapers.[16]

Dr Turck:
Great points to end on. I want to thank both Dr Meara and Dr Brown for reviewing the role of IL-6 in PMR as well as the clinical and safety data for KEVZARA, an IL-6 receptor inhibitor, in PMR.[16]

It's been a real pleasure speaking with you both today.

Dr Meara:
Thank you for having me today.

Dr Brown:
Yes, thank you; I really enjoyed the conversation.

ReachMD Announcer:
This medical industry feature was sponsored by Sanofi. To revisit any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.