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From Primary Care to Rheumatology: Evolving PMR Management in an Era of Innovative Treatment Options

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Dr. Turck:
Welcome to ReachMD. I'm Dr Charles Turck and today, we'll be talking about the diagnosis and treatment of polymyalgia rheumatica, from both primary care and rheumatology perspectives. Joining me in this discussion are 2 experts, Dr Mona Amin, who's a rheumatologist at Arizona Arthritis & Rheumatology Associates, and Dr Shital Patel, who's an internal medicine specialist at HonorHealth. Both doctors practice in Scottsdale, Arizona. Dr Amin, Dr Patel, thank you both for being here!

Dr. Amin:
It's my pleasure.

Dr. Patel:
Thank you for having me.

Dr. Turck:
To get us started, Dr Patel, can you tell us why diagnosing patients with polymyalgia rheumatica, or PMR, is often challenging and could take a long time?

Dr. Patel:
The journey to a PMR diagnosis can be quite complicated and often long for some patients. Many patients go weeks or even months without a proper diagnosis, which may impact their quality of life.[1,2] Patients typically present with pain and stiffness, primarily in the neck, shoulders, and hips, although other areas can be affected as well.[3-5]

When symptoms develop, some patients may go to see their primary care physicians, while others may see orthopedic specialists or other doctors to address their symptoms. During this time, some may receive a PMR diagnosis, but others could be misdiagnosed because there are many conditions that mimic PMR symptoms. In some cases, patients may receive treatment without a definitive diagnosis for about 6 to 24 months.[1,6,7]

This complexity of diagnosis is compounded by the diverse ways patients describe their symptoms, ranging from severe pain and muscle aches to pain secondary to stiffness.[8]

Dr. Amin:
I agree—diagnosing PMR can be quite challenging because there is no specific confirmatory test for it.[9] Clinicians need to look at the patient's clinical history, inflammatory markers, and other laboratory results.[10] Sometimes, imaging is also necessary to differentiate PMR from other conditions.[6]

Dr. Turck:
Thank you. Dr Patel, how do you approach diagnosing PMR?

Dr. Patel:
I start by reviewing the patient's clinical history for common PMR symptoms and consider classification criteria, such as age over 50, bilateral shoulder pain, morning stiffness over 45 minutes, and elevated CRP and ESR levels. However, it is important to note that some patients may have normal ESR and CRP levels.[10-14]

If a patient is showing PMR symptoms, I then consider excluding mimicking conditions like systemic disorders, such as rheumatoid arthritis, inflammatory myopathies, and fibromyalgia, as well as localized conditions that can cause proximal musculoskeletal pain, such as rotator cuff pathology, frozen shoulder, or greater trochanteric pain syndrome.[7,12,15]

Once I do all of that, I typically refer patients to a rheumatologist for confirmation of diagnosis and treatment.

Dr. Amin:
Also, PMR may begin simultaneously or consecutively with giant cell arteritis, or GCA. About 10% to 30% of patients diagnosed with PMR are also found to have GCA.[16,17] Due to risks of serious ischemic complications and vision loss, GCA should be treated as a medical emergency.[18]

Given the complexities of these cases, a prompt referral to a rheumatologist is essential.[6,12]

Dr. Turck:
I'd like to dive deeper into the topic of referrals in PMR. Can you explain when an early referral to rheumatology is recommended?

Dr. Patel:
Once I suspect PMR, I typically refer my patients to a rheumatologist. I refer to a rheumatologist with more urgency when patients have atypical clinical presentations or there is diagnostic uncertainty. This could include situations where PMR was initially suspected but patients don't respond well to corticosteroids, or when patients are contraindicated to corticosteroids or need long-term corticosteroids.[12]

Dr. Amin:
Right. To add on to that, collaboration between primary care and rheumatology providers is key to ensuring our patients receive optimal care.[6]

In fact, a delay of more than 1 week in specialist evaluation can lead to a greater number of patients receiving unnecessary corticosteroids, which may complicate further evaluation and may be associated with frequent adverse effects when used at high dose or for long periods of time.[6,19]

Today, we'll be taking a look at KEVZARA (sarilumab) indicated for treatment of adult patients with polymyalgia rheumatica (PMR) who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper.[20] A timely referral to rheumatology will help appropriate patients access this treatment option.[20]

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

Voiceover:
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.[20]

Avoid use of KEVZARA in patients with an active infection. Reported infections include:[20]

- 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[20]
- Invasive fungal infections, such as candidiasis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease[20]
- Bacterial, viral and other infections due to opportunistic pathogens[20]

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.[20]

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection.[20]

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

Dr. Turck:
So now that we've reviewed some Important Safety Information for KEVZARA, let's turn back to you, Dr Amin. Could you explain how KEVZARA works, and how might it impact our patients with PMR?

Dr. Amin:
KEVZARA is the first and only IL-6 inhibitor approved for patients with PMR.KEVZARA offers an option for adults with PMR who have had an inadequate response to corticosteroids, or can't tolerate the CS taper.[20]

It works by binding 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-6levels in PMR.[20]

KEVZARA has been approved by the FDA for treating three different diseases. It's indicated for the 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,
- adult patients with PMR who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper,
- and patients who weight 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA).

The KEVZARA clinical program in RA, PMR, and pJIA encompasses more than 10 years of studies.[20,22-30]

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr Charles Turck, and I'm speaking with Drs Mona Amin and Shital Patel about PMR treatment.

Dr. Patel, can you tell us more about the clinical trial for KEVZARA in PMR?

Dr. Patel:
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, or GC, taper against placebo and a 52-week taper of GCs.[20]

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.[20]

The study population included patients with active PMR symptoms who had at least 1 episode of PMR flare, while tapering to at least 7.5 mg of prednisone per day in the 12 weeks prior to randomization. Additionally, they required 10 mg/day or more for 8 weeks before randomization.[30]

Dr. Turck:
With that in mind, Dr Amin, what was the study's primary endpoint?

Dr. Amin:
So, the primary endpoint in this trial was the percentage of patients achieving sustained remission at Week 52, which was a composite endpoint.[20]

Sustained remission in this trial was defined as meeting all 4 components[20]

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 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. Successful adherence to prednisone taper from Week 12 through Week 52. Successful adherence to the prednisone taper from Week 12 through Week 52 is defined as patients who did not take rescue therapy from Week 12 through Week 52 and might include the use of any excess prednisone (beyond the per protocol CS tapering regimen) with a cumulative dose of ≤100 mg (or equivalent), 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.[20,31-33]

Dr. Turck:
So then, Dr Patel, what was the result of this composite endpoint in the SAPHYR trial?

Dr. Patel:
Well, the result was 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 this endpoint over a 52-week taper, whereas 28.3 percent of patients receiving KEVZARA with a 14-week CS taper achieved this composite endpoint.[20]

Dr. Turck:
And what about the other endpoints that supported the approval of KEVZARA in PMR, Dr Amin?

Dr. Amin:
KEVZARA showed improvement across all components of sustained remission.[20]

For example, 46.7 percent of patients treated with KEVZARA achieved disease remission by Week 12 compared to 37.9 percent in the placebo group.[20]

By Week 12, patients on KEVZARA were on 3 mg of daily CS, while patients in the placebo group were receiving 9 mg of daily CS per protocol, excluding rescue CS.[34]

55 percent of patients on KEVZARA did not experience flares from Weeks 12 through 52 versus 32.8 percent in the placebo group.[20]

Additionally, 66.7 percent of patients on KEVZARA achieved sustained reduction of CRP of less than 10 mg/L from Weeks 12 through 52, compared to 44.8 percent in the placebo group,[20] and 50 percent of patients treated with KEVZARA achieved successful adherence to prednisone taper from Week 12 through 52 versus 24.1 percent on placebo.[20]

Lastly, the trial also showed that KEVZARA had a steroid-sparing effect, resulting in a lower cumulative corticosteroid dose during the 52-week treatment period in the KEVZARA arm compared to the placebo-controlled arm.[20]

Dr. Turck:
With that being said, Dr Patel, can you dive deeper into the steroid-sparing effects of KEVZARA based on the findings from the SAPHYR trial?

Dr. Patel:
Absolutely. Over the 52-week study period, patients treated with KEVZARA received a median cumulative corticosteroid dose of 777 mg vs 2044 mg in the placebo group.[20]

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.[20]

And so, if we convert these numbers into a mean daily dose, patients in the KEVZARA plus 14-week CS taper averaged at 3.17 mg per day compared to 7.23 mg per day in the placebo plus 52-week CS taper arm.[34]

Dr. Turck:
Now, let us look at one more aspect of this trial. Dr Amin, what can you tell us about the safety profile of KEVZARA?

Dr. Amin:
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 reasons for 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.[20]

Lastly, 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.[20]

Dr. Turck:
Thank you both for breaking this data down 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.[35]

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 included pneumonia and cellulitis.[35]

Hold treatment with KEVZARA if a patient develops a serious infection or an opportunistic infection.[35]

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.[35]

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.[35]

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.[35]

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.[35]

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.[35]

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.[35]

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.[35]

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.[35]

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.[35]

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.[35]

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.[35]

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.[35]

Use caution when treating the elderly.[35]

Advise patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use). Please see full Prescribing Information, including Boxed WARNING, at adjacent link or at **kevzarahcp.com**.

Dr. Turck:
Can you share with us how KEVZARA is administered and what the recommended dosage of KEVZARA is for PMR?

Dr. Amin:
The recommended dosage of KEVZARA for PMR is 200 mg once every 2 weeks, given as a subcutaneous injection in combination with a tapering course of systemic corticosteroids.[20]

There are no recommended dose adjustments based on age, gender, race, or weight.[20]

Dr. Turck:
Now before we close, do you have any final thoughts to share with our audience?

Dr. Patel:
I just want to remind the audience that KEVZARA has an established safety profile with more than 10 years of studies between RA, PMR, and pJIA, and it should be considered for appropriate patients with PMR.[20,22-29]

Dr. Amin:
Remember that patients in the KEVZARA arm received a median cumulative corticosteroid dose of 777 mg versus 2044 mg in the placebo group. Patients received an average of 3.17 mg of corticosteroids per day versus a mean daily dose of 7.23 mg per day in the placebo arm.[34] This difference can be meaningful for patients as they navigate CS tapering.

Appropriately referring PMR patients to rheumatologists gives them the opportunity to be considered for KEVZARA, an FDA-approved option for PMR patients who need options beyond corticosteroids.[6,20]

Dr. Turck:
That's a great comment to round out our program, and I want to thank my guests, Drs Mona Amin and Shital Patel, for sharing how we can optimize PMR care and the key data on KEVZARA. Dr Amin, Dr Patel, it was a pleasure speaking with you both today.

Dr. Amin:
Thank you for having me.

Dr. Patel:
Yes, thank you so much; I really enjoyed our conversation.

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