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Early Referral in PMR Management and the Impact on Outcomes

Dr. Turck:
Welcome to today's podcast. I'm your host, Dr Charles Turck. Today we're going to be diving into the topic of early referral for polymyalgia rheumatica, or PMR.

Here to guide us through is Dr Amar Majjhoo, a doctor of rheumatology and partner at Shores Rheumatology PC. With us also Dr Naureen Alim, a partner and rheumatologist at CLS Health, Houston.

Dr Majjhoo:
Thank you for having us.

Dr Alim:
Happy to be here.

Dr. Turck:
Dr Majjhoo, to start us off—what's the current landscape like when it comes to referring PMR patients to specialists?

Dr Majjhoo:
Well, until recently, there wasn't a clear consensus on when patients with suspected PMR should be referred. PMR can be difficult to diagnose. The symptoms are often vague, variable, and overlap with many other conditions. And because PMR typically affects older adults, who often have multiple health issues, the diagnostic process becomes even more complex. There's no gold-standard test for PMR, which means misdiagnosis is common. General practitioners encounter only about three new PMR cases per year on average and some studies estimate that PMR is correctly diagnosed only about 50% of the time.[1,2] Even among rheumatologists, misdiagnosis rates may reach up to 30%.[2]

A recent global survey highlighted just how much variation exists in PMR diagnosis and management. Only about 25% of patients were referred to a specialist for diagnostic confirmation, and most of those patients had already started steroids by the time they saw a rheumatologist.[3]

Dr. Turck:
Dr Alim, would you tell us about when patients should be referred to a specialist to optimize outcomes?

Dr Alim:
Yeah. So, if a patient is diagnosed with PMR in primary care, it's important to think about referring them to a specialist—especially when the presentation isn't typical. So that could mean signs like peripheral inflammatory arthritis, systemic symptoms, low inflammatory markers, or if the patient is 50 years of age or older.[4,5] Before referring, primary care should complete a detailed history, physical exam, and basic lab work.[4]

Referral is also key when there's limited experience managing PMR or patients that may be at a higher risk of therapy-related side effects, relapse, or prolonged steroid use, such as patients with diagnostic uncertainties or comorbid conditions that may complicate the treatment of PMR.[2,4]

In fact, recent guidance from Europe suggests that delaying referral, especially by more than one week in patients suspected of PMR who may be exhibiting severe symptoms, or when disease mimics have not been ruled out, can lead to unnecessary or prolonged use of

corticosteroids.[2] Starting steroids should be delayed until after the specialist evaluation, if possible. This not only complicates the diagnosis but also increases the risk of steroid-related side effects. These adverse events can be significant, especially in older adults.[2,6-8]

Dr. Turck:
Dr Majjhoo, why is early referral to a rheumatologist such an important step in PMR care?

Dr Majjhoo:
There are several key reasons.

- First, about 1 in 5 patients diagnosed with PMR may also have giant cell arteritis, or GCA.[5] That's a medical emergency and needs immediate treatment.[9]
- Second, PMR symptoms can overlap with other conditions, including rheumatoid arthritis or fibromyalgia.[10,11] As I mentioned earlier, there is no single test for PMR, so a thorough evaluation, which often includes imaging, is needed to confirm the diagnosis and rule out mimics.[4,11,12] Common PMR mimics include rheumatoid arthritis, fibromyalgia, infection, and cancer, among others.[11]
- Third, early referral can be associated with a faster diagnosis of PMR and the potential of a decreased starting dose of corticosteroid treatment.[13]
- And finally, there are targeted therapies that have been approved for the treatment of PMR, which some patients may benefit from.[14] Timely referral can help ensure that patients have access to these options, supported by specialist input to manage them appropriately.[2]

That's why guidelines for PMR management suggest referral to a rheumatologist and emphasize early referral as a priority for certain patients.[4,15]

Dr. Turck:
Dr. Alim, would you comment on what you find particularly significant about the impact of early referral on patient outcomes?

Dr Alim:
I see early and rapid referral as an essential component of optimizing treatment outcomes, especially prior to initiating steroids. In my experience, diagnostic and treatment decisions from the outset, have a huge impact on disease course and potential outcomes.[15]

Dr. Turck:
Dr Majjhoo, what will it take to implement these guidelines effectively?

Dr Majjhoo:
Effective management relies on strong collaboration between primary care and rheumatology.[15] In my practice, we do our best to accommodate urgent referrals from primary care. At the healthcare system level, expanding specialist access is crucial - particularly in underserved or rural areas.[3] With an aging population, the prevalence of PMR may increase.[16,17] Combined with a shortage in rheumatologists, these factors make it essential to plan ahead for workforce and resource needs.[18]

Dr. Turck:
You mentioned earlier that there are alternative therapies available. Would you elaborate on that?

Dr Majjhoo:
Yes. There are targeted treatments for PMR, such as KEVZARA® (sarilumab), the first and only IL-6 receptor inhibitor approved for PMR.[14,19] It is indicated for adult patients with PMR who have had an inadequate response to steroids or who can't tolerate the steroid taper.[14]

Besides PMR, KEVZARA is approved for adult patients with moderate-to-severe active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs. KEVZARA is also approved for patients who weigh over 63 kg, or 139 lbs, with active polyarticular juvenile idiopathic arthritis.[14]

However, there is 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.[14]

Avoid use of KEVZARA in patients with an active infection.

Reported infections include[14]:

- **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.[14]

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection.[14]

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

Dr. Turck:
Dr Alim, would you explain to us how KEVZARA works?

Dr Alim:
Sure. KEVZARA is a human monoclonal antibody that binds with a high affinity to both soluble and membrane bound IL-6 receptors.[14]

It has been shown to inhibit IL-6-mediated signaling, to help counteract the effects of chronically elevated IL-6 levels in PMR.[14]

While other cytokines are also implicated in the pathogenesis of PMR, IL-6 has an approved therapy specifically designed to inhibit its activity.[14,20,21]

Dr. Turck:
Thank you for that explanation. And Dr Majjhoo, would you provide us with an overview of the clinical trial for KEVZARA in PMR?

Dr Majjhoo:
Of course. 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 corticosteroid taper against placebo and a 52-week corticosteroid taper.[14]

In this trial, patients were randomized into two arms. The KEVZARA arm received 200 mg as a subcutaneous injection every 2 weeks with a predefined 14-week taper of prednisone. In the placebo group, the placebo was received every 2 weeks with a predefined 52-week taper of prednisone.[14]

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 dose equivalent per day in the 12 weeks prior to the randomization. In addition, these patients had a history of at least 8 weeks of corticosteroid treatment with a minimum of 10 mg/day prednisone equivalent.[22]

At baseline, over half of the patients presented with comorbidities such as hypertension, osteoporosis, cataracts, and hypothyroidism. Conditions like these may require additional considerations when managing PMR patients.[19]

Dr. Turck:
Dr Alim, would you elaborate on the study's primary endpoint and its significance?

Dr Alim:
Of course. The primary endpoint in this trial was the percentage of patients achieving sustained remission at Week 52, which was a composite endpoint.[14]

So sustained remission in this trial was defined as meeting all of the following 4 components.[14]

- First, the absence of signs and symptoms, and a CRP level of less than 10 mg/L, indicating disease remission, no later than Week 12.
- Second, the 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 due to active PMR, along with an increase in corticosteroid dose.
- Third, sustained reduction of CRP to less than 10 mg/L from Week 12 through Week 52, and
- Lastly, successful adherence to the steroid taper from Week 12 through Week 52. This was defined as patients who did not require rescue therapy from Week 12 through Week 52. This could include the use of any excess prednisone, beyond the protocol-defined taper, provided the total excess dose did not exceed 100 mg (or equivalent). This additional prednisone could be used for managing adverse events unrelated to PMR. And the cumulative dose of excess prednisone use was counted from baseline to Week 52.[19]

It is important to highlight that this composite endpoint had never been studied before in PMR.[23-25]

Dr. Turck:
Thanks for walking us through that. And Dr Majjhoo, would you share the results related to this composite endpoint?

Dr Majjhoo:
The results were quite promising - nearly three times as many patients in the KEVZARA arm achieved statistically significant, sustained remission at Week 52 compared to the placebo plus corticosteroid arm. Specifically, 10.3% of patients receiving the placebo plus corticosteroids reached this endpoint over a 52-week taper, while 28.3% of patients receiving KEVZARA with a 14-week steroid taper achieved this composite endpoint.[14]

Dr. Turck:
That's a significant difference. And would you also walk us through the data for each component of the composite endpoint?

Dr Majjhoo:
Sure. KEVZARA showed improvement across all components of sustained remission.

- 46.7% of patients in the KEVZARA arm achieved disease remission by Week 12 vs 37.9% of patients in the placebo group.[14]
- By Week 12, patients in the KEVZARA arm were only on 3 mg of daily corticosteroids per the protocol, while patients in the placebo-controlled arm were receiving 9 mg, excluding rescue steroids.[14,19]
- 55% of patients in the KEVZARA arm achieved an absence of disease flares from Weeks 12 through 52 vs 32.8% in the placebo group.[14]
- 66.7% of patients in the KEVZARA arm achieved sustained reduction of CRP from Week 12 through 52 vs 44.8% in the placebo group.[14]
- 50% of patients in the KEVZARA arm achieved successful adherence to steroid taper from Week 12 through 52 vs 24.1% in the placebo group.[14]

Furthermore, the trial demonstrated that KEVZARA had a steroid-sparing effect, with patients in the KEVZARA arm receiving a lower cumulative corticosteroid dose over the 52-week period compared to the placebo group.[14]

Dr. Turck:
Thank you, Dr Majjhoo, for the thorough explanation of the results. Dr Alim, would you also elaborate on the steroid-sparing effects of KEVZARA observed in the SAPHYR trial?

Dr Alim:
Certainly. So, one component of sustained remission was adherence to the steroid taper. And 30 out of 60 patients in the KEVZARA arm achieved successful adherence to this taper from Week 12 through Week 52, compared with only 14 out of 58 in the placebo-controlled arm.[14]

Additionally, over the 52-week study, patients treated with KEVZARA received a median cumulative corticosteroid dose of 777 mg, compared to 2044 mg in the placebo group.[14]

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.[14]

And so, when we convert these numbers in a mean daily dose, patients in the KEVZARA arm plus the 14-week steroid taper averaged 3.17 mg per day compared to 7.23 mg per day in the placebo arm.[14,19]

Dr. Turck:
Dr Majjhoo, would you provide details on the safety profile of KEVZARA?

Dr Majjhoo:
Of course. KEVZARA has an established safety profile, spanning over 10 years of combined studies across RA, PMR and pJIA.[14,22,26-32]

In the SAPHYR trial, common adverse reactions occurring in 5% or more of patients treated with KEVZARA were neutropenia at 15.3%, leukopenia at 6.8%, constipation at 6.8%, myalgia at 6.8%, pruritic rash at 5.1%, fatigue at 5.1%, and injection site pruritus at 5.1%. 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, or 3.4%, 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 and infections. Neutropenia occurred in 3 patients, or 5.1%. Infections, also occurred in 3 patients, including one patient who had COVID-19, one patient who had intervertebral discitis, and one patient who had pneumonia.[14,19]

The incidence of infections was lower in the KEVZARA group at 37.3% compared to the placebo group at 50%. The incidence of serious infections, however, was similar in the KEVZARA and placebo-controlled groups, at 5.1% and 5.2%, respectively.[14]

Dr. Turck:
Thank you for clarifying 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.

ReachMD Announcer:
CONTRAINDICATION
Do not use KEVZARA in patients with known hypersensitivity to sarilumab or any of the inactive ingredients.[14]

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.
    - 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.[33]

- ***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.[33]
- ***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.[33]

- ***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.[33]
- ***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.[33]
- ***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.[33]
- ***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. Prior to initiating treatment, it is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines.[33]

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.[33]

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.[33]
- 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.[33]

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.[33]
- Use caution when treating the elderly.[33]

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

Please see full Prescribing Information, including Boxed WARNING.

Dr. Turck:
Before we conclude, is there anything else either of you would like to share with our audience?

Dr Alim:
Absolutely. Remember that patients with suspected or newly diagnosed PMR should be considered for specialist evaluation.[15]

And before referring, primary care should complete a detailed history, physical exam, and basic lab work.[4]

Dr Majjhoo:
I would also add, that if symptoms are severe, patients should be referred through a rapid access pathway—ideally within one week.[15]

Starting steroids should be delayed until after the specialist evaluation, if possible.[13,15]

And finally, there are targeted therapies, such as KEVZARA, for PMR patients who have had an inadequate response to corticosteroids or can't tolerate the steroid taper.[14]

Dr. Turck:
That's an excellent point to wrap up on. And I want to thank Dr Majjhoo and Dr Alim for highlighting the importance of early referral to a rheumatologist and for discussing KEVZARA as a treatment option for appropriate patients diagnosed with PMR. It's been a pleasure to talk with you today.

Dr Alim:
It was wonderful to speak with you as well.

Dr Majjhoo:
Thank you for having us.

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