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An FDA-Approved Therapeutic Treatment Option for Polymyalgia Rheumatica

ReachMD Announcer:
You're listening to ReachMD. This broadcast replay titled "KEVZARA (sarilumab), The First FDA-Approved Biologic for The Treatment of Polymyalgia Rheumatica" is sponsored by Sanofi and Regeneron. Here's Dr. Ara Dikranian and Dr. Priya Reddy.

Dr. Dikranian:
Coming to you from the ReachMD studios, I'm Dr. Ara Dikranian.

Dr. Reddy:
And I'm Dr. Priya Reddy.

Dr. Dikranian:
This special live broadcast titled, KEVZARA: The First and Only FDA Approved Biologic for the Treatment of Adult Patients with Polymyalgia Rheumatica, sponsored by Sanofi and Regeneron.

Today we'll be discussing KEVZARA, indicated for the treatment of adult patients with polymyalgia rheumatica who have had an inadequate response to corticosteroids, or who cannot tolerate corticosteroid taper.

KEVZARA is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who've had an inadequate response or intolerance to one or more disease modifying antirheumatic drugs, and adult patients with polymyalgia rheumatica who've had an inadequate response to corticosteroids or who can't tolerate a corticosteroid taper.

The important safety information for KEVZARA includes a warning on the risk of serious infections. Patients treated with KEVZARA are at increased risk for developing serious infections that may lead to a 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 the 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.

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So, our agenda for today will include some general thoughts and facts about polymyalgia rheumatica. We'll discuss, KEVZARA's use in polymyalgia rheumatica as the first and only IL-6 receptor inhibitor indicated for polymyalgia rheumatica. We'll talk about KEVZARA's access, for appropriate patients, and we'll talk about a deeper dive into how we can get the manuscript discussing the SAPHYR clinical trial results we'll discuss today.

Now, we know that IL-6 plays a critical role in polymyalgia rheumatica, as well as rheumatoid arthritis. And though there are similarities, there are some differences between these two disease states as well in terms of the age groups that are affected, in terms of the type of arthritis. Generally we don't think of polymyalgia rheumatica as causing a erosive arthritis. The onset may involve multiple joints, or a small number of joints, it may be acute or subacute in – in the two disease states. And obviously, antibodies characterize rheumatoid arthritis, where none have yet been identified for polymyalgia rheumatica.

However, since IL-6 plays an important pathophysiologic role in both disease states, we know that in both disease states the pain, the morning stiffness, the elevated inflammatory markers, as well as the steroid responsiveness and disease flares are shared features that are common with IL-6 as far as the pathophysiology.

Dr. Reddy, we'll turn to you for some quick facts to ground-set us on PMR.

Dr. Reddy:
Absolutely. So, just jumping into some of the clinical presentation, we know that PMR is an inflammatory condition, it causes pain and stiffness, and this is really the distribution of that proximal girdle, or proximal muscle group. So, it can involve the shoulders, adjacent neck area, and then the hips of course and the adjacent lower back. It's generally affecting patients who are 50 years of age or older.

It's more prevalent in, but not limited to women and people of Northern European and Scandinavian descent. And in older adults – and this is an important fact – the incidence of PMR is higher than RA and other inflammatory rheumatic diseases, and so this is important to consider that, while we have a differential diagnosis that includes RA and inflammatory rheumatic disease, that PMR is actually higher in incidence.

Now, what is the standard of care for PMR? Now, it definitely starts with corticosteroids. We tell patients usually at the outset that initial diagnosis is made, that we are going to be treating patients with steroids. And this slide is really going into the recommendations on PMR management by the ACR and EULAR groups. And this is pretty consistent, I think, with what we're seeing in clinic and what we do, where once that diagnosis is made, patients are started on prednisone 12.5 to 25 mg a day dose typically really depending on that initial presentation, what is the disease burden and other comorbidities would generally tend to dictate that dosing that you land on within that range. And typically, patients will improve on the selected dose, and we continue to taper the prednisone to 10 mg per day.

Now, this is where things get interesting, right? Because in my fellowship I was taught that relapse is the rule when it comes to PMR. And so, what you see happening is once you get that patient to that 10 mg per day dose, you are either have been successful tapering them to that dose and they have resolution of clinical symptoms, and then as you continue to taper there's continued success, or during that taper, a patient will flare at a specific dose and then you have to increase that prednisone to the previously effective dose and, again, adjust the dose until they get to remission where by then you're able to then taper the prednisone further.

Now, this is that vicious circle, or cycle of PMR that most of us are doing when we're treating patients. So, that initial period of higher dose, monitoring 2 to 4 weeks, and then once you get to remission dose, then monitoring either from 4 to 8 weeks, and then going on this path, if you will, of reducing steroids as they taper and go into remission.

Now, as we're going through this cycle, what we're seeing is that not all patients have an adequate response to corticosteroids and may require long-term corticosteroid use. So, many patient flare during that tapering period, as I talked about earlier, and if you look at this nice bar graph on the right of the slide, what you're seeing here is that at 1, 2 or 5 years the percentage of patients who are still taking corticosteroids. And you see at 1 year it's almost 80% at 77% of patients, at 2 years it's 51%, and then at 5 years it's 25% of patients in this study who are still taking glucocorticosteriods and that's a considerable number if you think about the number of patients who still have to be on steroids, and after 5 years, right, which is a – a good amount of time.

What about using corticosteroids for that longer duration of time, or even at low doses, or even higher doses for shorter durations. I mean, corticosteroids are – we know, are associated with complications, right, even at these low doses. So, in a study here on this slide of 175 PMR patients treated with corticosteroids, 70% of them had adverse events with using corticosteroids, right? The median daily dose was about 8 mg here, the range was anywhere from 1 to 45.8 mg over a period of 2 years. And what is it that we're counseling patients on? I mean, I usually will say, alright, I'm putting you on this medication. Let me talk about side effects so that you understand why we are constantly evaluating and wanting to taper you off of this medication. Well, there's side effects, there's osteoporosis, fractures, glaucoma/cataracts, arterial hypertension. And, one of the other things I highlight to patients is the likelihood of avascular necrosis, even though it's not very high compared to these other complications, it is a serious adverse effect that patients should be aware of.

Now, the other thing is we know the complications of corticosteroids, but what about patients who have existing comorbidities, or other conditions where we have to be very judicious in the use of corticosteroids. So, if someone already has glaucoma or uncontrolled

hypertension, we have to monitor these underlying comorbidities very closely and carefully while they're on steroids, and of course, diabetes – this is a big one, even at low doses. Sometimes you have that patient who is very sensitive to steroids, and have, spikes in their blood sugar even at lower doses. And of course, joint infection, other, infections – active infections you want to use steroids with caution. Or peptic ulcer disease or heart failure. And then, of course, osteoporosis is another comorbidity that we need to consider, monitor, and track while patients are on corticosteroids because of the added risk in these disease states.

And with that, I'm going to have Dr. Dikranian go over IL-6 in this disease state.

Dr. Dikranian:
Thank you, Dr. Reddy.

So, why are we talking about IL-6 in this disease state? Now, it wasn't that long ago that the importance of IL-6 in the pathophysiology of PMR was elucidated. So, about 30 years ago, there was a small study done out of the Mayo Clinic, that you see on the left side of the slide, that looked at healthy controls and their levels of IL-6 compared to patients that were newly diagnosed with PMR before starting treatment. And as you can see from the spread of IL-6 levels there was a difference between the levels in the PMR patients prior to starting therapy versus those healthy controls. Another piece of information is elucidated on the right side of the slide. This is from a group in Italy that looked at soluble IL-6 receptor levels at baseline when patients were diagnosed with PMR.

And separating those in the lowest quartile versus those in the highest quartile of IL-6 receptor levels, it noted that there was almost a predictability of who would, either, not have a relapse or who might relapse either once or more than twice depending on that baseline IL-6 receptor level.

So, these are clues as to why we would consider an IL-6 receptor antagonist in the management of polymyalgia rheumatica. Now, we know that IL-6 itself is a pleotropic proinflammatory cytokine, and it utilizes a dual signaling mechanism, which means that there are certain cell types, usually hematopoietic cells, as well as hepatic cells, that have the IL-6 receptor as part of the membrane. So, this membrane-associated IL-6 receptor goes through CIS signaling, and carries the signal inside the cell where it is then translated to affect nuclear function. In cell types that don't have the membrane-associated IL-6 receptor, such as fibroblasts like synoviocyte such as osteoclasts, and many others, soluble IL-6 receptor can attach to IL-6 and when it finds a transmembrane receptor, the gp130 complex, it can engage with this and introduce its signal – inflammatory signal to then affect various intracellular secondary messengers, such as the JAK-STAT system, such as the MAP kinase system, as well as PI3K system to then have an affect on nuclear function.

Now, it's important to note that the JAK-STAT system has obviously been very well characterized in many different disease states, and we know that IL-6 may certainly signal through the JAK-STAT system, but not exclusively so. And the converse of that is also true, there are many other inflammatory proteins and hormones, and other colony-stimulating factors that also can signal through the JAK-STAT system. So, this is part of what leads to the pleiotropism of IL-6.

Now, in the condition of – of polymyalgia rheumatica that we're discussing today, the importance of IL-6 inhibition really rests on understanding IL-6 and its biology with inhibiting with KEVZARA inhibiting the signal either by attaching to the soluble receptor or the membrane-bound receptor. And by attaching to it, prevents, obviously, the engagement of IL-6 to its receptor that then would have it's down regulatory functions on the inflammatory system.

So, understanding this, let's have a look now at the clinical study used to gain information and data on this particular condition.

Dr. Reddy:
Alright. So, with that, I'm going to go into the SAPHYR study, and this is looking at efficacy and safety of KEVZARA, and this is a randomized double-blind multi-center Phase 3 clinical trial in which patients who were diagnosed with PMR – they were 50 years of age or older with this diagnosis who had at least one episode of PMR flare while tapering their prednisone greater than 7.5 mg/day, or equal to, within a 12-week period prior to screening who also had a history of being treated for at least 8 weeks with prednisone at 10 mg/day, or – or greater, were randomized 1:1, either to the KEVZARA or treatment group where they received KEVZARA 200 mg Q2 sub-Q with a 14-week corticosteroid taper, or randomized to the placebo arm, which was another sub-Q injected – injection placebo at Q2 weeks with a 52-week taper of corticosteroid. The primary endpoint, which I'll get to with the next slide, was evaluated at Week 52, and then there was a 6-week follow-up period.

And the primary endpoint is – is important to highlight, I think, in the SAPHYR trial because it was a composite endpoint. It consisted of several different criteria that had to be met. And it has never been studied before in PMR. But I think it really speaks clinically to the different things that we look for when we want to treat patients and say that, okay, you're responding to treatment. So, what was that? So, the primary endpoint was the percentage of patients that achieved this composite endpoint called in sustained remission at Week 52, and the 4 criteria were as follows.

So, the first thing was that patients had to have an absence of signs and symptoms and a CRP of less than 10 achieved by Week 12. Then, they had to have absence of disease flare from Week 12 through Week 52, a sustained reduction of that CRP that was less than 10 mg/L from Week 12 to Week 52, and successful adherence to prednisone taper from that Week 12 to 52.

The select secondary endpoints were the different components that I just went over of the sustained remission composite endpoint at Week 52. So, we looked at those individually. And then total cumulative corticosteroid dose over 52 weeks, time to first PMR flare after clinical remission, and safety endpoints. And the other analysis that was included was, corticosteroid-free resolution of PMR signs and symptoms. And if we look, now, at select demographic and patient characteristics among the two groups, you can see that the age very close in age equigender in the two groups. There may have been a slight increase in the median PMR duration in the placebo group, slight higher levels of CRP ESR in the KEVZARA treated group, but overall, the numbers were quite similar in the two groups.

And this slide, I do really like because it answers the question of what were these doses that patients were receiving of corticosteroid. So, if you look, they're in orange. You see the Kevzara treated group with a 14-week corticosteroid taper. You can see the different dosing in that 14 weeks and how these patients were tapered.

And then you compare that to the placebo arm that went all the way out to 52 weeks and – and how that taper kind of evolved during that time. And you know, in the KEVZARA group the corticosteroid was tapered over 14 weeks, and you can see that KEVZARA can be used as monotherapy after tapering off of corticosteroid.

And, Dr. Dikranian, can you go into some more details of those endpoints?

Dr. Dikranian:
Happy to. So, when we're looking at the primary endpoints, which is this sustained remission. So, these are again, patients that have achieved remission by Week 12, who've not lost it for the further 52 weeks of the study. So, patients have not relapsed, they haven't had increases in their CRP. They are adhering to the steroid taper that they've been assigned. So, we see that just under 30% of patients achieved that sustained remission and that was significantly more than patients in the placebo group of just about 10%.

Now, for the cynics in the virtual audience today that might say, well, of course KEVZARA is going to perform better because it has a biologic effect on reducing CRP, you'd be right. And so, to do a sensitivity analysis on this primary endpoint, the same parameters were looked at for remission. Now, this time taking out the acute phase reactant, and you see that the difference between the two groups is the same 18-point difference that we saw between the groups in the primary analysis, which certainly suggests that the achievement and maintenance of remission – so, sustained remission – was not entirely dependent only on the acute phase reactants.

Now, if we look at each of the components that Dr. Reddy mentioned in this sustained remission response, first, we have the achievement of disease remission by Week 12. So, remember that by Week 12, patients in the KEVZARA arm were taking about 3 mg of prednisone, those in the placebo arm were on 9 mg of prednisone according to that proscribed taper schedule. And we see that patients about 46% of the time achieved disease remission as compared to the placebo group – about 37% of the time.

The next component is the maintenance of that remission. So, absence of disease flare after Week 12. Again, we see a higher number of patients in KEVZARA being able to maintain that remission free of flare for the – the –entirety of the study. Now, the sustained reduction in CRP – this might be sort of an obvious conclusion – so, a numerically higher number of patients in KEVZARA were able to show that sustained reduction in CRP. And finally, adherence to the prednisone taper.

Now after 12 weeks, patients who had relapses were certainly allowed to be on higher doses of prednisone, but then they'd be considered nonadherent to therapy, and therefore would be considered non-responders.

But here we see that adhering to the prednisone taper was more common – about twice as common – in the KEVZARA group as compared to the placebo group.

Now, if we look at the steroid-sparing effect of KEVZARA, we see data here where, either, if we look at the median, actual dose of corticosteroids, or the mean actual dose of corticosteroids on the right, that – there's less exposure in the KEVZARA group as compared to the placebo group. And I think what's interesting here is that, highlighted in the orange box that you see on the slide, that if we look at the expected versus the actual dose of steroids that patients got – so, the expected dose is what was prescribed in the – in the steroid taper, but again, if patients had relapses, either in the first 12 weeks of the study, or even afterwards, or they were given steroids for other reasons, that would count for the actual dose. So, the median [of the] difference between the actual and the expected dose was actually 0 in the KEVZARA group and was about 200 mg in the placebo group. *[On-screen Text]: The mean difference between the actual and expected cumulative CS dose was 297.6 mg in the KEVZARA arm vs 455.1 mg in the placebo arm.*

Meaning that about half the time, patients in the KEVZARA group were taking the expected dose of steroids that was preset, even

before the trial began.

The other important piece of steroid-sparing information is patients who received rescue therapy. So, 32% of patients during the 52 weeks of the study needed rescue therapy in the KEVZARA arm and about 59% of patients in the placebo group needed rescue therapy during the 1-year conduct of the study. *[On-screen Text]: Results are descriptive. No definitive conclusions can be made as data were not multiplicity controlled.*

Now, for some other interesting endpoints, Dr. Reddy, I'll turn it back to you.

Dr. Reddy:
Absolutely. So, what about corticosteroid-free resolution of PMR signs and symptoms? So, let's look at that data, and we're going to look at it in two different ways. First, we have the intention-to-treat population analysis, and at Week 52 45% of patients in the KEVZARA arm, versus 14% in the comparative placebo arm, had corticosteroids-free resolution of PMR signs and symptoms. Now, if we look at the analysis of observed cases, we saw that at Week 52 of those who completed treatment 64% in the KEVZARA arm, versus 22% in the placebo arm, had corticosteroid-free resolution of PMR signs and symptoms.

Now, analyses are based on this type of observed cases, or evaluable patients, they're restricted to a subset of patients who are defined based on post-randomization variables. So, this can lead to, potentially, biased comparisons between treatment arms and limits the interpretability of this type of result. And it's difficult to determine in this scenario whether any differences that were observed were due to the effects of the treatment, or differences in patient characteristics between the subsets of randomized patients in the two arms. *[On-screen Text]: Results are descriptive. No definitive conclusions can be made as data were not multiplicity controlled.*

Now, the other thing is that the percentage of patients who did not experience a PMR flare during that Week 12 through – all the way through Week 52 was 55% in the KEVZARA treated arm, versus 32.8% in the placebo arm. So, it eliminated PMR flares in the majority of the patients who had PMR.

And then additionally, the reduction in risk of PMR flares in the KEVZARA arm was 44% compared to placebo, and the median time to the first flare was 99 days in the placebo arm, whereas the median value was actually not reached, or detected in the KEVZARA plus 14-week corticosteroid taper arm, and was not calculable because the study timed out before it could res – you know, could reach that median value.

[On Screen Text]:

- *These assessments were not pre-specified in the testing hierarchy with control of type I error rate (false positive rate); therefore, it is not possible to ascertain the probability that these findings were attributable to treatment with KEVZARA rather than merely due to chance.*
- *These endpoints condition on a post-randomization variable (i.e., a patient first achieving remission) and, therefore, would be difficult to determine whether observed differences in groups were due to treatment or to differences in patient characteristics between subsets of randomized patients who achieve remission.*
- *Results are descriptive. No definitive conclusions can be made as data were not multiplicity controlled.*

And, with that, I will ask Dr. Dikranian to dive into a little bit of information on safety. We know that this is always the thing that's most important to our patients – important to us as well, but that's usually the first question I get asked: You're going to put me on this therapy, doc, what are the side effects? Right?

Dr. Dikranian:
Absolutely. So, it is important to consider the safety since we're talking about a – obviously a – a medication as an alternative to steroid use in a condition that can last a while, sometimes chronic. And so, safety is actually very important to consider. Now, before we dive into some of the safety information, let's recall that KEVZARA has been studied in rheumatoid arthritis for a while. And we'll recall that there have been many studies that are outlined here that looked at patients with active rheumatoid arthritis that were considered to be moderate or severe, that were either, methotrexate inadequate responders – those are the MOBILITY studies – that were TNF inadequate responders in the TARGET study. We have some safety studies listed here as well as immunogenicity studies. And then, probably the one that we tend to remember most is the MONARCH study, which was a superiority study of Kevzara against adalimumab used as monotherapy in patients with active RA who had an inadequate response, or intolerance, to methotrexate.

So, from these studies, you see, at the top of the slide we have the long-term extension studies of EXTEND and MONARCH primarily. And then, we obviously are going to look at the SAPHYR data as far as safety is concerned. You can see here where these studies fed

into the long-term extension. And what's important to remember here is that we have certainly, much longer follow-up with these studies – so, almost 10 years of follow-up in the EXTEND study, up to 7 years of safety data, no unexpected safety signals as we've previously seen. And so when we consider this history of KEVZARA in rheumatoid arthritis, it is important to keep this in mind.

Now, when we look at the safety information, the SAPHYR study looked at 117 patients with PMR, of whom half – about half got 200 mg of KEVZARA subcutaneously every 2 weeks. The total duration of this PMR population led to a patient years of follow-up of just over 47 patient years during this 12-month double-blind placebo-controlled study.

And then the most common adverse events - and we'll characterize these in just a minute –included those that happened in 5% or more of patients: neutropenia, leukopenia, constipation, pruritic rash, myalgias, fatigue, and injection site pruritis.

Now, for a little more detail, Dr. Reddy, I'll ask you to help us decipher some of the safety information listed here.

Dr. Reddy:
Sure. So, let's take a closer look at the adverse events that were seen. Now, if we look at the placebo group, we see that overall infections were more frequent in this comparator arm compared to the KEVZARA arm, so 50% versus 37.7% [37.3%] respectively. But serious infections were comparable within the two groups 5.2 and 5.1% respectively. Now, neutropenia, leukopenia, injection site erythema, and pruritis did not occur in the placebo arm, while there were 3.4% of patients with ALT increased in the placebo arm versus 0 in the KEVZARA arm.

Long-term safety was studied over a cumulative observation period of 10,322 patient years. The safety profile was comparable between the RA and PMR trials, as well as long-term safety population. Overall, infections were similar in the combination therapy and monotherapy trials for RA, and for the long-term safety population the overall infections were 57.5%. In patients with PMR, overall infections were similar to those in the RA trials, as we mentioned earlier, occurring in 37.3% of patients in the SAPHYR trial. Neutropenia occurred in similar rates across trials, and this was ranging from 13.6 to 19.1%, as did injection site erythema and pruritis. The incidence of hypertriglyceridemia ranged from 0 to 4.2%, while leukopenia ranged from 0 to 6.8%.

With that, I will go into the very important safety information. The contraindication for KEVZARA is to avoid use in patients with known hypersensitivity to sarilumab and any of the inactive ingredients. As we know, infections are an important adverse event to consider, these could be serious or fatal. This can be bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens. Among the opportunistic infections, TB, candidiasis, pneumocystis have been reported. And remember that, you know, when we evaluate someone to get treatment with biologics – and KEVZARA isn't any exception – we evaluated for other high-risk history or comorbidities that make them at increased risk for infection. And this is important to consider or monitor because if a patient develops serious infection or opportunistic infection, we're going to hold KEVZARA.

TB is something that we screen for at baseline because latent TB can be reactivated in patients who are on immunosuppressive therapy and patients who have latent TB should be treated with standard antimicro – mycobacterial therapy. And if you're not sure if they have had TB or an appropriate – or if they've not had an appropriate course of treatment for TB, it's best to treat these patients and then continue to monitor them. Especially patients who've come from endemic regions, or continue to travel to endemic regions. So, it's really important to weigh that risk/benefit in terms of infection, because this is one of the adverse events, as well as viral reactivation has been reported, and cases of herpes zoster were observed in the clinical studies with KEVZARA.

Lab abnormalities are important. We do check CBC, we check CMP, because we have seen neutropenia, leukopenia, we've seen transaminitis. And also monitoring lipid parameters at baseline, and then at 4 weeks and then 6 months thereafter is important because we have seen abnormalities occur in the lipid profile. GI perforation can be increased, and typically, it's with concurrent diverticulitis, or other treatments of NSAIDS and corticosteroids. Remember, too, that immunosuppressants can cause malignancies, so, to monitor patients for development of malignancies is important. As I mentioned, hypersensitivity is a contraindication and patients can have either itchy rash, all the way to urticaria or anaphylaxis, and it's important that patients get medical attention if this happens. And it's not recommended in patients who have active hepatic disease or hepatic impairment because transaminitis has been reported. As well, we avoid administering live vaccines in patients who are on KEVZARA but there's no risk for if you have a family member who received a – well, we don't know if there is an actual risk because it hasn't been studied – if you have a family member who receives a live vaccine and – and you're on KEVZARA.

Now, the adverse reactions for RA can be summarized as neutropenia, increased ALT, injection site erythema, URTI and UTI, and in PMR with the SAPHYR study that we just reviewed, the common adverse reactions were neutropenia, leukopenia, constipation, pruritic rash, myalgia, fatigue, and injection site pruritis. The drug/drug interactions to be aware of is when they're co-administered with CYP substrates or CYP3A4 substrates. This is warfarin, theophylline, or oral contraceptives and statins because the drug levels can be altered with co-administration of an IL-6 inhibitor. And, as far as pregnancy or lactating women, we have to exercise caution and weigh

the potential benefit to the mom versus the risk to the fetus, or the infant before continuing therapy with KEVZARA. And we use with caution when we're treating elderly patients.

And with that, I will ask Dr. Dikranian to go over other important information, as well as dosing for PMR.

Dr. Dikranian:
Certainly. Thank you, Dr. Reddy.

So, getting into some of the nuts and bolts, what do we need to know about as far as the practicality? So, the recommended dose for KEVZARA in treating patients with PMR is 200 mg every 2 weeks subcutaneously in combination with a tapering course of systemic steroids. Once the steroids are tapered, KEVZARA is able to be used as monotherapy continuing for the duration it will be used. Now we have no dose adjustments that are recommended based on either age or gender, race or weight. And, as far as adverse events we are to discontinue KEVZARA in patients who achieve certain parameters with neutropenia, thrombocytopenia, or transaminitis with transaminase levels greater than 3 times the upper limit of normal.

For appropriate patients that we might consider KEVZARA, KEVZARA Connect is available to provide support in getting started with, and staying on, and saving with KEVZARA, and one can scan this QR-code to learn more information.

As far as the coverage; about 99% of all payers have included KEVZARA on their formulary in-line with the label and we can address specific coverage questions in our areas to our representatives.

And, as a souvenir for attending today's program you can scan this QR-code to gain access to the *New England Journal of Medicine* article published on the SAPHYR study that was just published about less than 2 months ago. So, it'll create for more interesting reading and we hope spark additional questions and considerations.

So, we've said a lot, we've talked a lot, Dr. Reddy, summarize where we've been and where we're going.

Dr. Reddy:
I will do that. Thank you, Dr. Dikranian.

So, we started with an agenda, we know kind of what we were going to cover during the talk today. And then, I'm going to end it now with a summary of what we've learned. So, remember that KEVZARA is the first and only FDA approved steroid sparing treatment indicated for PMR. It demonstrated statistically significant sustained remission at Week 52. Patients used less corticosteroids if they were on Kevzara, as demonstrated from the SAPHYR trial where we compared the KEVZARA plus 14-week corticosteroid taper arm with the 52-week corticosteroid taper arm and placebo. And then, we saw that numerically fewer patients who were treated with KEVZARA experienced flares after clinical remission from Week 12 through Week 52.

And finally, in PMR, the overall safety profile that was observed in the KEVZARA group, compared to the placebo group, was generally consistent with the known safety profile of KEVZARA in RA.

And – and with that, I invite you all to learn more by visiting www.KEVZARAHCP.com.

Dr. Dikranian:
So that's all the time we have for today. I'd like to thank the audience for joining today's conversation, and especially would like to thank my coproducer and good friend, Dr. Reddy for joining me in this discussion about KEVZARA. To learn more about KEVZARA please visit KEVZARAHCP.com. Thank you again, and we wish you a wonderful rest of the day.

Dr. Reddy:
And thank you everyone for spending time with us today. I want to thank my cohost here, Dr. Dikranian, and the entire team. Thank you all out there in the audience for spending time with us today and – and discussing this topic. Thank you.

ReachMD Announcer:
Please continue watching for a presentation of the full Important Safety Information, and see adjacent link for full Prescribing Information, including Boxed WARNING.

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.

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.

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

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