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Managing MS: The Role of Immunoglobulins in the Immune System and Long-Term Safety Data for a B-Cell RMS Therapy

Announcer
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This medical industry feature, titled, "Managing RMS: The Role of Immunoglobulins in the Immune System and Long-Term Safety Data for a B-Cell RMS Therapy" is sponsored by Novartis Pharmaceuticals Corporation. [Today's speaker was not compensated for appearing in this program.]

Dr Hauser
As physicians, we always have to remember that we're not treating relapsing multiple sclerosis, or RMS; we are treating people. And we need to understand that, while RMS may be the most significant problem a patient has, an overriding feature in our approach to patient care is doing everything possible to preserve their long-term overall health. So of course, risk of infections and serious infections are two of the many important considerations we think about in the best interest of our patients. And when we talk about risk of infections, immunoglobulins are important to discuss, because they play an essential role in the normal functioning of the immune system.

Dr Caudle
I'm very excited to dive into this topic with you, Dr Hauser. But before we do, could you tell us a little bit about yourself?

Dr Hauser
Sure. My name is Dr Stephen Hauser, and I've been specializing in the care of patients with RMS for 45 years. I'm affiliated with UCSF Medical Center and I'm a professor of neurology and director of the UCSF Weill Institute for Neurosciences, which is an umbrella organization that brings together all of the clinical and basic neurosciences at UCSF. In addition to my experience in patient care, I've played a role in advancing the field of neuroimmunology, specifically in the context of B-cell therapies for RMS.

Dr Caudle
Thank you, Dr Hauser. Now, you were just mentioning the role of immunoglobulins in the immune system. Can you tell us more about that?

Dr Hauser
Of course! So immunoglobulins, or "I-Gs" for short, can be thought of as chemical bullets of the humoral immune system. They're made by populations, or clones, of distinct B cells. There are billions of B cells in each of our bodies, and they develop through somatic mutation of precursor immunoglobulin gene segments. Every B cell and its progeny share an identical sequence of their unique B-cell receptor, also known as an immunoglobulin molecule, which can target a highly specific surface structure, for example, on an invading bacterium or virus. And B cells producing immunoglobulins that also cross-react with normal tissues of the body must be eliminated or suppressed. This mechanism, when working properly, ensures that immunoglobulins do not cross-react with other infectious organisms or with our own body's tissues. So, immunoglobulins are one of the key signaling molecules in our immune system, as they fine-tune our bodies' responses selectively and efficiently.

Now, there are a few different types of Ig, but today we're only going to talk about two of them: IgG and IgM. IgG protects the body from infection and accounts for approximately 80 percent of antibodies in blood serum. And IgM is the immune system's primary response to infection and accounts for approximately 5% of antibodies in blood serum.

Because immunoglobulins fight off infection, something we have to think about with B–cell depleting therapies is that with the reduction

of B cells comes a reduction in immunoglobulins, which may increase the risk of infection.

Dr Caudle
Thank you for providing us with that background, Dr Hauser. Now today, we're also going to be talking about a once-monthly self-administered subcutaneous B-cell RMS therapy known as KESIMPTA® (ofatumumab). But before we dive into the data, what do we need to know about this treatment option?

Announcer
KESIMPTA is an anti-CD20 therapy that has up to 5 years of data on changes in serum Ig levels and risk of infection. It's indicated for the treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. It's contraindicated in patients with active hepatitis B virus infection, or history of hypersensitivity to ofatumumab, or life-threatening injection-related reaction to KESIMPTA. Hypersensitivity reactions have included anaphylaxis and angioedema.

To summarize the Important Safety Information, which can be heard in full at the end of this podcast, KESIMPTA may cause infections, injection-related reactions and hypersensitivity reactions, reduction in immunoglobulins, and fetal risk. The most common adverse reactions with an incidence greater than 10% are upper respiratory tract infection, headache, injection-related reactions, and local injection-site reactions. The full Prescribing Information can be accessed on this website.

And now, let's head back to Dr Caudle and Dr Hauser's discussion.

Dr Caudle
Now I know today's conversation is about the safety profile of KESIMPTA. But can you quickly talk about its demonstrated efficacy?

Dr Hauser
Absolutely, and I think it's important to touch on it because it is notable. In Phase 3 clinical trials, KESIMPTA demonstrated superior annualized relapse rate, or ARR, reductions compared to teriflunomide. In ASCLEPIOS I, we see that the ARRs for KESIMPTA and teriflunomide were 0.11 and 0.22, respectively. And in ASCLEPIOS II, the ARRs for KESIMPTA and teriflunomide were 0.10 and 0.25, respectively. For KESIMPTA, that's 1 relapse every 10 patient-years. So to summarize, in the core trials, KESIMPTA significantly reduced relapses by 51% in ASCLEPIOS I and by 58% in ASCLEPIOS II compared to the active comparator, teriflunomide.

KESIMPTA also suppressed active areas of inflammation, as measured by the mean number of gadolinium-enhancing T1 lesions by MRI, with superior reductions of 98% and 94% compared with teriflunomide, as reported in ASCLEPIOS I and II, respectively. Similarly, KESIMPTA suppressed mean new and enlarging T2 lesions compared with teriflunomide, with reductions of 82% and 85%, respectively, in ASCLEPIOS I and II. Overall, KESIMPTA treatment resulted in near-complete suppression of gadolinium-enhancing T1 and in T2 lesion activity. Finally, a prospective pooled analysis showed that KESIMPTA significantly reduced the risk of 3-month confirmed disability progression, or CDP, by 34% and 6-month CDP by 32% compared with teriflunomide.

And now we have 5 years of efficacy data for KESIMPTA from the ALITHIOS extension trial, which continue to show results with an ARR of 0.06. This is a 73% risk reduction in ARR in patients who switched from teriflunomide to KESIMPTA. This open-label extension study was not blinded, not controlled, and included inherent self-selection bias for remaining in the trial. No conclusions of statistical or clinical significance can be drawn.

Dr Caudle
Thank you for highlighting the efficacy data for our audience, Dr Hauser. Now what about the safety of KESIMPTA? What can you tell us about the long-term Ig data?

Dr Hauser
For KESIMPTA, changes in serum Ig levels were assessed up to week 120 in a subgroup analysis of the ASCLEPIOS studies, and up to 5 years in a long-term safety analysis from the open-label, single-arm Phase 3b ALITHIOS extension trial. In the ASCLEPIOS trials, no decline in IgG was observed at the end of the study, and about 14 percent of patients treated with KESIMPTA experienced a decrease in serum IgM that reached a value below 0.34 g/L. In the extension analysis, patients on KESIMPTA maintained stable mean IgG levels for up to 5 years and mean IgM levels declined but remained above the lower limit of normal. So overall, Ig levels were maintained within the reference ranges. And in the analysis, the overall incidence of serious infections was low (<2 per 100 patient years), with 5.38% or 106 patients experiencing ≥1 serious infection within 1 month prior to and until 1 month after any series of drops in IgG or IgM below the lower limit of normal. Infections included herpes zoster, upper respiratory tract infection, urinary tract infection, COVID-19, bronchitis, pneumonia, pyelonephritis chronic, and COVID-19 pneumonia.

Announcer:

Most patients [(98%)] had IgG levels above the lower limit of normal for up to 5 years. Of the patients [(2%)] whose IgG levels dropped below the lower limit of normal, 3 experienced serious infections, all of which resolved.

Serious, including life-threatening or fatal, bacterial, fungal, and new or reactivated viral infections have been observed during and following completion of treatment with anti-CD20 B-cell depleting therapies. Any closing thoughts on the long-term Ig data for KESIMPTA, Dr Hauser?

Dr Hauser:
Preclinical evidence also suggests that depletion of B cells in the lymph nodes is thought to be promoted by subcutaneous administration of KESIMPTA, and this targeted depletion may spare B cells in the spleen, which could potentially help maintain components of immune function. So it's great to see the actual safety and Ig data out to 5 years in patients treated with KESIMPTA.

Dr Caudle
For those of you who are just tuning in, you're listening to NeuroFrontiers on ReachMD. I'm your host, Dr Jennifer Caudle, and I'm speaking with Dr Stephen Hauser about the role of immunoglobulins in the immune system and the long-term safety data on the treatment option KESIMPTA for patients with RMS.

So, Dr Hauser, now that we know more about the role Igs play, how do you monitor them in your patients?

Dr Hauser
In my clinical practice, our standard is to longitudinally monitor serum Ig levels before, during, and after treatment. My personal practice is to always obtain a baseline value of Ig levels, especially IgG and IgM, which is also recommended in the KESIMPTA prescribing information. In those patients with low serum immunoglobulin levels, it is advised to consult immunology experts before initiating treatment with KESIMPTA.

Dr. Caudle
Thank you, Dr Hauser. Now I'd like to switch gears here and focus on the COVID-19 pandemic, which made the risk of infections a very real concern for both physicians and patients. Can you tell us what you've seen in terms of outcomes for patients who contracted COVID-19 during treatment with KESIMPTA?

Dr Hauser
Yes. Although the data that we have regarding KESIMPTA safety during the COVID-19 pandemic are not airtight—simply because we don't have the volume of data that one might wish for—I still think it's encouraging in terms of a serious viral pandemic and the safety of KESIMPTA use during that period, even in patients whom we know have been infected with COVID-19.

Results from an analysis of the ALITHIOS study from the start of the COVID-19 pandemic in December 2019 to September 25, 2022, show no increased risk of severe or serious COVID-19 outcomes in patients taking KESIMPTA over 5 years. And if we dive into the numbers, 648 of the 1703 patients, or 38 percent, enrolled in ALITHIOS who received KESIMPTA reported that they had contracted COVID-19.

99 percent of patients who were infected with COVID-19 recovered, were recovering, or had recovered at study cutoff with no cases of reinfection. In addition, 94 percent of cases were mild to moderate in severity, while 50 cases were considered serious, with an 82 percent recovery rate at the cutoff. Now unfortunately, there were 5 fatal outcomes, or 0.8 percent of patients, which was lower than the rate reported in the general population at 2.1 percent. Three of these patients were unvaccinated while the other 2 patients were fully vaccinated.

The 5 fatal cases consisted of 2 patients with COVID-19, 1 with COVID-19 pneumonia, 1 with COVID-19 and COVID-19 pneumonia, and 1 with COVID-19 pneumonia and pneumothorax. Among those affected with COVID-19, KESIMPTA was not permanently discontinued in any patient, except for the 5 people who had a fatal COVID-19 outcome. COVID-19 cases with severe, serious outcomes, vaccination status, and breakthrough infections were all included in this analysis which was not blinded and not controlled.

Therefore, no statistical or clinical conclusion can be made. Speaking personally, this data is aligned with what I have seen in my clinical practice.

Dr Caudle
And aside from COVID-19, what can you tell us about the overall safety profile of KESIMPTA?

Dr Hauser
In ASCLEPIOS I and II, the proportion of patients with adverse events was similar in the KESIMPTA and teriflunomide groups, at 83.6 percent versus 84.2 percent, respectively. The most common adverse reactions with incidence greater than 10 percent in patients

taking KESIMPTA were upper respiratory tract infections, headache, injection related reactions, and local injection site reactions.

The overall rate of infections and serious infections in KESIMPTA-treated patients was similar to teriflunomide-treated patients, 51.6% vs 52.7%, and 2.5% vs 1.8%, respectively. Additionally, data from the ALITHIOS trial released at the American Academy of Neurology 2023 Annual Meeting demonstrated the long-term safety for KESIMPTA for up to 5 years. No new safety signals were identified, and the nature and frequency of the most common adverse events were comparable with those reported in ASCLEPIOS I and II.

Dr Caudle
Thanks for breaking down all those data for us, Dr Hauser. And as we come to a close, my final question is a two-parter. First, how do the long-term safety data affect your perception of KESIMPTA? And second, what is most important for neurologists to understand when it comes to KESIMPTA and the prevention of infections in patients with RMS?

Dr Hauser
Well, to answer your first question, the safety data as reflected in the IgG and IgM levels, and in the risk for other conditions, including serious infections, remain encouraging with KESIMPTA. These Ig data add to what we know about the established safety profile of KESIMPTA.

And for neurologists, the data really drive home the point that KESIMPTA is a safe and effective therapeutic option for patients who want to start therapy today. And for patients who are currently on KESIMPTA, they can continue therapy with confidence.

Dr Caudle
Well, as those final comments bring us to the end of today's program, I'd like to thank my guest, Dr Stephen Hauser, for joining me to share the long-term safety data on KESIMPTA. Dr Hauser, it was a pleasure speaking with you.

Dr Hauser
You as well, Dr Caudle. Thank you.

Dr Caudle
For ReachMD, I'm your host, Dr Jennifer Caudle and please stay tuned to hear the Important Safety Information for KESIMPTA.

IMPORTANT SAFETY INFORMATION

Indication: KESIMPTA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Contraindications: KESIMPTA is contraindicated in patients with active hepatitis B virus (HBV) infection, or history of hypersensitivity to ofatumumab, or life-threatening injection-related reaction to KESIMPTA. Hypersensitivity reactions have included anaphylaxis and angioedema.

WARNINGS AND PRECAUTIONS

Infections: Serious, including life-threatening or fatal, bacterial, fungal, and new or reactivated viral infections have been observed during and following completion of treatment with anti-CD 20 B-cell depleting therapies. The overall rate of infections and serious infections in KESIMPTA-treated patients was similar to teriflunomide-treated patients (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until resolved.

Consider the potential increased immunosuppressive effects when initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA.

Hepatitis B Virus: *Reactivation*: No reports of HBV reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients treated with ofatumumab at higher intravenous doses for chronic lymphocytic leukemia (CLL) than the recommended dose in MS and in patients treated with other anti-CD20 antibodies.

Infection: KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. Perform HBV screening in all patients before initiation of KESIMPTA. Patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], should consult liver disease experts before starting and during KESIMPTA treatment.

Progressive Multifocal Leukoencephalopathy: No cases of progressive multifocal leukoencephalopathy (PML) have been reported for

KESIMPTA in RMS clinical studies; however, PML resulting in death has occurred in patients being treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. In addition, JC virus infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. If PML is suspected, withhold KESIMPTA and perform an appropriate diagnostic evaluation. If PML is confirmed, KESIMPTA should be discontinued.

Vaccinations: Administer all immunizations according to immunization guidelines: for live or live-attenuated vaccines at least 4 weeks and, whenever possible at least 2 weeks prior to starting KESIMPTA for inactivated vaccines. The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy. For infants whose mother was treated with KESIMPTA during pregnancy, assess B-cell counts prior to administration of live or live-attenuated vaccines. If the B-cell count has not recovered in the infant, do not administer the vaccine as having depleted B-cells may pose an increased risk in these infants.

Injection-Related Reactions and Hypersensitivity Reactions: KESIMPTA can result in systemic injection-related reactions and hypersensitivity reactions, which may be serious or life-threatening. Injection-related reactions with systemic symptoms occurred most commonly within 24 hours of the first injection, but were also observed with later injections. There were no life-threatening injection reactions in RMS clinical studies.

In the post-marketing setting, additional systemic injection-related reactions and hypersensitivity reactions have been reported, including anaphylaxis, angioedema, pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, dizziness, nausea, and tachycardia. Most cases were not serious and occurred with the first injection. Symptoms of systemic injection-related reactions may be clinically indistinguishable from acute hypersensitivity reactions.

The first injection of KESIMPTA should be performed under the guidance of an appropriately trained health care professional. If systemic injection-related reactions occur, initiate appropriate hypersensitivity reactions with KESIMPTA should be instructed to seek immediate medical attention. If local injection-related reactions occur, symptomatic treatment is recommended.

Reduction in Immunoglobulins: As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Fetal Risk: Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose.

Most common adverse reactions (>10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection-site reactions.

Please see full Prescribing Information, including Medication Guide.

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