## Transcript Details

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Reviewing a Powerful Therapy for Relapsing MS

**Announcer:**
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This medical industry feature, titled "Reviewing a Powerful Therapy for Relapsing MS" is sponsored by Novartis. This program is intended for physicians.

Here's your host, Dr. Doghramji.

**Dr. Doghramji:**
This is ReachMD, and I'm Dr. Paul Doghramji. Joining me to discuss a targeted therapy for relapsing multiple sclerosis is Dr. Pavle Repovic, a neurology specialist at Multiple Sclerosis Center at Swedish Medical Center in Seattle, Washington. Dr. Repovic, thanks for being here today.

**Dr. Repovic:**
Thank you for having me.

**Dr. Doghramji:**
So let's start off. What is Kesimpta – and what is the indication for Kesimpta?

**Dr. Repovic:**
Kesimpta is a CD20 directed cytolytic antibody, indicated for the treatment of relapsing forms of multiple sclerosis in adults. These forms include clinically isolated syndrome, relapsing-remitting multiple sclerosis, and active secondary-progressive multiple sclerosis.

**Dr. Doghramji:**
Okay. And what is the recommended dosage of Kesimpta?

**Dr. Repovic:**
The recommended dosage of Kesimpta is 20 mg, that is administered by subcutaneous route – injection – first dosing at weeks zero, one and two, followed by subsequent dosing, once a month, starting at week four, at 20 mg by subcutaneous injection.

**Dr. Doghramji:**
And again, how is Kesimpta administered?

**Dr. Repovic:**
Kesimpta is administered subcutaneously, using a prefilled Sensoready pen, once a month. The first dose is administered under the guidance of a health care professional.

**Dr. Doghramji:**
So sometimes there are some screening tests that – that health care providers do, so which screens should health care providers conduct prior to initiating Kesimpta? And – and what should they be looking for?

**Dr. Repovic:**
Prior to initiating Kesimpta, the patients should be screened for hepatitis B virus infection, because Kesimpta is contraindicated in patients with active hepatitis B infection. That screening should include at least surface antigen and core antibody testing for hepatitis B, and perhaps other tests according to local guidelines. In addition, patients' serum immunoglobulin should be assessed prior to initiation

of Kesimpta. If serum immunoglobulins are low, a consultation with an immunology expert is recommended. And lastly, a vaccine status of the patient should be assessed prior to initiating Kesimpta.

**Dr. Doghramji:**
Well, speaking of vaccination, are there any vaccination requirements prior to the first dose?

**Dr. Repovic:**
Because vaccination with live attenuated, or live vaccines, is not recommended during treatment with Kesimpta, all immunizations should be administered according to immunization guidelines prior to initiating Kesimpta. For live, or live attenuated vaccines, those should be administered at least four weeks prior to starting Kesimpta. For inactivated vaccines, those should be administered at least two weeks prior to Kesimpta.

**Dr. Doghramji:**
Let's talk next about administration instructions. So what do you tell a patient about the administration of Kesimpta?

**Dr. Repovic:**
The Kesimpta is administered by subcutaneous injection only. It is intended for patient self-administration. The instructions for use contain more detailed instructions on the preparation of Kesimpta. Kesimpta should be administered in the abdomen, thigh, or upper outer arm, using an injection under the skin. Injections should not be administered into moles, scars, stretch marks, or other areas where the skin is tender, bruised, red, scaly or hard.

**Dr. Doghramji:**
What are some of the warnings and precautions related to Kesimpta?

**Dr. Repovic:**
An increased risk of infection has been observed with other anti-CD20 B-cell depleting therapies. Kesimpta has a potential for an increased risk of infections. If a patient is currently having an infection, administration of Kesimpta should be delayed until the infection is resolved. Hep-B virus screening should be performed and those with active hepatitis B should not receive Kesimpta. Kesimpta may also interfere with the effectiveness of vaccinations. For that reason, all immunizations should be administered according to the guidelines, prior to starting treatment with Kesimpta.

**Dr. Doghramji:**
So what are the risks of infection associated with Kesimpta?

**Dr. Repovic:**
Kesimpta has the potential for an increased risk of infections, including serious bacterial, fungal or viral infections, including reactivations. The overall rate of infections with Kesimpta was similar to patients who were treated with teriflunomide. This was seen in 51.6% of patients with Kesimpta, and 52.7% of patients with teriflunomide. The rates of serious infections were also similar – 2.5% with Kesimpta and 1.8% with teriflunomide. The most common infections reported by Kesimpta-treated patients in MS trials included upper respiratory tract infections, in 39% of the patients, and urinary tract infections, in 10% of the patients. If a patient is having an active infection, the administration of Kesimpta should be delayed.

**Dr. Doghramji:**
So does Kesimpta reactivate hepatitis B virus, or cause PML?

**Dr. Repovic:**
There were no reports of hepatitis B virus reactivation in MS patients with Kesimpta. However, hepatitis B virus reactivation, in some cases leading to hepatitis – fulminant hepatitis, hepatic failure and death, has occurred in patients treated with ofatumumab for chronic lymphocytic leukemia, at doses higher than those recommended in multiple sclerosis, but for a shorter period of time, and in patients with other – treated with other anti-CD20 therapies. Although no cases of PML have been reported with Kesimpta in clinical studies of multiple sclerosis, PML resulting in death has occurred in patients treated with ofatumumab for chronic lymphocytic leukemia at those doses that are higher than the ones in MS, but for a shorter period of time. In addition, PML has been observed in patients treated with other anti-CD20 antibodies so if PML is suspected in a patient with multiple sclerosis, appropriate workup needs to take place, and additional dosing of Kesimpta needs to be held until that workup is complete.

**Dr. Doghramji:**
Let's switch next to injection-related reactions. What is the difference between injection site and injection-related reactions to a patient experienced in Kesimpta studies?

**Dr. Repovic:**

Injection-related reactions refer to systemic reaction to this medication, whereas injection site reaction is a local reaction to the medication. Injection-related reactions – systemic ones – are, that were seen include fever, headache, muscle aches or pain, chills and fatigue. They most commonly occurred within 24 hours of the injection. They were most commonly seen following the first injection, and if they do occur, symptomatic treatment is recommended. 99.8% of these reactions were mild to moderate, and there were no life-threatening injection-related reactions in clinical studies. By contrast, local injection site reactions are localized, and they may involve redness of skin, swelling, itching or pain. They were seen in 11% of Kesimpta patients, and 6% of teriflunomide patients.

**Dr. Doghramji:**
Sometimes in these types of medications, premedication may occur. Is premedication required prior to administration of Kesimpta?

**Dr. Repovic:**
Actually, premedication is not required prior to administration of Kesimpta. Only limited benefit of premedication with corticosteroids, antihistamines or acetaminophen was observed in MS clinical studies of Kesimpta. However, if any reactions do occur symptomatic treatment is recommended.

**Dr. Doghramji:**
Let's switch our attention now to adverse reactions. What adverse events were seen in Kesimpta in the clinical trials?

**Dr. Repovic:**
The most common adverse reactions, occurring in more than 10% of patients treated with Kesimpta, and more commonly than with teriflunomide, were upper respiratory tract infections, injection-related reactions – those are systemic reactions, headache, and injection site reactions – those are the local reactions.

**Dr. Doghramji:**
And what were some of the rates of common adverse events in Kesimpta arm compared with the teriflunomide arm in clinical trials?

**Dr. Repovic:**
So for upper respiratory tract infections, those were seen in 39% of patients with Kesimpta, and 38% of patients in the teriflunomide arm. The injection site reactions – local reactions – were seen in 11% of patients with Kesimpta, and 6% of patients with teriflunomide. Injection-related reactions – those are systemic reactions – were seen in 21% with – of patients treated with Kesimpta, and 15% of patients treated with teriflunomide. The most common cause of discontinuation for patients treated with Kesimpta was low immunoglobulin M, in 3.3% of patients.

**Dr. Doghramji:**
So what types of infections were seen with Kesimpta in clinical trials?

**Dr. Repovic:**
From the clinical trial experience, the most common infection seen with Kesimpta was upper respiratory tract infection.

**Dr. Doghramji:**
So Dr. Repovic, what type of injection reactions were seen with Kesimpta in clinical trials?

**Dr. Repovic:**
So, injection reactions that were seen in the clinical trials were grouped into injection-related reactions, which are systemic, and injection site reactions, which are local. The systemic reactions that were most commonly seen were fever, headache, muscle aches or pain, chills or fatigue. The incidence of these was highest in the first injection. It was seen in 14.4% of the patients, but then it diminished, so that by the third injection, less than 3% of patients reported them. The local injection site reactions – the most commonly type of those were redness of the skin, pain, itching and swelling, and those were predominantly mild to moderate in severity.

**Dr. Doghramji:**
Let's switch our attention now to immunogenicity. What is the risk of immunogenicity with Kesimpta?

**Dr. Repovic:**
In clinical trials, the antidrug antibodies to Kesimpta were very infrequent. They were only detected in two out of 914 patients. In general, there was no discernable impact of these antidrug antibody titers on pharmacokinetics, safety profile, or B-cell kinetics in these patients. However, because there were so few patients with them, these data are not adequate to assess the impact of antidrug antibodies on the safety and efficacy of Kesimpta.

**Dr. Doghramji:**
So let's talk about drug-drug interactions. What kind of drug interactions should health care providers be concerned about with

Kesimpta?

**Dr. Repovic:**
Combining Kesimpta with other immunosuppressant drugs, including systemic corticosteroids, can lead to additive immune system effects, leading to an increased risk of infection. So these considerations should be taken into account when combining the use of Kesimpta with any other immune-active medications. The interactions between Kesimpta and other medicinal products have not been investigated in formal studies, because this is a monoclonal antibody that is degraded through the patterns that do not involve the cytochrome P450 mechanisms or, or some of the other common causes of drug-drug interactions.

**Dr. Doghramji:**
Dr. Repovic, you mentioned monoclonal antibodies. Expound on that, please. What kind of molecule is Kesimpta?

**Dr. Repovic:**
Kesimpta is a recombinant human anti-CD20 monoclonal antibody, of the IgG1 type, that induces lysis of cells that express protein CD20. Vast majority of these cells are B cells, although some minor population of CD20 T-cells might also be targeted. It is believed that these cells play an important role in MS pathogenesis.

**Dr. Doghramji:**
So let's talk next about clinical pharmacology. What is the mechanism of action of Kesimpta?

**Dr. Repovic:**
The precise mechanism by which Kesimpta works is not fully elucidated, but is presumed to involve binding to CD20, uh, on the CD20-expressing cells, leading to the lysis of those cells, either through a complement mediated process, or antibody-dependent cellular cytolysis.

**Dr. Doghramji:**
Let's talk next about pharmacodynamics. How long does it take for repletion of B cells after treatment discontinuation of Kesimpta?

**Dr. Repovic:**
The data from relapsing MS clinical studies showed that B cell recovery above the lower limit of normal, in at least 50% of patients, occurs between 24 and 36 weeks after stopping ofatumumab. However, modeling and simulation of B cell repletion supports this data, predicting that the median time to B cell recovery is about 40 weeks after stopping Kesimpta.

**Dr. Doghramji:**
And what is the effect of Kesimpta on clinical outcomes in Phase 3 trials?

**Dr. Repovic:**
There were two Phase 3 trials of efficacy of Kesimpta, called ASCLEPIOS I and ASCLEPIOS II. In both of those Phase 3 trials, the primary outcome measure was reduction in annualized relapse rate. That reduction was compared to teriflunomide. So, compared to teriflunomide, Kesimpta reduced annualized relapse rate by 51% in one trial, and 59% in the other trial. In addition, the secondary outcomes in these trials included reduction in active, or gadolinium-enhancing MRI lesions. That reduction was pretty significant and profound – by 98% in ASCLEPIOS I trial and 94% in ASCLEPIOS II trial, compared to teriflunomide. As well, uh, the reduction in new or enhance – or enlarging T2 lesions was seen in these trials as well. 82% less in ASCLEPIOS I and 85% less in ASCLEPIOS II in Kesimpta patients, compared to teriflunomide cohort. Lastly, Kesimpta reduced the accrual of disability. The combined data from these two trials was analyzed for three months confirmed disability progression, and that progression was seen in 34.4% fewer patients in Kesimpta arm compared to teriflunomide.

**Dr. Doghramji:**
Excellent information, Dr. Repovic. Uh, good comments for us to think on as we come to the end of today's program. I want to thank my guest, Dr. Repovic, for helping us better understand Kesimpta, a treatment for multiple sclerosis in adult patients. Dr. Repovic, it was great speaking with you today.

**Dr. Repovic:**
Thank you very much for having me.

**Dr. Doghramji:**
I'm Dr. Paul Doghramji. Thanks for listening.

**Announcer:**
**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.

**IMPORTANT SAFETY INFORMATION**

**Contraindication**

KESIMPTA is contraindicated in patients with active hepatitis B virus infection.

**WARNINGS AND PRECAUTIONS**

**Infections:** An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. KESIMPTA has the potential for an increased risk of infections including serious bacterial, fungal, and new or reactivated viral infections; some have been fatal in patients treated with other anti- CD20 antibodies. 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 hepatitis B virus (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:** 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.

The first injection of KESIMPTA should be performed under the guidance of an appropriately trained health care professional. If 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.

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