Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/treating-two-sides-relapsing-multiple-sclerosis-rms/13221/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Treating the Two Sides of Relapsing Multiple Sclerosis (RMS)

Announcer:
You're listening to ReachMD.

This medical industry feature, titled "Treating the Two Sides of Relapsing Multiple Sclerosis (RMS)," is sponsored by Sanofi. Your ReachMD host, Dr. Jennifer Caudle has been compensated by ReachMD, and your guest host Dr. Sharon Stoll has been compensated by Sanofi.

Here's your guest, Dr. Sharon Stoll. Dr. Stoll is a board-certified neurologist and assistant professor in the department of neurology at the Yale School of Medicine.

She is a DO who specializes in multiple sclerosis (MS) and neuroimmunology.

Dr. Caudle:
In relapsing multiple sclerosis, RMS, disability accumulates from the start. And that's why it's important to prioritize both reducing relapses and delaying disease accumulation.

In this episode, we discuss a treatment that may help with both.

Dr. Caudle:
This is ReachMD. And I'm your host, Dr. Jennifer Caudle. And joining me today is Dr. Sharon Stoll to discuss the different components of RMS treatment, and how the once-daily oral disease-modifying therapy, AUBAGIO®, teriflunomide, might help.

Dr. Stoll, thanks so much for being here today.

Dr. Stoll:
Dr. Caudle, thank you so much for having me. I'm a huge fan. I just had to throw that in there.

Dr. Caudle:
Oh, you're so kind. We're very excited to have you today. But before we begin, let's take a moment to review some important safety information.

INDICATION

AUBAGIO® (teriflunomide) 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

WARNING: HEPATOTOXICITY AND EMBRYOFETAL TOXICITY

- **Clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, has been reported in patients treated with AUBAGIO in the postmarketing setting. Concomitant use of AUBAGIO with other hepatotoxic drugs may increase the risk of severe liver injury.**
- **Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for 6 months after starting AUBAGIO. If drug-induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or activated charcoal. AUBAGIO is contraindicated in patients with severe hepatic**

impairment. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.

- AUBAGIO is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Teratogenicity and embryolethality occurred in animals at plasma teriflunomide exposure lower than that in humans. Exclude pregnancy before the start of treatment with AUBAGIO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during AUBAGIO treatment and during an accelerated drug elimination procedure after AUBAGIO treatment. Stop AUBAGIO and use an accelerated drug elimination procedure if the patient becomes pregnant.

Please find additional Important Safety Information, including **boxed WARNING**, later in this program and listed below, and full Prescribing Information listed below.

Dr. Caudle:
So now that we've reviewed some of the important safety information, let's jump right in. Dr. Stoll, what are some of the considerations of treating a patient with relapsing MS?

Dr. Stoll:
Thanks, Dr. Caudle. I often say that one of the only things my RMS patients have in common is that every one of them is different. There is an enormous heterogeneity in the way the disease presents. And that means that each RMS case is unique, and therefore, requires individual consideration.

There's additional complexity in that there are so many different disease-modifying therapies available now. And the treatment landscape is expanding all the time.

Dr. Caudle:
You know, that makes a lot of sense. I mean, what are we up to now? Are we up to over 19 options?

Dr. Stoll:
That's right, over 19. So broadly speaking, we need to consider a patient's personal characteristics and then weigh the risk-benefit profile of any of these DMT options against the severity of that patient's disease.

So matching the appropriate treatment to the right relapsing MS patient requires us to weigh a number of different factors.

For today's discussion, I want to keep in mind the individual's need of your RMS patients, including those with less aggressive disease.

Dr. Caudle:
Wonderful, and now that we've acknowledged those considerations, you know, how do you go about managing an RMS patient's disease?

Dr. Stoll:
Great question. There are two important aspects of RMS disease progression that I like to consider—acute focal inflammation and accumulating disease.

As you're aware, it's important to reduce acute inflammation, relapses, and lesions. But we also need to consider the impact of accumulating disease, which includes disability progression, brain volume loss, and total lesion volume.

Dr. Caudle:
Right. So, you're looking to reduce relapses for today, while also delaying disability progression for tomorrow. Is that correct?

Dr. Stoll:
Exactly. Delaying disability progression should be a focus very early in a patient's treatment journey, even when relapses and lesions may be more pronounced.

And disease-modifying therapy should be started right away because disability can begin to develop even in the early stages of relapsing MS.

Dr. Caudle:

For those just tuning in, you're listening to ReachMD.

I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Sharon Stoll about different components of RMS treatment and how the once-daily oral disease-modifying therapy, AUBAGIO, may help.

That's an excellent point. I'm so glad that you made that point. It's very important.

Now we've spoken about looking for a DMT that manages both the acute focal and accumulating aspects of RMS, now let's shift over to where AUBAGIO comes in.

So Dr. Stoll, how does AUBAGIO address these two components of RMS?

Dr. Stoll:
Well, AUBAGIO both reduces relapses and delayed disability progression in two phase 3 clinical trials.

Let's begin with relapses. In the TEMSO core and extension trials, AUBAGIO maintained the strength to reduce relapses in the first two years of the trial, and over time.

Both the 14-milligram and 7-milligram doses provide a 31% relative risk reduction for relapses versus placebo. There were 358 patients taking the 14-milligram dose, and 365 taking the 7-milligram dose, 363 taking the placebo. When the core and extension trial data are combined, those results were maintained for up to seven and a half years.

The results were similar in the TOWER core and extension trials. In the core trial, the annualized relapse rate, or ARR, was 0.319 for AUBAGIO 14-milligram and 0.389 for AUBAGIO 7-milligram versus 0.501 for placebo.

There were 370 patients taking the 14-milligram dose, 407 taking the 7-milligram dose, and 388 taking placebo. And those who stayed on AUBAGIO experienced an average of only one relapse over six years.

Dr. Caudle:
Alright, so AUBAGIO reduced relapses. You know, that's one piece of the puzzle. How did it impact disability progression?

Dr. Stoll:
Another great question.

AUBAGIO was the only oral DMT to delay disability progression in 2 phase 3 core trials.

In TEMSO extension trial, AUBAGIO continued to delay disability progression for up to seven and a half years. In the combined core and extension trials AUBAGIO 14-milligram and 7-milligram kept 61% and 61.5% of patients free from disability progression, respectively.

And for those patients that did experience disability progression during the extension study, there was a mean change of less than 0.5 on the expanded disability status scale.

Consider what the real-life implications of a less than 0.5 change would be for your patients.

Dr. Caudle:
So AUBAGIO both reduced relapses and delayed disability progression over time in its core and extension trials, which may address those two components of treatment we were talking about at the start of our discussion. But what do we know about its safety profile?

Dr. Stoll:
Yes, safety data is important. AUBAGIO demonstrated a long-term safety profile across four clinical trials including over 2000 patients.

Dr. Stoll:
In the pooled core clinical trials, the most common adverse events were headache, ALT increase, diarrhea, alopecia, and nausea.

This chart shows the events for the 14- and 7-milligram doses as well as placebo. And a common adverse event was defined as an event that occurred in greater than or equal to 10% of AUBAGIO patients, and greater than or equal to 2% of placebo patients.

Dr. Caudle:
And how many patients experienced those common events?

Dr. Stoll:
For headaches, it was 18% for AUBAGIO 7-milligram, 16% for AUBAGIO 14-milligram, and 15% for placebo. ALT increased with 13, 15, and 9%, respectively. Diarrhea, it was 13, 14, and 8%, respectively. Alopecia 10, 13, and 5%. And nausea 8% for the AUBAGIO 7-milligram, 11% for AUBAGIO 14-milligram, and 7% for placebo.

Dr. Caudle:
And what about serious adverse events?

Dr. Stoll:
Serious adverse events occurred in 13%, 12%, and again 12% of the patients in the AUBAGIO 14-milligram, 7-milligram, and placebo groups, respectively. These included hepatotoxicity, infectious, peripheral neuropathy, and blood pressure effects.

There were also four cardiovascular deaths reported among the approximately 2600 patients exposed to AUBAGIO in the pre-marketing database, and that included three sudden deaths and one myocardial infarction in a patient with a history of hyperlipidemia and hypertension.

No relationship between AUBAGIO and cardiovascular death has been established.

Dr. Caudle:
Okay, and how many patients discontinued due to side effects?

Dr. Stoll:
The overall discontinuation rate due to adverse events were 12.5% with AUBAGIO 14-milligram, 11.2% with AUBAGIO 7-milligram, and 7.5 in the placebo arm.

In the pool core clinical trials, treatment discontinuation rates due to common adverse events were less than or equal to 3.3%.

This is not a comprehensive list of the adverse events associated with AUBAGIO. And for the full list, you should refer to the full prescribing information for details.

Dr. Caudle:
And, Dr. Stoll, do you have any other thoughts on AUBAGIO and what we might take away from these data?

Dr. Stoll:
Thank you, Dr. Caudle. AUBAGIO has now over 17 years of combined trial and real-world experience including nine years postmarketing.

As of today, over 92,000 patients have been prescribed AUBAGIO. In my experience, it's a well-established treatment.

And looking at its safety and efficacy data, AUBAGIO may be a good fit for your RMS patients, including those with less aggressive disease.

Dr. Caudle:
Well, that's a great way to round out our discussion on the subject. And before we close, let's take a moment to review some important safety information.

Announcer:

INDICATION

AUBAGIO® (teriflunomide) 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

WARNING: HEPATOTOXICITY AND EMBRYOFETAL TOXICITY

- **Clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, has been reported in patients treated with AUBAGIO in the postmarketing setting. Concomitant use of AUBAGIO with other hepatotoxic drugs may increase the risk of severe liver injury.**
- **Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for 6 months after starting AUBAGIO. If drug-induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or activated charcoal. AUBAGIO is contraindicated in patients with severe hepatic impairment. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.**
- **AUBAGIO is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Teratogenicity and embryolethality occurred in animals at plasma**

teriflunomide exposure lower than that in humans. Exclude pregnancy before the start of treatment with AUBAGIO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during AUBAGIO treatment and during an accelerated drug elimination procedure after AUBAGIO treatment. Stop AUBAGIO and use an accelerated drug elimination procedure if the patient becomes pregnant.

CONTRAINDICATIONS

- Patients with severe hepatic impairment.
- Pregnant women and females of reproductive potential not using effective contraception.
- Patients with a history of hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in AUBAGIO.
- Co-administration with leflunomide.

WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Clinically significant liver injury, which could be life-threatening, can occur at any time during treatment with AUBAGIO. Patients with pre-existing acute or chronic liver disease, or those with serum ALT >2 times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with AUBAGIO. In clinical trials, if ALT elevation was >3 times the ULN on 2 consecutive tests, patients discontinued AUBAGIO and underwent accelerated elimination. Consider additional monitoring if co-administering AUBAGIO with other potentially hepatotoxic drugs; monitor patients who develop symptoms suggestive of hepatic dysfunction (eg, unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine).
- **Embryofetal Toxicity:** AUBAGIO may cause fetal harm when administered in pregnant women. Teratogenicity and embryofetal lethality occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than that in humans at the maximum human recommended dose of 14 mg/day. AUBAGIO is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception.

  Exclude pregnancy before starting AUBAGIO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during AUBAGIO treatment and during an accelerated drug elimination procedure (AEP) after AUBAGIO treatment. If a woman becomes pregnant while taking AUBAGIO, stop treatment, apprise patient of the potential risk to a fetus, and perform an AEP to achieve an AUBAGIO plasma concentration of <0.02 mg/L. Upon discontinuing AUBAGIO, it is recommended all females of reproductive potential undergo an AEP.

  Women receiving AUBAGIO who wish to become pregnant must discontinue AUBAGIO and undergo an AEP, until plasma concentrations of AUBAGIO are <0.02 mg/L. Men wishing to father a child should also stop AUBAGIO and either undergo an AEP or wait until plasma concentration of AUBAGIO is <0.02 mg/L.

  Women who become pregnant while taking AUBAGIO may enroll in the AUBAGIO pregnancy registry by calling 1-800-745-4447, option 2.

- **Procedure for Accelerated Elimination of Teriflunomide:** Teriflunomide is eliminated slowly from the plasma—it takes an average of 8 months, or up to 2 years, to reach plasma concentrations <0.02 mcg/mL. Elimination may be accelerated by administration of cholestyramine or activated charcoal, but this may cause disease activity to return in patients who were responding to AUBAGIO.
- **Bone Marrow Effects/Immunosuppression Potential/Infections:** Decreases in white blood cell counts, mainly of neutrophils and lymphocytes, and platelets have been reported with AUBAGIO. Thrombocytopenia, including rare cases with platelet counts less than 50,000/mm3, has been reported in the postmarketing setting. Obtain a complete blood cell count within 6 months before starting treatment, with further monitoring based on signs and symptoms of bone marrow suppression. AUBAGIO is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe uncontrolled infections. Tuberculosis (TB) has been observed in clinical studies of AUBAGIO. Before starting treatment, screen patients for latent TB infection with a tuberculin test. Treatment in patients with acute or chronic infections should not be started until the infection(s) is resolved. Administration of live vaccines is not recommended. The risk of malignancy, particularly lymphoproliferative disorders, or infection may be increased with the use of some medications with immunosuppressive potential, including teriflunomide.
- **Hypersensitivity Reactions:** AUBAGIO can cause anaphylaxis and severe allergic reactions. Signs and symptoms have included dyspnea, urticaria, and angioedema including lips, eyes, throat, and tongue. Inform patients of the signs and symptoms of anaphylaxis and angioedema.
- **Serious Skin Reactions:** Cases of serious skin reactions, sometimes fatal, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with

AUBAGIO. Fatal outcomes were reported in one case of TEN and one case of DRESS. Inform patients of the signs and symptoms of a serious skin reaction and instruct them to discontinue AUBAGIO and seek immediate medical care. Unless the reaction is clearly not drug-related, discontinue AUBAGIO and begin accelerated elimination immediately. In such cases, patients should not be re-exposed to teriflunomide.

- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** DRESS, also known as multiorgan hypersensitivity, has occurred with AUBAGIO. One fatal case of DRESS that occurred within 34 days of initiation of AUBAGIO treatment has been reported in the postmarketing setting. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (eg, fever, lymphadenopathy) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately.

  Discontinue AUBAGIO, unless an alternative etiology for the signs or symptoms is established, and begin an accelerated elimination procedure immediately. In such cases, patients should not be re-exposed to teriflunomide.

- **Peripheral Neuropathy:** Peripheral neuropathy, including polyneuropathy and mononeuropathy, has been reported with AUBAGIO. Age >60 years, concomitant neurotoxic medications, and diabetes may increase the risk. If peripheral neuropathy is suspected, consider discontinuing treatment and performing accelerated elimination.
- **Increased Blood Pressure:** Blood pressure increases and hypertension have occurred with AUBAGIO. Measure blood pressure at treatment initiation and manage any elevations during treatment.
- **Respiratory Effects:** Interstitial lung disease (ILD), including acute interstitial pneumonitis, has been reported with AUBAGIO. ILD may be fatal and may occur acutely at any time during therapy with a variable clinical presentation. If discontinuation of the drug is necessary, consider initiation of an accelerated elimination procedure.
- **Pancreatitis in Pediatric Patients:** AUBAGIO is not approved for use in pediatric patients. In a pediatric clinical trial, cases of pancreatitis were observed in patients receiving AUBAGIO. If pancreatitis is suspected, discontinue teriflunomide and start an accelerated elimination procedure.

Adverse Reactions: The most frequent adverse reactions (≥10% and ≥2% greater than placebo) with AUBAGIO 7 mg and 14 mg and placebo, respectively, were headache (18% and 16% vs 15%), ALT increased (13% and 15% vs 9%), diarrhea (13% and 14% vs 8%), alopecia (10% and 13% vs 5%), and nausea (8% and 11% vs 7%).

Drug Interactions: Monitor patients when teriflunomide is coadministered with warfarin, or with drugs metabolized by CYP1A2, CYP2C8, substrates of OAT3 transporters, substrates of BCRP, or OATP1B1/1B3 transporters.

Use in Specific Populations: Women should not breastfeed during treatment with AUBAGIO.

Please see Full Prescribing Information, including **boxed WARNING.**

Dr. Caudle:
I'd like to thank my guest, Dr. Sharon Stoll, for helping us see why AUBAGIO continues to be an option for RMS patients, including those with less aggressive disease. Dr. Stoll, it was so great speaking with you today.

Dr. Stoll:
Dr. Caudle, the pleasure was all mine. I hope we can do this again soon. And yay Philly girls.

Dr. Caudle:
Completely agreed. Completely agreed. I'm your host, Dr. Jennifer Caudle, and thanks for listening.

Announcer:
This program was brought to you by Sanofi. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be Part of the Knowledge.