

Transcript Details

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Guiding Long-Term Care in Friedreich Ataxia

Announcer:

You're listening to ReachMD. This is the audio only version of the medical industry feature, titled "Guiding Long-Term Care in Friedreich Ataxia." This program is sponsored by Biogen and our speakers have been compensated by Biogen. We'll be covering information about SKYCLARYS, which is indicated for the treatment of Friedreich ataxia in adults and adolescents aged 16 years and older.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS for SKYCLARYS include:

Elevation of Aminotransferases

Treatment with SKYCLARYS can cause an elevation in hepatic transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). The incidence of elevations of ALT or AST above 5 times and 3 times the upper limit of normal (ULN) was 16% and 31%, respectively, in patients treated with SKYCLARYS. There were no cases of concomitant elevation of transaminases and total bilirubin observed. Maximum increases in ALT and AST occurred within 12 weeks after starting SKYCLARYS. Increases in serum aminotransferases were generally asymptomatic and reversible following discontinuation of SKYCLARYS.

These are not all the Warnings and Precautions. Please see additional Important Safety Information as well as full Prescribing Information available on this page.

And now here's your host, Dr Jennifer Caudle.

Dr Caudle:

This is ReachMD, and I'm your host, Dr Jennifer Caudle. This program is sponsored by Biogen and our speakers have been compensated by Biogen.

Joining me to discuss long-term management strategies and safety considerations for patients with Friedreich ataxia receiving SKYCLARYS are Drs David Lynch and Laura Bleekrode. Dr Lynch is a professor of neurology and attending neurologist at the Children's Hospital of Philadelphia and director of the Friedreich Ataxia Program.

Dr Lynch's contribution to our current understanding of Friedreich ataxia is extensive. His research has helped to uncover critical aspects of the disease, and he led the landmark study for the first and only FDA-approved prescription medication for Friedreich ataxia.

Dr Lynch, welcome to the program.

Dr Lynch:

Thanks, it's great to be here.

Dr Caudle:

Of course, and Dr Bleekrode is a pediatrician and owner of Alpharetta Pediatrics in Georgia. In addition to her role as a dedicated clinician, she brings her unique perspective as a mother to 3 children who have Friedreich ataxia. Dr Bleekrode, thank you so much for joining us.

Dr Bleekrode:

Of course, thanks for having me.

Dr Caudle:

Absolutely. And now, our discussion today will start by framing our understanding of Friedreich ataxia, or FA—the most common form of inherited ataxia and a progressive neurodegenerative genetic disorder. We'll then discuss the role of SKYCLARYS, or omaveloxolone, a treatment that has demonstrated an effect on disease progression in clinical studies of patients with FA.

So, with that context in mind, Dr Lynch, you know, when you're talking with patients, how do you help them understand disease progression in FA and the individuality of their experience?

Dr Lynch:

Well, I usually begin by explaining that FA is progressive, and due to this progression, symptoms will worsen over time.² I also emphasize that while the clinical course may look different for each patient, the disease itself does continue to progress.^{3,4}

As that neurological dysfunction advances, patients can gradually lose certain functional abilities.⁵ Now, symptoms don't always appear in a predictable order, and the rate of progression can vary significantly from one person to another. However, ataxia remains a hallmark feature of the disease.³

Some patients may first notice falls or clumsiness, feeling off balance, loss of sensation, or fatigue.^{3,5-7} But over time, we often see lower limb coordination decline, and so mobility aids like a cane or walker become helpful.³ Additionally, speech can become more slurred as bulbar function is affected, and hands and arms may become less coordinated, which impacts typing, writing, and fine motor tasks.^{3,5,6}

Due to those symptoms, many patients ultimately require a wheelchair, often around 10 to 15 years after symptom onset.³ But again, that timeline isn't identical for everyone.^{3,4} Beyond the neurologic features, we also have to monitor for complications like cardiomyopathy or diabetes, which are part of a broader disease burden.^{3,4}

And when these conversations come up, I explain that FA is associated with shorter life expectancy overall.³

But at the same time, I remind patients that while FA is progressive, your experience will be your own.³⁻⁵ Treatments including physical therapy and speech therapy as well as SKYCLARYS help support the goal to slow down disease progression and support function at every stage.

Dr Caudle:

And if we turn to you now, Dr Bleekrode, how do you help patients understand how disease progression in FA is measured and what that may mean for their everyday activities?

Dr Bleekrode:

Thank you Dr. Caudle, that is a great question. I believe the most important thing is to listen to your patients. You need to be on the lookout for some of these symptoms and see how these are affecting their function, independence, and activities of daily living. I sometimes reference a tool used in clinical trials and natural history studies called the modified Friedreich Ataxia Rating Scale, otherwise known as mFARS.⁸ While it's primarily used in research settings,⁸ it can help frame discussions between patients and providers about how the disease is progressing and how treatment may be affecting function over time.

The mFARS exam evaluates 4 key areas that relate directly to daily activities^{8,9}

1. Lower limb coordination, which can affect things like putting on socks and shoes.
2. Upright stability, such as walking, standing in line, sitting in a car, and showering.
3. Upper limb coordination, which involves things like getting dressed, eating, brushing teeth, typing, pointing, reaching, or turning a doorknob.
4. And lastly, mouth and throat, or bulbar function, like speaking clearly and coughing effectively.

I explain that mFARS ranges from zero to 93 points. A lower score means less functional impairment, and a higher score reflects greater impairment. Increases in mFARS score indicate that the patient is worsening in 1 or more of these categories.⁸

However, in my opinion, the best way to measure progression in clinical practice is to ask the patient, because there is high variability in clinical presentation among patients with FA, and mFARS is meant to assess progression at a population level. Also, there is variability in examiners assessing and scoring each patient, and mFARS has relative insensitivity to change over brief periods of time.^{10,11}

Now, this is where I think it's important to set expectations with patients regarding changes in mFARS. Natural history data suggests that, on average, patients with FA may experience progression of about 2 points per year.¹² Utilizing a scale like mFARS can not only help quantify functional decline representing more challenges in activities of daily living, but can also encourage conversations about treatment and care.

Dr Caudle:

That's a great way to shift our focus to intervention, because as I understand it, the MOXIe Phase 2 trial was an international, multicenter, double-blind, registrational study that evaluated the efficacy and safety of SKYCLARYS in patients with FA.²

But before we continue, let's take a moment to review the Indication and Important Safety Information for SKYCLARYS, also known as omaveloxolone.

Dr Lynch:

INDICATION

SKYCLARYS® (omaveloxolone) is indicated for the treatment of Friedreich ataxia in adults and adolescents aged 16 years and older.¹

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Elevation of Aminotransferases

Treatment with SKYCLARYS can cause an elevation in hepatic transaminases (alanine aminotransferase, also called ALT, and aspartate aminotransferase, also called AST. The incidence of elevations of ALT or AST above 5 times and 3 times the upper limit of normal was 16% and 31%, respective, in patients treated with SKYCLARYS. There were no cases of concomitant elevation of transaminases and total bilirubin observed. Maximum increases in ALT and AST occurred within 12 weeks after starting SKYCLARYS. Increases in serum aminotransferases were generally asymptomatic and reversible following discontinuation of SKYCLARYS.¹

After initiation, liver function tests should be monitored every month for the first 3 months, and then periodically thereafter. If aminotransferase levels rise to greater than 5 times the upper limit of normal, or greater than 3 times the upper limit of normal with evidence of liver dysfunction, SKYCLARYS should be discontinued and liver function tests repeated as soon as possible. If levels stabilize or resolve, treatment may be reinitiated with appropriate monitoring.¹

Please see full Prescribing Information provided at the link above this video.

Dr Caudle:

So, Dr Lynch, when you introduce SKYCLARYS to patients, how do you summarize the MOXIe trial in the context of disease progression?

Dr Lynch:

When I talk to my patients about SKYCLARYS, I try to anchor the discussion in what we just talked about: progression over time and how that translates into function.

In MOXIe, patients aged 16 to 40 with genetically confirmed FA were randomized to receive 150 milligrams once daily of SKYCLARYS or placebo. The primary endpoint was the change from baseline in mFARS at 48 weeks.^{1,2}

At that point, the least squares mean difference between treatment groups was negative 2.41 points. In other words, that means the patients who received SKYCLARYS experienced less physical impairment relative to placebo over that time as reflected in mFARS measures of limb coordination, upright stability, and bulbar function.^{1,2}

The post hoc propensity-matched analysis also helps frame conversations with patients about what they may expect in terms of disease progression with treatment. In this analysis, patients from the MOXIe open-label extension were compared with matched patients from the FA-COMS natural history study. Over 3 years, progression was 3 mFARS points in the SKYCLARYS group vs about 6.6 points in the matched natural history group. That corresponded to about 55 percent slower progression at 3 years in the treated group.¹³

Now, with that being said, I do make it clear to patients that this was 3-year comparison that was exploratory and conducted outside of a randomized, controlled setting, so the findings should be interpreted cautiously.¹

And so ultimately, I explain that our main goal in treating FA is to slow progression while proactively monitoring and managing adverse events.

Dr Caudle:

So, building on that point about monitoring, Dr Bleekrode, how do you share the safety findings from the MOXle trial when setting expectations for patients starting SKYCLARYS?

Dr Bleekrode:

When I review safety findings with patients, I start with the overall picture.

In the MOXle trial, adverse events were generally considered mild to moderate in severity.² The most common adverse reactions, occurring in at least 20 percent of patients and more frequently than placebo, included elevated liver enzymes, headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain.¹ I discuss these results with patients to help them understand what they may experience.

Three patients did report serious adverse events while taking SKYCLARYS, and 2 reported them after discontinuation. Treatment discontinuation due to adverse reactions occurred in 8 percent of patients in the SKYCLARYS group compared with 4 percent in the placebo group.² Reasons for discontinuation in the SKYCLARYS group included ventricular tachycardia, elevated ALT and AST, muscle spasms, and rosacea.¹⁴

The most common adverse reactions were transient and generally resolved within 35 days of the event start date.¹⁵ On the graph you'll see the most common adverse events listed along the x-axis, and on the y-axis, the respective durations represented by median and quartile values. You should be aware that side effects can occur or reoccur at any point while taking SKYCLARYS.

And to Dr Lynch's earlier point, I reassure my patients that we have a structured approach in place to monitor and manage these potential side effects while they are taking SKYCLARYS.

Dr Caudle:

Now earlier in our conversation, elevated liver enzymes was mentioned. So, let's talk more about routine hepatic monitoring.

Dr Lynch, can you walk us through how you counsel patients about liver enzyme monitoring in those first few months?

Dr Lynch:

Absolutely. So I explain to patients that hepatic monitoring becomes part of routine care when initiating therapy.

Before starting treatment, we obtain baseline laboratory values, including alanine aminotransferase, aspartate aminotransferase, and total bilirubin. After initiation, liver function tests are monitored every month for the first 3 months, and then periodically thereafter based on clinical judgment.¹

Now, in the MOXle trial, maximum increases in alanine aminotransferase and aspartate aminotransferase typically occurred within 12 weeks of starting therapy. These elevations were generally asymptomatic and reversible following discontinuation.¹

So from a management standpoint, if aminotransferase levels rise to greater than 5 times the upper limit of normal or greater than 3 times the upper limit of normal with evidence of liver dysfunction, then treatment should be discontinued immediately and liver function tests repeated as soon as possible.¹

If those levels stabilize or resolve, we can then reinstate SKYCLARYS with increased frequency of monitoring.¹ Framing it this way helps my patients understand our process to help detect laboratory changes, modify therapy appropriately, and the broader goal of slowing progression safely.

Dr Caudle:

Let's stay with you, Dr Lynch, and look beyond hepatic monitoring. Are there any other safety considerations for your patients who are taking SKYCLARYS?

Dr Lynch:

Yes, there are a couple of additional safety considerations that are important to incorporate into treatment plans and to communicate to patients.

One is cardiac monitoring, specifically B-type natriuretic peptide, or BNP. Treatment with SKYCLARYS can cause an increase in BNP, which is a marker of atrial stretch, or in some ways, cardiac function. Elevations may indicate cardiac failure in some cases, and should prompt further evaluation of cardiac function. So, we obtain a BNP level prior to initiating therapy.¹

In addition to laboratory assessment, the Prescribing Information recommends monitoring patients for symptoms of fluid overload, such

as sudden weight gain, which is defined as 3 pounds or more in 1 day or 5 pounds or more in one week. Other symptoms include peripheral edema, shortness of breath, and palpitations. If fluid overload or worsening heart failure is suspected, treatment interruption may be necessary.¹

This is particularly relevant in FA, since cardiomyopathy can be part of the underlying disease process.^{3,17} So we're thoughtful about distinguishing baseline cardiac involvement from treatment-related changes.

Another consideration is lipid abnormalities. Treatment can cause changes in cholesterol level. So, we assess lipid parameters before starting therapy and monitor periodically during treatment. If abnormalities occur, they're managed according to standard clinical guidelines.¹

So, while there are several monitoring components—hepatic, cardiac, and metabolic—they all follow a defined protocol.¹ And with baseline evaluation and scheduled follow-up, this can be incorporated into care plans in a manageable way.

Dr Caudle:

As we begin to wrap up today's discussion, I'd like to ask each of you whether you have any additional strategies you've found effective for helping patients on their treatment journey. Dr Bleekrode, let's start with you.

Dr Bleekrode:

Well, I focus on making therapy practical and manageable for my patients.

Most importantly, I encourage them to set up a reminder, such as a daily phone reminder, to take their medication. I tell them to mark their calendars for follow-up appointments, and I strongly encourage them to document their experiences. Once they document experiences in the follow-up, it gives us a great tool to manage the different side effects they may be experiencing. And finally, I emphasize that they should reach out if they have questions about managing side effects.

When my patients feel supported, informed, and organized, they're more likely to stay engaged in their treatment journey.

Dr Caudle:

And what about you, Dr Lynch?

Dr Lynch:

I agree with the insights that Dr Bleekrode shared. I'd also like to zoom out to the broader context of care. We now have real-world experience with more than 3,000 patients prescribed SKYCLARYS globally,¹⁸ demonstrating that this therapy can be incorporated into clinical practice with structured monitoring.

It also helps to emphasize a multidisciplinary care approach. Because FA affects multiple systems, patients will require coordinated input from a multidisciplinary team as it progresses. Ideally, a neurologist or primary care physician helps lead and coordinate that care.¹⁹

When treatment is delivered within that coordinated framework, it aligns with our overarching goal: slowing FA progression to help preserve function, sustain independence, and support long-term quality of life.

Dr Caudle:

Thank you both, these are really great takeaways from our discussion today. And as that brings us to the end of today's program, I'd like to thank my guests, Drs David Lynch and Laura Bleekrode, for sharing their practical considerations and clinical insights on the long-term care of patients with Friedreich ataxia receiving SKYCLARYS.

Dr Lynch and Dr Bleekrode, it was great speaking with you both today.

Drs Lynch:

Happy to be here.

Dr. Bleekrode:

Thank you so much for having me.

Dr Caudle:

Of course. And for ReachMD, I'm your host, Dr Jennifer Caudle.

Please stay tuned to hear additional Important Safety Information.

Dr. Lynch:

WARNINGS AND PRECAUTIONS

Elevation of B-Type Natriuretic Peptide

Treatment with SKYCLARYS can cause an increase in B-type natriuretic peptide (BNP), a marker of cardiac function. A total of 14% of patients treated with SKYCLARYS had an increase from baseline in BNP value above the ULN (100 pg/mL), compared to 4% of patients who received placebo. The incidence of elevation of BNP above 200 pg/mL was 4% in patients treated with SKYCLARYS. Cardiomyopathy and cardiac failure are common in patients with Friedreich ataxia. Whether the elevations in BNP are related to SKYCLARYS or cardiac disease associated with Friedreich ataxia is unclear.

Elevations in BNP may indicate cardiac failure and should prompt an evaluation of cardiac function. Check BNP prior to the initiation of SKYCLARYS. Monitor patients for the signs and symptoms of fluid overload, such as sudden weight gain (3 pounds or more of weight gain in one day, or 5 pounds or more of weight gain in a week), peripheral edema, palpitations, and shortness of breath. If signs and symptoms of fluid overload develop, worsen, or require hospitalization, evaluate BNP and cardiac function, and manage appropriately. Management of fluid overload and heart failure may require discontinuation of SKYCLARYS.

Lipid Abnormalities

Treatment with SKYCLARYS can cause changes in cholesterol. In Study 1, 29% of patients treated with SKYCLARYS reported elevated cholesterol above upper limit of normal at one or more time points. Mean increases were observed within 2 weeks of initiation of SKYCLARYS and returned to baseline within 4 weeks of discontinuing treatment. A total of 16% of patients treated with SKYCLARYS had an increase in low-density lipoprotein cholesterol (LDL-C) from baseline, compared to 8% of patients who received placebo. The mean increase in LDL-C for all SKYCLARYS treated patients was 23.5 mg/dL at 48 weeks. A total of 6% of patients treated with SKYCLARYS had decreases in HDL-C, high-density lipoprotein cholesterol, from baseline compared to 4% of patients who received placebo. The mean decrease in HDL-C for all SKYCLARYS-treated patients was 5.3 mg/dL at 48 weeks.

Assess lipid parameters prior to initiation of SKYCLARYS and monitor periodically during treatment. Manage lipid abnormalities according to clinical guidelines.

ADVERSE REACTIONS

The most common adverse reactions in Study 1 ($\geq 20\%$ and greater than placebo) were elevated liver enzymes (AST/ALT), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain.

DRUG INTERACTIONS

Avoid concomitant use of SKYCLARYS with moderate or strong CYP3A4 inhibitors. If use cannot be avoided, dosage modifications are recommended.

Avoid concomitant use of SKYCLARYS with moderate or strong CYP3A4 inducers.

Refer to the prescribing information for dosing instructions for concomitant use of CYP3A4 and CYP2C8 substrates and monitor for lack of efficacy of the concomitant treatment.

Advise patients to avoid concomitant use with combined hormonal contraceptives, implants, and progestin only pills.

SPECIFIC POPULATIONS

Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SKYCLARYS during pregnancy. Healthcare providers are encouraged to enroll pregnant patients, or pregnant women may register themselves in the program by calling 1-866-609-1785 or by sending an email to SkyclarysPregnancySurveillance@ppd.com.

There are no adequate data on the development risks associated with the use of SKYCLARYS in pregnant women.

Lactation

There are no data on the presence of omaveloxolone or its metabolites in human milk. The effects on milk production and the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYCLARYS and any potential adverse effects on the breastfed infant from SKYCLARYS or from the underlying maternal condition.

Hepatic Impairment

Avoid treatment with SKYCLARYS in patients with severe hepatic impairment, including those who develop severe hepatic impairment. Reduced dosage in patients with moderate hepatic impairment with close monitoring for adverse reactions is recommended.

INDICATION

SKYCLARYS® (omaveloxolone) is indicated for the treatment of Friedreich ataxia in adults and adolescents aged 16 years and older

Announcer:

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