

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/friedreich-ataxia-diagnosis-to-treatment/54613/>

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Taking Action in Friedreich Ataxia From Diagnosis to Treatment

Announcer:

You're listening to ReachMD. This is the audio only version of the medical industry feature, titled "Taking Action in Friedreich Ataxia From Diagnosis to Treatment." 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.

Now here's your host, Dr Jennifer Caudle.

Dr Caudle:

Welcome to ReachMD. I'm your host, Dr Jennifer Caudle and this program is sponsored by Biogen. Our speakers have also been compensated by Biogen.

Here with me to share strategies for recognizing and treating patients with Friedrich ataxia 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 Caudle:

Dr Lynch, thank you so much for being here today.

Dr Lynch:

Thanks for having me.

Dr Caudle:

Of course, and also with us is Dr Bleekrode. She's 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, it's great to have you with us, as well.

Dr Bleekrode:

Thank you, it's great to be here.

Dr Caudle:

Today, we're going to focus on the most common form of inherited ataxia.² So to help ground our discussion, let's begin with a hypothetical patient scenario you might encounter in clinical practice.

So, Dr Lynch, would you care to start us off?

Dr Lynch:

Absolutely.

Let's call our hypothetical patient Charles. He's 32 years old and visits his primary care physician because he's been having problems with balance and coordination.³

He first became concerned after several falls walking up the stairs, and he just felt "off balance." He also noticed some occasional jerky movements when he was picking up objects.³

On physical exam, his primary care physician noted areflexia, the lack of deep tendon reflexes.³ Routine laboratory work, including complete blood count, serum creatinine, and liver enzymes, were normal.³⁻⁵ He does not have any current infections.⁵

The findings from this initial assessment did not clearly point to any specific condition, and no diagnosis was established at that time.

The PCP made no further referrals and recommended semi-annual follow-up.

About 1 year later, at age 33, his physician noticed persistent areflexia and an abnormal gait.³ Repeat labs included hemoglobin A1c, complete blood count, basic metabolic panel, and liver enzymes, all of which were again normal. He remained without a history of recent infection.³⁻⁵

On neurologic examination at that time, he had a mild gait ataxia with his eyes open and closed. He had mild impairment in fast alternating hand movements, and normal muscle tone.^{3,4,6} When he was asked about his earlier symptoms, he reflected that he had actually been getting clumsier for about 3 years. He mentioned slower typing and more frequent typos at work.³ Lastly, there was no known family history of neurologic disease.⁷

Dr Caudle:

Thank you so much for sharing those details with us, Dr Lynch. And if we turn to you now, Dr Bleekrode, what diagnosis comes to mind, and how would you approach evaluating a patient like Charles?

Dr Bleekrode:

When I hear a case like this, there are a number of steps in the workup or differential diagnosis to rule out more likely causes of these symptoms, such as tumor or vascular disease.⁵ But once I've ruled those out, I'd consider the neurological symptoms as consistent with an ataxia, and I'd make sure to rule out Friedreich ataxia because it is the most common form of inherited ataxia and there is a treatment available.⁸

So if we take a closer look at what FA can look like in practice, it's a multisystem disorder, with a wide range of clinical manifestations.^{2,3,10}

From a neurologic standpoint, we commonly see gait abnormalities, slurred speech, incoordination in fine motor tasks, fatigue, and difficulty swallowing.¹¹ There are also abnormal eye movements, though these are subtle in FA.³

Limb and gait ataxia are the most common features present in nearly all patients.^{3,12} Personally, I have seen areflexia first before other features.³

In Charles' case, FA presented with some neurological symptoms, but FA can also include cardiomyopathy, diabetes, scoliosis, and foot deformities.^{2,3} And while the manifestations are predominantly physical, also in my experience, depression is a common comorbidity with neurodegenerative disorders like FA.¹³

Charles, our patient, does not have any heart complications, but when patients with FA do present with cardiac symptoms, referral to a

cardiologist is recommended.

Dr Lynch:

And just to add to what Dr Bleekrode discussed, there are differences in presentation of symptoms in early-onset disease vs late-onset disease.

For late-onset disease, I see problems with gait generally present first. These patients usually also present with hyperreflexia. They do not, however, have auditory neuropathy, true cardiomyopathy, or scoliosis, unless they developed during their teenage years. And in my clinical experience, if these patients have diabetes, it is typically driven by lifestyle factors rather than caused by FA.^{3,14}

Earlier-onset FA is generally associated with more rapid progression and greater severity, while later-onset disease usually progresses more slowly and can present more mildly.^{3,15}

Late-onset FA can also present atypically, sometimes with retained reflexes even spasticity, which makes diagnosis even more challenging.³ Because of this variability, clinicians may attribute symptoms to other neurologic conditions. Common misdiagnoses include Charcot-Marie-Tooth disease, inherited neuropathy, cerebellar abnormalities, multiple sclerosis, and inner ear disorders.^{3,16,17}

Due to these nonspecific and slowly progressive symptoms, diagnosis can take years.^{16,18,19} In fact, about one in 4 patients are initially misdiagnosed, and see more than 4 physicians before receiving a diagnosis.¹⁶ Median time to diagnosis is approximately 3 years in typical-onset FA and closer to 5 years in late-onset disease.^{15,19}

But because FA causes progressive loss of neurologic function resulting in movement and sensory symptoms, it's important to recognize patients early rather than evaluating each symptom in isolation.³

Dr Caudle:

Now, coming back to you Dr Bleekrode, what can clinicians do for patients like Charles, and why is diagnosis so important?

Dr Bleekrode:

In a case like Charles', once genetic ataxia is suspected, genetic testing should be done and testing should include FA.¹⁰

This is particularly important for FA because, as we discussed earlier, it's the most common inherited form of ataxia, and treatment may be available for patients with FA.²

Since there are nuances to the genetic testing process, often it will be the neurologist who orders these tests, but it's helpful to understand background around why genetic testing is needed.

FA is caused by mutations in the *FXN* gene.^{8,20,21} In almost all patients, the underlying mutation is a biallelic GAA triplet-repeat expansion in the *FXN* gene.²

Two main approaches are commonly available in clinical practice.²¹

The first is a broad multigene ataxia panel, but please note that not all broad panels include *FXN* GAA triplet-repeat analysis. Without this particular analysis, you may have a false negative, so it's very important to confirm that it's included, perhaps by ordering a panel for all recessive ataxias, or ask that it be added separately.^{7,20}

The second approach is single-gene testing of the *FXN* repeat expansion, which is a direct and efficient approach if clinical suspicion of FA is high.²¹

If you have access to a genetic counselor, they may be able to advise you on the appropriate approach. For my primary care peers in the audience, you may not have easy access, so you may want to work closely with a neurologist to ensure the patient has the appropriate testing completed.

Because FA is a progressive disease, timely genetic confirmation is essential, and any patient who's suspected of having FA should be considered for genetic testing.²²

Dr Caudle:

Well, now that we've discussed diagnosis, let's talk about monitoring clinical symptoms. So, Dr Lynch, how is disease progression measured in FA?

Dr Lynch:

That's a critical question because FA is often disabling and fatal.^{3,8} As mobility declines, patients may require assistive devices, such as canes, walkers, or wheelchairs. That increasing need for support can affect independence and overall quality of life.³

FA can also present with non-neurological symptoms such as scoliosis, cardiomyopathy, and diabetes, with cardiomyopathy being the most common cause of death.^{2,3}

But going back to your question, progression is commonly measured in clinical trials and natural history studies using the modified Friedreich Ataxia Rating Scale, or mFARS. It's a validated and clinically relevant assessment that evaluates changes in mobility, balance, coordination, and speech.²³

The scale includes 4 domains²³

- Lower limb coordination
- Upright stability
- Upper limb coordination and
- Bulbar function

It's scored from zero to 93, with higher scores indicating that more severe physical impairment.²³ And as FA progresses, mFARS scores increase.²⁴

In fact, data from a large longitudinal natural history studies show that mFARS scores worsen by about 2 points per year on average.²⁴

In my opinion, the best way to measure progression in clinical practice is to ask the patient how they are doing, because there is high variability in clinical presentation among FA patients, and the mFARS is meant to assess progression at a population level. There is also variability in examiners assessing and scoring each patient, and mFARS has relative insensitivity to change over brief periods of time.^{18,25}

And remember, for FA, the rate of progression correlates with age at symptom onset, as later onset is generally associated with slower progressions.^{3,15}

Clinicians now have an opportunity to treat patients with FA for individuals aged 16 years and older with the approval of the first treatment 3 years ago.¹ That's why accessing progression is so important.

Dr Caudle:

So now that we've reviewed diagnosis and progression in FA, let's shift our discussion to treatment with SKYCLARYS.

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%, 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.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 picking up with you, Dr Bleekrode, could you briefly explain how SKYCLARYS works to treat FA?

Dr Bleekrode:

Well, the precise mechanism is not fully understood, but SKYCLARYS has been shown to activate the nuclear factor erythroid 2-related factor 2, or Nrf2 pathway. This cellular pathway helps regulate the body's antioxidant response to oxidative stress and supports mitochondrial function.^{1,26,27}

Dr Caudle:

That's really interesting. Now, let's turn our attention then to the clinical data, as the efficacy and safety of SKYCLARYS were evaluated in the MOXIe Phase 2 trial.⁸

So, Dr Lynch, what did the MOXIe trial show about the impact of SKYCLARYS on disease progression in patients with FA?

Dr Lynch:

So the MOXIe trial was an international, multicenter, registrational study that enrolled 103 patients with genetically confirmed FA, aged 16 to 40 years, in a randomized, double-blind design. These patients had a wide range of disease severity and were randomized to receive SKYCLARYS 150 milligrams once daily or placebo.^{1,8}

The primary endpoint was measured in least squares mean change from baseline in mFARS at 48 weeks. When it came to the findings, we observed that treatment with SKYCLARYS resulted in a group difference of negative 2.41 points compared with placebo. In practical terms, that means that patients who received SKYCLARYS experienced less physical impairment relative to patients on placebo at 48 weeks.^{1,8}

Dr Caudle:

Thank you for that, Dr Lynch. And if we look beyond the initial 48-week analysis, what do we know about the efficacy outcomes?

Dr Lynch:

To better understand longer-term outcomes a post hoc propensity-matched analysis was conducted comparing patients treated with SKYCLARYS in the MOXIe open-label extension with external controls from the FA-COMS natural history study.²⁸

For some background, FA-COMS is a large, longitudinal observational study that has enrolled over 1250 patients with FA and has followed them for up to 15 years.²⁸⁻³⁰ Given that design, it's played an important role in mapping the natural history of the disease and validating outcome measures such as mFARS.

But in this analysis, patients from the MOXIe open-label extension—all receiving 150 milligrams of SKYCLARYS once daily—were matched 1-to-1 with FA-COMS patients based on age, age at onset, sex, baseline mFARS score, and baseline mFARS gait score.²⁸

After 3 years, matched, untreated FA-COMS patients progressed by 6.61 mFARS points, whereas patients treated with SKYCLARYS progressed by 3 points. That resulted in a group difference of negative 3.61 points, with a standard error of 0.93. So this corresponded to a 55 percent slower progression in the SKYCLARYS-treated group over 3 years.²⁸

However, it's important to emphasize that this was an exploratory analysis, and the results should be interpreted cautiously given the limitations inherent to comparisons outside of a randomized controlled setting.¹

Dr Caudle:

Thank you for that, Dr Lynch. Let's talk about safety next. So, Dr Bleekrode, can you walk us through the safety of SKYCLARYS?

Dr Bleekrode:

Sure. The adverse events were generally considered mild to moderate.⁸ The most common adverse reactions included elevated liver enzymes, headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain.¹

As far as serious adverse events, 3 patients reported them while taking SKYCLARYS, and 2 patients reported them approximately 2 weeks after discontinuation.⁸

On that front, treatment discontinuation due to adverse reactions occurred in 8 percent of patients in the SKYCLARYS group, compared with 4 percent of patients in the placebo group. Reasons for discontinuation in the SKYCLARYS group included ventricular tachycardia, elevated ALT and AST, muscle spasms, and rosacea.^{8,32}

The most common adverse reactions were transient and generally resolved within 35 days of the event start date.³¹ 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.

Dr Caudle:

So, Dr Bleekrode, once a patient is diagnosed with FA and you've decided together to initiate treatment, how do you think about starting SKYCLARYS in clinical practice?

Dr Bleekrode:

I think about it as a stepwise process. First, I confirm the diagnosis genetically and ensure we've had a discussion with the patient about treatment goals and expectations, including the warnings and precautions about taking SKYCLARYS. Second, I obtain baseline laboratory values, including ALT and AST, total bilirubin, B-type natriuretic peptide, and a lipid panel to ensure treatment is an option and remind the patient that we will monitor these values throughout treatment. Once those 2 steps are completed, treatment can begin.

Now on the practical side of things, SKYCLARYS is a once-daily oral prescription medication. The recommended dose is 150 milligrams daily, consisting of three 50-milligram capsules taken once per day. It should be administered on an empty stomach, at least 1 hour before or 2 hours after eating.¹

Patients have the option to swallow the capsules whole or use sprinkle administration. If the patient can swallow capsules, they should be taken whole and not crushed or chewed. For patients who have difficulty swallowing, the capsules may be opened and the entire contents sprinkled onto 2 tablespoons, or 30 milliliters, of applesauce. The mixture should be stirred until homogeneous and swallowed immediately. Regardless of the dosing route, SKYCLARYS shouldn't be stored, mixed with milk or orange juice, or administered via enteral feeding tube.¹

If a dose is missed, the patient should take the next dose at the scheduled time the following day and should not double the dose.¹

I also make sure to review all concomitant medications, including over-the-counter drugs and herbal products, and advise patients to avoid grapefruit and grapefruit juice.¹

So based on all of this, treatment initiation follows a clear and manageable structure: obtain baseline labs, start once-daily dosing, and plan routine monitoring.

Dr Caudle:

And as we begin to wrap up, Dr Lynch, what does ongoing monitoring look like in real-world practice once a patient has started treatment with SKYCLARYS?

Dr Lynch:

After initiation, liver function tests should be monitored every month for the first 3 months, and then periodically thereafter.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.

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

In the MOXle trial, slight increases in B-natriuretic peptide levels were observed with SKYCLARYS relative to placebo, but not associated with clinical heart failure symptoms.³² Nevertheless, since B-type natriuretic peptide is a marker of cardiac function, clinicians should obtain a BNP level prior to initiating therapy and monitor patients for signs and 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

And finally, we need to assess lipid parameters before starting therapy, and monitor periodically during treatment because treatment can cause changes in cholesterol levels. If abnormalities occur, they're managed according to standard clinical guidelines.²⁴

So while monitoring is important, clinicians can generally follow a clearly defined protocol. And with baseline assessment and scheduled follow-up, it can be incorporated into routine clinical practice in a structured and manageable way.

Dr Caudle:

Thank you so much, Dr Lynch, for discussing monitoring with us.

Dr Bleekrode, where does SKYCLARYS fit into the clinical guidelines for managing FA?

Dr Bleekrode:

SKYCLARYS has a strong recommendation in the FA Clinical Management Guidelines to treat individuals aged 16 and older, as opposed to no treatment.³⁴

This recommendation was updated in November 2024. It's based on a moderate level of evidence and is aligned with FDA-approved labeling. Importantly, the guidelines also consider the progressive nature of FA and the limited treatment options available. All of this reinforces the importance of discussing treatment with patients once a diagnosis is confirmed.³⁴

Dr Caudle:

Well, with those final thoughts in mind, I want to thank my guests, Drs David Lynch and Laura Bleekrode, for helping us explore the early recognition, progression, and treatment of Friedreich ataxia. Dr Lynch and Dr Bleekrode, it was great speaking with you both today.

Dr. Lynch:

Thanks for having me.

Dr. Bleekrode:

It was great to be here.

Dr Caudle:

For ReachMD, I'm your host, Dr. Jennifer Caudle

Let's take a moment to review 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.

Announcer:

This medical industry feature was sponsored by Biogen and speakers are paid spokespersons for Biogen. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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