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Advancing the Treatment of ATTRv-PN: What's in the Pipeline?

Announcer:
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Dr. Khella:
This is CME on ReachMD, and I'm Dr. Sami Kella. Here with me today is Dr. John Berk.

John, can you give us an overview of the current data and ongoing clinical trials focused on ATTRv polyneuropathy?

Dr. Berk:
Sami, it would be a pleasure. I'd first like to start with a quick overview of the therapeutic landscape for TTR amyloid. There are pills, which are protein stabilizers and injectables that are TTR gene silencers. Protein stabilizers inhibit TTR misfolding, preserving circulating TTR. Typically, these drugs slow but don't completely stop the progression of nerve injury. In contrast, gene silencers prevent the liver from producing TTR. This eliminates the amyloidogenic protein more effectively, halting disease progression.

There are 2 first-generation agents to keep in mind. One is inotersen, and it required 300 mg of injection weekly and was complicated by low platelet counts, rare kidney injury, and flu-like reactions that might occur later in the course of administrations.

Patisiran, in contrast, is an intravenous agent given every 3 weeks, requiring pre-infusion steroids, vein cannulation for intravenous drug administration, and consequently, there could be rare drug leakage into tissues.

There are 2 pivotal trials: NEURO-TTRansform, involving about 168 patients, examining eplontersen, the second-generation agent, with some patients getting inotersen, using standard neurologic metrics and quality of life questionnaires to see if there is change over 15-months' treatment. And then HELIOS-A, a similar number of patients, examining the second-generation agent vutrisiran versus the first-generation patisiran. And looking at nerve changes over a 9-month period but extending the observations to a full 18 months.

I think it's really important to keep in mind that, as tempting as it is, these trial designs differ, making direct comparison of the drugs involved really unreliable. NEURO-TTRansform, there were a small number of patients that were randomized to inotersen, the first-generation agent, and 20% to 30% of those patients exhibited low platelet counts. And importantly, those patients who are on eplontersen actually improved TTR suppression from 74% on those starting on inotersen to 81% on those ending up on eplontersen.

HELIOS-A, vutrisiran is the drug. 88% TTR suppression at 18 months and fully 50% of people improved their neurologic measures and quality of life metrics. Notably, patients benefited from drug regardless of neuropathy severity at the time of entry in the trial. And, by multiple measures, this was true. It wasn't just a finding with one particular nerve measure. Transitioning from patisiran to vutrisiran, there was no change in TTR suppression or neuropathy scores over a full 18 months. Vutrisiran was just as effective as patisiran. And the adverse events were really minor with vutrisiran.

So in conclusion, there is second-generation TTR gene silencers now, significantly more potent and safer than the first-generation agents. They require infrequent injections for eplontersen, that's monthly, for vutrisiran, that's quarterly, and they're more convenient

treatments.

Dr. Khella:
Oh, that's great, John. Can you just give us one takeaway regarding the future of treatment?

Dr. Berk:
So I think the focus has been that our experience over time demonstrates that amyloidogenic protein suppression, elimination of the building block for amyloid, is the best approach to controlling amyloid systemic disease, whether we're talking about AA amyloid, AL amyloid, or TTR amyloid.

Dr. Khella:
Wow, thank you. This has been a great bite-sized discussion, John, but unfortunately, our time is up. Thanks for listening.

Announcer:
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