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New Insights on Integrating Chronic Migraine Preventatives in Clinical Practice

Announcer:
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Dr. Silberstein:
Hi, I'm Dr. Stephen Silberstein, Professor of Neurology at Thomas Jefferson University, and the Director of the Jefferson Headache Center. It's my great pleasure to be here today with Dr. Stewart Tepper, who's a long-term friend and colleague. Stew, would you introduce yourself?

Dr. Tepper:
Yes, thank you Steve for having invited me. I'm a Professor of Neurology at the Geisel School of Medicine in New Hampshire, and I am Vice President of the New England Institute for Neurology and Headache in Stamford, Connecticut.

What we really achieved in the last decade is the understanding that if we target calcitonin gene-related peptide, or CGRP, and take as much of it out of circulation or reduce the effectiveness of CGRP as possible, we can prevent both episodic and chronic migraine. And the magnitude of the change when we eliminate most of CGRP function can actually move people from chronic migraine back to episodic migraine, and dramatically changed people's lives.

Dr. Silberstein:
I agree. And, you know, when I started to think about this, Stew, I thought about antibodies that were given for multiple sclerosis and cancer. And I said, how can they make an antibody that's specific to CGRP and safe? And then I learned, it's all about engineering. You can have a car that can be anywhere from a Ferrari to a station wagon, the antibodies are engineerable. So you can take away the part of the antibody that interacts with other cells to destroy tissue, make it clean, safe, and just specifically target an antigen; in this case, CGRP, or its receptor. Would you agree, Stew?

Dr. Tepper:
I do. And the remarkable aspect about this is that these targeted monoclonal antibodies against the CGRP itself, against the ligand, or against the receptor, are so specific in terms of how they work, that the side effects are minimal. And because, as you taught me, monoclonal antibodies go through the reticuloendothelial system, and not through the liver and the kidney, drug-drug interactions don't seem to occur.

An additional point that you also taught me is that most monoclonal antibodies in other therapeutic areas, are immunologically active and carry with it long-term risk for immune changes, opportunistic infection or neoplasm. Whereas monoclonal antibodies targeting CGRP are not immunologically active. And they work apparently mostly peripherally in the meninges and dura, taking out the CGRP action, and in so doing, preventing the migraine mechanisms of pain in particular.

Dr. Silberstein:

I'd like to comment again. Most of the time we add a new drug, we worry about what it does to the liver or interacting with another drug. When a drug is taken up and interacting with the liver, it's metabolized. As you said, an antibody is different. It's taken up by the reticuloendothelial cell, and they're things on the surface of the antibody that protect it from degradation, and then it's released back into the circulation without being degraded. So basically, the reticuloendothelial cells prevent the metabolism of the antibody and keep it safe and effective.

Dr. Tepper:
And we are very fortunate that in the development of these monoclonal antibodies, we have had 4 that have been studied and FDA approved for prevention of all of migraine, episodic and chronic migraine, with and without aura, with and without medication overuse. And very briefly, those 4 include 1 which targets the CGRP receptor, erenumab, 3 which target the CGRP itself, the ligand, and those are fremanezumab, galcanezumab, and eptinezumab. The first 3, erenumab, fremanezumab, and galcanezumab can be administered by patients at home monthly, or in the case fremanezumab, also quarterly with autoinjectors, while eptinezumab is given on a quarterly basis and is intravenous. And all of these monoclonal antibodies have very, very high safety, and very good tolerability.

What's been your experience with them, Steve?

Dr. Silberstein:
Yeah, I would point out, because of that protective mechanism of the antibodies and the reticuloendothelial cells, their half-life is a month or more. So that means that you can give these infrequently, and the effect persists. And what you can show is the fact that if you continue to follow CGRP levels, they go up, but most of them are bound to the antibody.

The second point I would make is if you inject an antibody, and this is something I recently learned, it takes about a week to get peak certain levels, because of the way it's transported in the lymphatic flow in them. Whereas when it's given intravenously, you get immediate high levels, which means all of your intravenous formulations may be for terminating a cluster attack, or for purposes of migrant status.

Dr. Tepper:
It's very interesting about the intravenous eptinezumab. Because as you point out, the onset of effect in migraine is very quick, very dramatic, with more than 50% drop in the likelihood of a migraine within 24 hours of intravenous presentation of eptinezumab for both episodic and chronic migraine.

But even more than that, the there is a study called the RELIEF study that Paul Winner authored, in which the eptinezumab intravenously was studied for acute effect in migraine, and it terminated migraine better than placebo for the usual outcome measures of pain freedom in 2 hours, and freedom for most bothersome symptom in 2 hours, compared to placebo. So eptinezumab works both acutely and preventively, and I think that's probably because of the intravenous formulation and some of the other features that were synthesized in its stereochemistry.

Dr. Silberstein:
I agree with you 100%. And what it tells us is, no matter what you're treating a patient with, the quickest that gets to the site of action, the faster works.

Dr. Tepper:
I don't think we can overestimate the magnitude of change that the monoclonal antibodies have brought to patients. These medicines that reverse chronic migraine, that reverse medication overuse, that decrease monthly migraine days, also affect every aspect of patients' lives in terms of patient-reported outcomes, and interictal burden, and all sorts of quality-of-life measures. And every single day a patient says to me, my life has completely changed with these medicines. It's really a dramatic change. And it's liberating and exhilarating for provider and patient alike.

Dr. Silberstein:
Where does it work, Stew? I mean, we used to always believe that many migraine drugs had to be in the brain itself. But particularly with the triptans and the other new drugs, we now believe that there's peripheral site of action. And correct me if I'm wrong, but CGRP is released from the small unmyelinated C fibers, and then the receptors on the A delta myelinated fibers. And what CGRP antibodies do, is they blocked the CGRP from going to the A delta fibers. Did I get that right?

Dr. Tepper:
Yes. And that's what Dr. Rami Burstein's work at Harvard has shown, that fremanezumab not only binds to the CGRP, but by so doing inhibits A delta fibers going back to the brainstem, and neurons that are in the brainstem that that A delta fiber connects with.

Dr. Silberstein:

Now, there's been some recent controversy about people finding antibodies in the spinal fluid, and some people are claiming that it presumes a central site of action, and other people claim just because it's there, it doesn't mean it's working for a living. And I think we should mention that. And my bias is that yes, there can be measured in the spinal fluid, several orders of magnitude lower than the serum. But that doesn't prove it's working. And if we assume for the sake of argument, that migraine is originated to the dura and its nerves, and that the cerebral spinal fluid is 2 layers deeper, perhaps there is no relationship, or perhaps there is. But that's the mystery of the science, neurology, and headache. We keep posing questions that keep us interested.

Dr. Tepper:
I agree and I think that we need to keep looking and keep evaluating this. I know that Lars Edvinsson thinks that the site of action is in the trigeminal ganglion. So we have multiple postulates for where the primary site of action is, meninges and dura, trigeminal ganglion, or more central, and I think this is an area that really merits further study.

Dr. Silberstein:
Stew, thank you so much for being here with me this afternoon. And I know we've been talking and doing things together for a long time. And it's really a pleasure for us to work again for something that's new and cutting edge and exciting again.

Dr. Tepper:
It's delightful, and I have to thank you for all these years of teaching and friendship.

Dr. Silberstein:
Thank you, Stew.

Announcer:
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