MIGRAINE WORLD SUMMIT

TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

UNOFFICIAL SIDE EFFECTS OF CGRP MONOCLONAL ANTIBODIES

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Introduction (00:05): GI issues are probably the most common thing I see. But I want to add one other thing: The other thing that is complicated about this is we always have to try and separate out a drug effect from an effect of the disease. So very often, someone will say, "It made my headache so much worse." But what we don't know is whether what they're really saying is, “The medicine didn't work and my headache got worse, or it was a consequence of the medicine.” And the only way you can figure this out is by talking it through, trying to work out what else was going on, actually listening to the patient, and trying to tease these things out.

Paula K. Dumas (00:51): Ever pick up your prescriptions and throw away the package insert without reading it? Many of us do just that. Yet those inserts give us valuable information on the side effects reported to the FDA [U.S. Food and Drug Administration]. The inserts don't tell you about nearly every drug's unofficial side effects — sometimes minor, sometimes very troublesome. The new wave of CGRP medications is no exception. We ask Dr. Robert P. Cowan from Stanford University to help us understand this class of medications and the side effects that sometimes occur. Dr. Cowan, welcome back to the Migraine World Summit.

Dr. Cowan (01:29): Thanks, it's great to be back.

Paula K. Dumas (01:31): Terrific. Well, for those unfamiliar with CGRP medications, what are they and how do they work?

Dr. Cowan (01:38): Sure. So, first, I think we should be clear as to what CGRP medications are and what they are not. So CGRP is actually a molecule that we have in our bodies that is everywhere: It's in your kidneys, in your heart, in your brain, in your lungs, in your bones, your gut — it's basically everywhere. It stands for calcitonin gene-related peptide. It doesn't have a whole lot to do with calcitonin or with calcium, to be honest, but it's something that's been preserved in our species for at least 250,000 years. So I think it's a fair assumption that it's there for a reason. So first, before we talk about things that block CGRP, which are the actual agents, let's talk for a minute about what CGRP does and doesn't do in the body so we understand what we're actually dealing with.

Dr. Cowan (02:33): So, CGRP is what we call a phase-reactant molecule. In other words, its numbers, its concentration in the blood goes up when there's a problem, and when they go up, they're serving a purpose; they're there for a reason and they have a lot to do with how the body responds to a crisis. To manage inflammation, it can increase inflammation, it can regulate inflammation. It helps with something called re-epithelialization. Re-epithelialization is the replacement of the lining of your gut, of your lungs, when there's been damage to it.

Dr. Cowan (03:14): OK, so if CGRP is such a good idea, why is blocking it such a good idea? And the reason it seems to be a good idea is that in migraine, CGRP levels go up and it's in response to pain. So it kind of goes back to the very, very basics. Why do we have pain? Well, pain is something that we die without.

Paula K. Dumas (03:41): So, can you help us focus on what the mechanism of action is, like how the CGRP medications work?

Dr. Cowan (03:48): Sure. It's incredibly complicated. So, CGRP works at a receptor, if you think of it as a lock-and-key mechanism. You have the CGRP receptor — one of the monoclonal antibodies for CGRP actually binds to the receptor. The other three monoclonal antibodies bind to the molecule itself. Now what happens when the receptor is activated by CGRP is very

complicated; it's probably beyond our scope here. But I think it's enough to say that it regulates inflammation. And inflammation — sometimes it's a good thing. I mean, we need inflammation when we have an injury. Sometimes it's a bad thing, as in the case of migraine, when it causes all these vasoactive peptides like CGRP to be released, and it causes kind of a negative feedback system.

Paula K. Dumas (04:47): So CGRP is everywhere in our body, and during a migraine attack it's activated. And what these medications are doing are attaching themselves in a key or lock format to that receptor and addressing the inflammation that might otherwise occur. Is that right?

Dr. Cowan (05:08): Yes. Here's where it becomes a problem, though. When we're a drug company designing a drug for migraine, we want our drug to be approved. And so, what we do is, we do what I call cherry picking, what many of us call cherry picking, in selecting who we're going to test this on. So as an extreme example, say we decided to test this on people who were at high risk for having heart attacks and strokes. And we know that population needs their CGRP, it's part of the healing process. Well, this drug would never get approved. If on the other hand, we design our study to accept only people who are extremely unlikely to have a stroke, or a heart attack, or kidney failure ... and they don't really need CGRP to respond to an insult, except migraine, then it should be safe to block it because there really isn't any tissue damage with migraine.

Paula K. Dumas (06:11): So they focus on very healthy subjects to increase the likelihood that it will get approved so that everyone will have access to it. But that helps explain why not all of us have a positive response to it, as we saw in clinical trials.

Dr. Cowan (06:27): Exactly. And we see this over and over again. When you see information that says this medication has been tested over a course of a year or two in healthy individuals and there's been no serious adverse events, we shouldn't get too comfortable with that.

Paula K. Dumas (06:45): Yeah, because sometimes you need a very diverse population and a lot of use before you're going to see how a drug actually affects people's bodies. So today we're talking about the unofficial side effects for CGRPs that some people are experiencing. So, let's talk about the four CGRPs that are currently available in the United States and rolling out in other areas: Aimovig, Emgality, Ajovy, and Vyepti. And the focus of our talk today is really about side effects. How are side effects, first of all, different from adverse events?

Dr. Cowan (07:25): The umbrella term is adverse events. So, side effects are kind of like the most gentle form of adverse events. This is really FDA terminology, and the FDA recognizes four different classes of adverse events, the mildest of which is side effects, OK. The others are psychological harm or trauma; death, of course; and injury. Those are the other three classifications. So, when we talk about an adverse event, that's something that happens to someone who's using the medication appropriately, and it is a reported consequence of using it appropriately. Side effects are things that happen as a response in some individual, in a given individual, which generally do not rise to the level of reportability.

Dr. Cowan (08:33): So the reporting of these things to the FDA is very, very haphazard. So I think we need to be careful as we go through these things. It should be incumbent on the pharmaceutical industry — whoever's made the drug, or the government — to catalog these and see when that crosses the threshold, and decide what that threshold would be. So obviously

one person who has that response in one place probably should not rise to the level of an interview that's going to be shown around the world. On the other hand, if it's common enough that there are many, many people experiencing this, even though it may not be a life-threatening adverse event, it's reportable. And for that reason, we should always be reporting these events to the FDA.

Paula K. Dumas (09:28): OK. Now, I know that you work around the world, and people come to your clinic from around the world, and you lecture in various places: In your experience, do other governing bodies in other countries have a different definition of side effects, or do they have a different lens on this problem?

Dr. Cowan (09:50): So the honest answer is, I don't know, but I can “wing it” a little bit and tell you that the European Federation tends to be much more strict than the FDA. I think the European Federation doesn't work quite as closely, or as much in concert, with manufacturers as the FDA does.

Paula K. Dumas (10:13): OK. Yeah, that's important to know because many of these are pending approval in other countries where many people are watching the Migraine World Summit and this interview. So they'll be curious to know if they can expect some different decisions or guidelines there. So, the first of these medications was approved in 2018, and now we have over five years of real-world experience with them in the general migraine population — again, not the clinical trial population — but the general population. So, in clinical trials, what were the most common side effects?

Dr. Cowan (10:48): So, the things that are reported most commonly were GI problems, particularly constipation, and then the usual upper respiratory infections, urinary tract infections — things that are pretty common in the general population, as well. And they were seen most commonly.

Paula K. Dumas (11:14): In practical use, what side effects are you seeing among your patients at Stanford?

Dr. Cowan (11:20): Well, full disclosure, I don't see a lot of patients anymore. Most of my time is spent in research. But two, three, four, five years ago, I was seeing a lot of patients, and the most common side effects that I was seeing were certainly GI problems, particularly when we only had the first of these medications out, which binds to the receptor. And ultimately that ended up becoming a black box warning in prescribing.

Dr. Cowan (11:53): So, GI issues are probably the most common thing I see. But I want to add one other thing: The other thing that is complicated about this is we always have to try and separate out a drug effect from an effect of the disease. So very often, someone will say, "It made my headache so much worse." But what we don't know is whether what they're really saying is, “The medicine didn't work and my headache got worse, or it was a consequence of the medicine.” And the only way you can figure this out is by talking it through, trying to work out what else was going on, actually listening to the patient, and trying to tease these things out.

Paula K. Dumas (12:40): We're all used to side effects like the brain fog from topiramate and the chest tightening from triptans. Do you think that every pharmaceutical drug carries some kind of side effect?

Dr. Cowan (12:54): I do. Whether it's something you notice, or whether it's important, or as I hear from my patients all the time, "It's worth it," is a real question. For example, if I see a patient who has a comorbid condition called Raynaud's syndrome, I'm not going to give them a triptan. I mean, well, I'm not going to give them a triptan, but I'm also not going to give them a monoclonal antibody.

Paula K. Dumas (13:20): Why is that?

Dr. Cowan (13:21): Well, because the action of the monoclonal antibody is vasoconstriction or prevention of vasodilatation. CGRP, in addition to modulating inflammation, is a very potent vasodilating agent. So when you block vasodilation and the medical condition is Raynaud's, which is a vasoconstriction, you lose the CGRP's ability to dilate those peripheral vessels. And you can thereby make the condition worse — not because you're causing vasoconstriction, but you're preventing vasodilation. So this is a theoretical decision that I make based on my knowledge of how this medication works. It's not in the package insert, but I think it's a good example of why these comorbidities are important, and it's also why it's important to understand what the mechanism of action is of CGRP and what the theoretical consequences of blocking it [are].

Paula K. Dumas (14:32): So if people watched the Migraine World Summit, they would hear a number of leading experts talking about how precise these CGRP drugs were. So it makes me wonder why should anyone be experiencing side effects at all?

Dr. Cowan (14:48): I think that we do our patients a disservice when we present drugs as being side-effect-free and being specific. As I said, CGRP is everywhere; it's hard for me to understand why it would be everywhere if it wasn't necessary. That's just not the way evolution works.

Paula K. Dumas (15:07): OK. So, let's talk about each of the side effects that people in our community report experiencing and what can be done to deal with them if the medication is producing good results. So, one we hear about is anxiety and panic attacks, which can also be a comorbidity. Is this common?

Dr. Cowan (15:32): So, this is a good example of separating the jockey from the horse. Anxiety and depression and panic attacks are so common in people with migraine that it's not unreasonable to think that if the CGRP agent is not helping the headache, the anxiety is going to get worse. So I don't know how to answer, "Is it the CGRP working that's making it worse? Or, is it the CGRP not working that makes the perception of anxiety worse?" That's a complicated issue, but theoretically, if the CGRP agent is working well for the migraine and the anxiety is related to the migraine, one would think that anxiety would get better.

Dr. Cowan (16:32): I can tell you that we've done work in our own laboratory where we've looked at anxiety and something called, "catastrophization" in patients who have chronic migraine compared with controls. And we've done functional imaging and testing for anxiety, and we find that people with chronic migraine not only have significantly, statistically significantly, higher scores on catastrophization and the generalized anxiety scores, but they also have enlarged amygdalas. And the amygdala is the part of the limbic system, part of the emotional brain we call it, that assigns emotional significance to sensory input. So it really ties in very nicely. Right now, we're looking at episodic patients to see whether addressing anxiety early on prevents the enlarged amygdala and decreases anxiety and prevents chronificaton. And whether treating anxiety separate from something like a monoclonal antibody in patients with

chronic migraine contributes to decreasing the frequency and severity of the headaches. So that's a tricky — that's a long answer to a short question, but...

Paula K. Dumas (17:56): Well, I think anxiety is intertwined with migraine in a not only a biological way but the disease itself. Anytime you have an unpredictable disease that can strike out of the blue, it's going to create a level of anxiety, even in people who are not otherwise prone to it.

Dr. Cowan (18:15): Exactly.

Paula K. Dumas (18:16): Tough to know. Next one that we have heard about is weight gain. Is this common? Or do you think it's caused by CGRP or something that many people who take — who use the CGRP drugs would experience in middle age anyway?

Dr. Cowan (18:34): So that's exactly part of the issue, but if we, again, go back to what CGRP does — so CGRP actually modulates something called glucose-stimulated insulin release. So it can lead to hyperglycemia, which is doctor speak for "too much sugar in the blood." So there is a theoretical basis for it. Once we have a couple of million people using these drugs, we can start to address this. But at least for the issue of weight gain, I can see a theoretical basis to say that in some people it could easily cause weight gain.

Paula K. Dumas (19:21): Another one we heard early on was about hair loss, and I wonder how common is hair loss? And again, is it correlation or causation or do we have any idea at this stage?

Dr. Cowan (19:36): We don't have any data because no one's doing this — you're not going to get these companies to fund that study, right? But there is a theoretical association because some of the tiniest vessels are the vessels that feed hair follicles. And so by blocking CGRP, this microvascular effect could conceivably relate to hair loss. So — and that's going to be my answer for a lot of these things: "Yes, there's a theoretical basis," or, "No, there's no theoretical basis that I can see." But in terms of being able to say that there's a clear cause and effect, you know, you just can't make that generalization without having data.

Paula K. Dumas (20:27): Of course. If somebody's getting good results from their CGRP medication, are there any hair-growth supplements that can help? What do you recommend? What do you know of doctors recommending that can help this situation?

Dr. Cowan (20:41): So, I will tell you if that is an important issue and someone thinks it's going on, they probably will need to switch because it's pretty hard to get around the blood supply, in terms of hair growth.

Paula K. Dumas (20:56): Here's one that surprised me, but is delightful: Jane, a person in our community, said she's experienced a much better mood and less anger since taking Ajovy, and she wonders if that might be why?

Dr. Cowan (21:11): Or maybe she's having fewer headaches or less severe headaches, and that's why.

Paula K. Dumas (21:17): It's true. Very possible.

Dr. Cowan (21:21): It's really hard to separate. There's no mood-elevating effect. In other words, it's not having an impact on serotonin or dopamine or anything that we know of.

Paula K. Dumas (21:30): Right. Bone density is another issue that we experience — or we have to address in middle age. So, Deanna is concerned that a loss of bone density could be linked to CGRP. Are there any reports of that and does it make any sense scientifically?

Dr. Cowan (21:48): It makes sense scientifically. I don't know whether there are any reports because we don't have a good system for reporting that stuff. There's not a case series; someone would have to study that longitudinally. Bone loss takes a lot of time. But again, when you think about microvascular supply and interfering with that by blocking CGRP, there's a theoretical basis to say that it could have an impact on bone density.

Paula K. Dumas (22:20): OK. Constipation was one of the earliest side effects that we heard about, and you mentioned it before. Is it true for all of them or just one of them?

Dr. Cowan (22:31): It's very interesting because at first, we thought it was just true for the CGRP receptor monoclonal, but we started hearing it and we hear from the gepants, too, but not consistently, and it doesn't seem to be in everyone, for sure. So it probably has a lot more to do with your own genetics and how — we know that CGRP is involved in the repair of the gut lining and that blocking the receptor definitely interfered with that. But it appears when you're interfering with CGRP binding with the ligand — so the key, not the lock — for some people it has an impact. Now maybe it's also — it's only in people who have underlying bowel disease; maybe it has something to do with their genetics and the way they metabolize these medications. We know a fair amount about how CGRP antagonists are metabolized in the gut and how antibodies are metabolized in the liver, in the kidney. So I suspect that on an individual basis it's worth watching. And if you notice this happening, it's not off the wall to think that it might be from the medication. But in terms of it being a warning on the label, other than in the case of the one binding to the receptor, it doesn't seem to have risen to the level where they're going to put a black box warning on it.

Paula K. Dumas (24:14): Right, and if you are dealing with constipation and the medication is helping you, there are solutions for that, right?

Dr. Cowan (24:22): Yes, there are, there are. Let me just qualify that there are solutions for that. And while they may help your overall bowel function — and I'm thinking of laxatives and things like that — if the real problem is actually with the re-epithelialization of the lining, it's not going to help with that.

Paula K. Dumas (24:40): And while this isn't technically a side effect where it's related, we're interested in understanding if CGRP plays a role in our immune system. And if it does, does suppressing CGRP also suppress our immune system?

Dr. Cowan (24:56): That's a great question and I don't have a data-driven response, but I have a theoretical response — is that it most certainly could. I mean, inflammation, B-cell suppression, all of these things have been looked at in relation to CGRP and there's clearly a role for CGRP in the immune system. But in terms of it having a clinical impact, I don't think I've seen any data. If I'm immunosuppressed, I would not be rushing to give someone — if I have a patient who's immunosuppressed, I would not be rushing to give them a monoclonal antibody. I'd look for other solutions first.

Paula K. Dumas (25:40): Got it. So, if someone experiences a side effect on the first CGRP that they've tried, how long do you advise they continue before switching to another one?

Dr. Cowan (25:50): Well, the problem with the monoclonal antibodies is you get that first dose, and if it's got a half-life of 28 days, which is the shortest of them, you can do the math. It's going to take five months for it to be out of your system.

Paula K. Dumas (26:05): So you're not really giving the second drug a clear trial because the first drug is still in your system?

Dr. Cowan (26:11): Exactly. And most people say five half-lives is what it takes to really clear something from the system.

Paula K. Dumas (26:20): OK, so is three to six months the general guideline?

Dr. Cowan (26:24): Yeah.

Paula K. Dumas (26:25): OK. So Krissy asked a great question: Are there any known risks or side effects caused by taking these drugs in combination with other medications, like a CGRP inhibitor and a gepant, or using brand names, Aimovig and Qulipta?

Dr. Cowan (26:44): Yes, another excellent question. Obviously we haven't had any studies where one company has said, "Well, gee, let's try this with another company's drug and see how it works out." Here's my — again, we're going back to theoreticals because that's all we have: If you have a monoclonal antibody that blocks say 85% of the CGRP action, OK, peripherally. And then you take, and let's ... [understand] it this way — say something happens, you've got a monoclonal antibody on board and you have a heart attack, or you break a leg, you've still got 15%, 20% of your CGRP out and available to work its magic in repair. If you add on top of that an antagonist which blocks, for example, that other remaining 15%, then you have no CGRP response. Is that OK? I mean, I guess it's OK if you don't need any CGRP.

Paula K. Dumas (27:57): But we need it for all kinds of things.

Dr. Cowan (27:59): Well, that's the issue. That's exactly the issue. So, I have on occasion suggested using a gepant in addition to the monoclonal antibody in a patient who for one reason or another can't use another kind of rescue. But in general, I don't do that if you can take a triptan ...

Paula K. Dumas (28:29): Mmhmm. So, the people watching this are obviously watching because they're experiencing some side effects or they're afraid of them. And I think you told us this answer before, but if someone is experiencing a side effect similar to, or different from, those we've discussed today, what should they do?

Dr. Cowan (28:47): Well, the first thing they need to do is talk to their doctor and get their input. Some medicines should not be stopped suddenly. And if you're having a drug interaction, which drug should be stopped and how should it be stopped? Is there anything else going on? So there's a lot of questions to be answered, so — but if you want to report a side effect, I wrote down the phone number, it's (800) 438-1985, but you can also go to the website for FDA MedWatch and report it there.

Paula K. Dumas (29:21): Start with your doctor and then if necessary and appropriate, contact the company that manufactures the medication and contact the governing body in your country, the FDA in the USA and NHS [National Health Service] and others.

Dr. Cowan (29:37): All these companies have — they're usually PhD pharmacologists, who are wicked smart people and pretty reliable in my experience, and are very accessible to us as providers. And when I get something I haven't heard of with a given drug, I'll go to them and they come back pretty darn quick with all of the data that they have on that particular issue. So, I'm sure a lot quicker and in a lot more authoritative way than what you're going to hear on the phone calling as a consumer. So go to your physician and ask your physician to check with their scientific liaison. It's easy to do.

Paula K. Dumas (30:23): Dr. Cowan, thank you so much for sharing your expertise with us today. It's tremendously valuable to everyone using a CGRP medication or considering it. Thank you.

Dr. Cowan (30:34): You're welcome.