MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT

EUROPEAN HEADACHE TREATMENT UPDATE

PATRICIA POZO-ROSICH, MD, PhD
HEAD OF NEUROLOGY SECTION
VALL d'HEBRON HOSPITAL AND INSTITUTE OF RESEARCH, SPAIN

Introduction (00:05): In 2023, the oral anti-CGRP therapies will be available in Europe, and so their way of administering is orally. The difference is that you will have to take them on a daily basis or almost-daily basis, depending on the drug, and the comparison would be that the others are injected, either on a monthly or trimester basis (or every three months).

Amy Mowbray (00:31): Like me, so many migraine patients have tried countless medications to no avail. The introduction of the new anti-CGRP medications and ditans over the last few years have dramatically changed the treatment landscape for patients and instilled a new wave of hope for the migraine community. Despite these huge advances in migraine research, access to these new drugs is still a barrier for many patients. Here to talk us through the different treatment options that are available to patients across Europe is Dr. Patricia Pozo-Rosich. Dr. Pozo-Rosich, welcome back to the Migraine World Summit.

Dr. Pozo-Rosich (01:06): Thank you. Thank you for having me back.

Amy Mowbray (01:10): Please can you start by explaining the difference between acute and preventive migraine treatment?

Dr. Pozo-Rosich (01:15): Sure. Acute treatment means treatment that is given during the migraine attack. I always like to share with my patients the fact that patients see migraine as the attacks, and they have either "migraine" or "not migraine" according to the attack. And suddenly, once they go to at least a physician that cares for them, they realize that we have two, or even three, types of treatment. We have acute treatments for when the attack happens — to what they call migraine. Then we have treatments that we call preventive, because they try to avoid or prevent the next attack; and those treat the condition, you could say, or I like to call it, a disease. And this is, kind of, a treatment that is given on a daily basis — or at least with the concept of constantly modulating this brain, and this body, that has this predisposition of getting very debilitating attacks. And you could even talk about a third type of treatment, which is your lifestyle, which is — I mean, it's not fundamental, but it helps a lot, because you might be doing things that might help trigger attacks without even noticing.

Amy Mowbray (02:28): Which patients should consider preventive treatment options?

Dr. Pozo-Rosich (02:32): If you would probably ask me, in the ideal world, I would say everyone, because I always tell my patients that the best acute treatment — so the best treatment for the attack — is not having one. So actually, probably, there's this saying that every ... so when, when you have at least three days of migraine per month, you're eligible for a migraine preventive treatment.

Amy Mowbray (02:58): What is the difference between the more traditional migraine preventive treatments we've been using, such as topiramate and amitriptyline, versus the new anti-CGRP medications we are now seeing, such as Aimovig and Emgality?

Dr. Pozo-Rosich (03:10): Well, I think they're fundamentally completely different. You know, amitriptyline and topiramate for example — but there are others — were found to be useful for migraine by chance. So, it was not thought [of] as a real migraine treatment. So the first big difference is that these new treatments are target-driven. We know that CGRP gets released in excess — so there's too much CGRP during an attack — and that by blocking it, controlling it, attacks modulate themselves in the sense that they become quieter, less aggressive, and then, little by little, less frequent. But from what I'm seeing already with anti-CGRP therapies, what

they value the most is the fact that even if they have a bit of pain, it's not as strong — so it's really kind of modulating pain a lot — and that when you take pain away, disability decreases. The summary is that they're target-driven, they're extremely well tolerated, and their efficacy is better, I think.

Amy Mowbray (04:20): So, going back to the older preventive treatment options, what are the different medications that are available to patients in Europe currently?

Dr. Pozo-Rosich (04:28): So, in Europe we have at least, I would say, seven or eight — depending on the country — seven or eight oral. We could say treatments that are — I wouldn't say the word "approved" because they're not approved, many — for migraine, but at least they're used or written in guidelines. You have a group of the antidepressants — you mentioned amitriptyline before. We have then the group of the drugs that control hypertension or blood pressure; so you have candesartan, and you can also include there, probably, beta blockers such as propanolol or metoprolol; or depending on the country, there's different beta blockers to be used. Then we have the third group, which is the anticonvulsants, or you can also call them neuromodulators; you mentioned topiramate, valproate — in some countries it's still very much used. And then we have the calcium channel blockers, such as flunarizine. So there are four big groups of drugs that are available. And if you have chronic migraine, in many countries, there's also onabotulinumtoxinA, which, actually, is quite helpful for many — to many patients.

Amy Mowbray (05:43): And how effective are these medications?

Dr. Pozo-Rosich (05:45): I would say that onabotulinumtoxinA is quite effective. And especially — I think that I especially like those medications that are very tolerable, because if something is effective — or efficacious; that's ... probably the right word in English — and you don't tolerate it well, so there's no adherence or persistence to the treatment, then it's kind of useless, you know? So at the end, you need a drug that has this nice combination of efficacy, tolerability, that then leads to adherence — so, kind of a persistence, and you want to keep on taking, or being, on that treatment. And I think that these new anti-CGRP therapies have this triad. So, they actually are very well tolerated by patients; they're, I would say, more efficacious than the ones that we had before; and, yeah, so that then creates like a sense of well-being, which is higher for our patients.

Dr. Pozo-Rosich (06:46): It is true, though, that not every patient responds to these new drugs, because, probably, we have — actually in our group, here in our research group, we have actually published, very recently, that we were able to correlate, first of all, the levels of CGRP according to the frequency of migraine during the month. So, if you had higher levels of CGRP — we actually measured this in saliva; we thought it was an easier way to monitor changes — so that was one of the important findings. And the other one was that the higher the levels, kind of the better, even, the response. And we even found a threshold of salivary CGRP after which, you know, you probably have much more possibilities, or probabilities of responding to the treatment.

Dr. Pozo-Rosich (07:40): So, the summary of this would be, that if you have a CGRP-dependent migraine, then you're lucky, because nowadays we have drugs that block this. Of course, we also found in our study that around 20 to 25% of patients do not have CGRP changes in their attacks, which actually means that their migraine is not CGRP-driven. We'll have to find out what drives them, drives their attacks, because clinically they are not too different from the ones that we call CGRP-dependent. So that is something for the future, to understand what is going on in

these other attacks — and even in CGRP attacks, CGRP is not the only molecule there. But it is a step forward in walking the pathway towards precision medicine; towards having a molecular-driven classification of migraine, which I think would be a tremendous step forward for patients, because suddenly you have a disease that can be measured, that can be quantified — and, you know, that response to treatment, if it makes sense that it responds to treatments — and it's much more tangible.

Amy Mowbray (08:59): Moving back to the preventive treatments, you mentioned Botox. What other injectable preventive treatments are available to patients in Europe?

Dr. Pozo-Rosich (09:09): Really, I would say Botox as a preventive is the only one. We also, in Europe and then the rest of the world, do a lot of anesthetic blocks, but they are more thought either for pregnant women, for example, or for the control of a status migrainosus: so, a moment where you realize that the attack is kind of not stopping, one of — not the only, but one of — the treatments that we can offer is, so we're just doing an anesthetic block. In the emergency department, or as I was saying, to treat very refractory attacks — very hard-to-treat attacks — we can also inject other types of drugs, such as steroids [by] IV, or NSAIDs — so anti-inflammatories — [by] IV. So there are treatments to be done — not maybe the ideal treatments — but treatments that might help in the emergency room setting, or what we also call the infusion center, or the hospital, which we actually, here in our center, we do have.

Dr. Pozo-Rosich (10:10): But the idea is that we try for those moments not to actually happen, and the best way, as I was saying, is to be on a proper preventive treatment. So there is a feeling that I — at least here in Spain, after many years of seeing a lot of patients — have felt, is that patients who have migraine, or people who have migraine, do not want to be on treatment. You know, in a way, they actually think that it will get cured or improve alone, maybe. Of course, you might think that this is because of the experience that they have on being on treatments that have not helped, or they have not been well tolerated, but it's not always the case. It's actually — there's a very strong movement against taking medication, and it's kind of an internal — almost, I would say, almost a personality trait — of those who suffer from migraine.

Dr. Pozo-Rosich (11:09): I would like to let all of you know that, if you [had] diabetes, if you [had] high blood pressure, you would never doubt the idea of taking a treatment. And with, I would say, adequate treatments that are ... started at the very beginning of the disease, you will never move into a chronic migraine status. So, ask for help and get a good treatment ... from the beginning, because I think it can change the quality of life and help you live much better the rest of your life.

Amy Mowbray (11:47): Speaking of effective treatments, specifically designed for migraine, let's now talk about the new CGRP medications. Firstly, how do they work?

Dr. Pozo-Rosich (11:58): Well, we have two types, I would say, of mechanisms. I mean the main target of these drugs — as you were already saying by the wording — is that they want to block the effect of this neuroinflammatory peptide, CGRP, which is a calcitonin gene-related peptide. CGRP does many functions in our system, in our bodies. It also is a potent vasodilator, so it kind of helps vessels, arteries and so on, dilate. It's also linked to other metabolisms such as healing, of wound healing, and bone structure, and so on. But our interest here is that during a migraine attack — and that also, of course, then, correlates with having a lot of attacks: If you have a lot of attacks, it's like having a permanent attack — the levels of CGRP increase, so more CGRP is released to the system.

Dr. Pozo-Rosich (12:57): So what these drugs try to do is either by washing out the peptide, or by blocking the receptor where the peptide actually works, to avoid this excess of effect that CGRP has. One question that I always get when I say this is, "Well, but then I will be left with no CGRP in my system?" And that is not exactly true. As I was saying, in our research group, we are very used to measuring saliva CGRP levels, and we see that when you are actually treated appropriately and respond, your CGRP levels are still there; they're just not as high. So they're normalized. So actually, these drugs are not kind of washing all of your CGRP away, probably they're just avoiding the extra impact of having too much CGRP around, especially too much CGRP in your — around the trigeminovascular system, which is the system that gets activated when the pain in migraine starts.

Amy Mowbray (14:04): And what is the difference between the different anti-CGRP medications on the market?

Dr. Pozo-Rosich (14:09): Well, there are mild differences, you could say. First one, as I was saying: Some of them block the receptor; some of them block the circulating peptide — so it's kind of the protein that is, like, flowing around our system. Then: Some of them are injectable antibodies. The word antibody here has no immunomodulatory — it doesn't change your immune system; it is just a medical word of understanding that this drug is surrounded by also another protein which we called an immunoglobulin, which actually allows the protein to be injected instead of swallowed. It's just a way of administering the drug.

Dr. Pozo-Rosich (14:57): And then we have others that are oral drugs. These, in Europe specifically, have been recently approved by the European medical agencies, and now in the next months, in 2023, the oral anti-CGRP therapies will be available in Europe, and their way of administering is orally. The difference is that you will have to take them on a daily basis or almost-daily basis, depending on the drug, and the comparison would be that the others are injected either on a monthly or trimester basis (so every three months).

Amy Mowbray (15:36): Are the injectable ones readily available for patients across Europe currently?

Dr. Pozo-Rosich (15:43): Yeah. In most countries, I would say that they are already available. You know, Europe has a very public healthcare policy, at least until now, and so I would add another word, which is that they are reimbursed. However, the approval by EMA [European Medicines Agency] — and you were asking before, so when does a patient need, or is eligible for prevention? And EMA approved this anti-CGRP treatment after, or when, you have four or more days of migraine per month. However, the reimbursement policy in each country is not exactly the same — it's different — and it is very much related to the cost effectiveness studies that have been done. Here, for example, in Spain where I live, our reimbursement policy says that you are eligible for an anti-CGRP therapy when you have already tried three preventive treatments — one of them being Botox, if you have chronic migraine — and when you have eight or more migraine days per month. So it already puts a higher threshold to access treatment, which I personally don't fully agree with, but at least we have that. And for all of those patients who have these criteria, or characteristics, they are eligible for the new treatments.

Amy Mowbray (17:16): With these new anti-CGRP medications, you mentioned they are being tolerated better by patients. Is the efficacy of them also better?

Dr. Pozo-Rosich (17:27): Yeah, as far as we know, it is. Of course, there are no direct phase 3 — we call them head-to-head — trials. However, actually, erenumab, one of the antibodies, did a trial in Germany — because the German authorities actually made them do it — against what they thought was the standard of care, in that case, topiramate. And they did find that it was not only better tolerated, but also it was — the efficacy was — much better than the efficacy of topiramate. And now, recently, in the Migraine Trust Symposium 2022 Congress, another trial done in 17 countries around the world tried to compare the standard of care of each country with erenumab, and this is called the APPRAISE trial.

Dr. Pozo-Rosich (18:21): And this trial actually has demonstrated, as far as we know, that at one year — so the endpoint was looked at, so the primary endpoint, we call it, was at one year — we saw that patients who initially were treated with erenumab stayed more in that arm of the trial — we call it the arm, so that kind of pathway of treatment — and the probability of staying in that treatment was 13 — one-three — times higher. That's what we call an odds ratio. That's a very high probability. And the probability of, at one year, having improved more than 50%, your migraine was 6.7 times better or more, or higher, which actually means that yes, I mean being on an anti-CGRP antibody in this particular case, erenumab — which is the only drug that has initiated these kinds of trials — is better, for many patients at least. I'm not saying it's the best, you know, drug or treatment for everyone, because there are some patients who do not respond, but for responders — and you don't know whether you're a responder or not, until you try it.

Amy Mowbray (19:34): Moving to acute treatment options, what acute treatments are traditionally offered to patients in Europe?

Dr. Pozo-Rosich (19:40): If you go to a primary care physician, mostly it's about anti-inflammatories and analgesics, you know, which are not too effective. Analgesics: very little effectiveness. And the inflammatories: a little bit better. Mostly — only if you go to a neurologist almost, you need — I mean, you need to go almost to a neurologist, I was saying, to get a triptan. But they are offered, and I mean they're being sold, and we give them here in our clinic a lot, but I'm just talking about in a general perspective. So, I would say that the three most given drugs are just simple analgesics, anti-inflammatories, and triptans; however, there is a slight movement moving towards opiates, the use of opiates — tramadol specifically. And that's another very important thing that you all need to know as patients: Please, if any physician gives you opiates, some type of tramadol or anything similar, please ask them — no. Ask them not to do it for migraine. It's not useful, first of all, and second of all, it might give you a better chance of developing medication overuse headache. So, just try to avoid them, and also, if needed, educate your physician.

Amy Mowbray (21:00): That's great advice; thank you. In 2019, we had a European headache specialist, Dr. Katsarava, say at the Summit that only 10% of people living with migraine in Europe were using triptans. Triptans are thought to be effective [in] up to 80% of people with migraine. Why do you think the number is so low, and do you think it will have improved in recent years?

Dr. Pozo-Rosich (21:23): The first — I'll answer your last question — I think it has improved, and that's mainly because there has been such a current, you know, in the last years' movement, because of this new specialized treatment, that then that kind of moves more people to ask for treatment, then to end up sometimes in specialized clinics. Right now, if I'm not wrong, for example, here in Spain — which actually when, probably, you mentioned this — so some years

ago the percentage of use was around 15 — so one-five percent — and now I think we are up to 25%. So it has gone a bit up, and I hope that it will keep on increasing. And in regards to why aren't they, you know, more used? I think that there are two or three main problems.

Dr. Pozo-Rosich (22:08): The first one was price, at least initially. Now we have generics, so price has gone really down here in Europe. And then the boxes: They're really small. You know, they were thought to treat one attack — you buy a very expensive box just for one attack, so patients saved their pills for this like very kind of special attacks. And then when you have a very special attack, you are treating it too late, already, within kind of a curve of the whole attack, and then it does not work. So there's also a time of use, and all of this needs education, and unless you are properly educated, and you're told that you don't have to wait for the special attack — that these drugs are not strong; they're just a bit expensive, and that's why the boxes were made smaller at the beginning.

Amy Mowbray (23:01): I'm sure there'll be lots of nodding heads of patients watching at home, hearing of that: saving the triptan and taking it too late.

Dr. Pozo-Rosich (23:08): Oh yeah.

Amy Mowbray (23:09): All the angst over taking it. Can you tell us about the new acute medications on the market? How do gepants work?

Dr. Pozo-Rosich (23:16): They block the receptor — a CGRP receptor. And the good thing about them is that as far as we have seen — and the knowledge that we know from animal models, from research, clinical research, that has been done — the good thing is that you could even take one gepant per day, and that is kind of — that's why it kind of converted, or turned into a preventive. Because actually gepants were thought initially as an acute treatment of migraine. They were thought to substitute triptan — "substitute" in the sense of: The "new" triptan, you know, was coming out. And suddenly we realized that they were not giving medication overuse, unlike triptans or other acute medications. So the good thing is that you can take one, but you can also take another one the next day, and another one the next day, and suddenly it becomes — you transform an acute treatment into almost a preventive treatment.

Amy Mowbray (24:07): Patients are often advised to take, as you said, an analgesic or an antiemetic with a triptan for abortive treatment. Will these medications also be required with gepants?

Dr. Pozo-Rosich (24:18): I think that, less. So, for example, the problem with an antiemetic, I mean, usually — I'm talking about generalities — but in most patients, nausea starts when the attack is quite evolved in time. So they're already, probably, they need always an antiemetic; that's because they're treating late, usually. So if you treat at the right time with a triptan, you shouldn't probably need an antiemetic.

Amy Mowbray (24:45): What are ditans?

Dr. Pozo-Rosich (24:46): Triptans block serotonin receptors, not CGRP receptors. And they block two types of receptors at the same time, so what we call 1B/1D, and some triptans [block] also a bit of 1F. So there's just types. Ditans are — ditans only block the 1F receptors, so they have a very, kind of, narrow focus on one of the receptors of serotonin. This receptor is more available also, at not only in the periphery where pain is mostly located, but also centrally. And this

receptor is only placed where the sensory nerves are, and not where the vessels or the arteries are; so it has no effect on vasodilation or vasoconstriction. So first of all, it is a safer drug at a cardiovascular level, so all of this, kind of, fear that is linked to triptans, with ditans goes away. And it, kind of, has a mechanism of action that is slightly different. And the same, as we were saying, you know, in order to do proper medicine, people will have to try different possibilities and choose the one that is best for them.

Amy Mowbray (26:05): Will the same apply with ditans as regards to medication overuse; that patients will be able to take them without fear?

Dr. Pozo-Rosich (26:12): Of that, I'm not that sure. I don't think we have so much evidence to clearly say this, and that's mainly because they have a central effect. And everything that kind of goes centrally, in a way also kind of creates, or might help create, some type of addiction. But I'm not sure that I can say this right now. I think we need more studies to be done with ditans.

Amy Mowbray (26:37): You said the gepants are likely to become available in Europe for patients at the start of 2023.

Dr. Pozo-Rosich (26:44): More or less, yeah, during the 2023 year.

Amy Mowbray (26:46): OK. When are ditans likely to become available?

Dr. Pozo-Rosich (26:49): Also [at] the same time.

Amy Mowbray (26:52): So we finally have migraine-specific treatments that are both effective and well tolerated. The next hurdle is getting these treatments to the patients that need them. How can patients across Europe now access these treatments?

Dr. Pozo-Rosich (27:04): Depends on the country. Here in Spain, I would say that, please, know that these treatments are available, and — just our way of doing it is, you have to first go to the primary care physician and then they actually send you to the neurologist. And the neurologist or specialized headache clinics will prescribe, or can prescribe, these types of treatments if you are the right person for them. I know other countries — for example, Germany — actually primary care can prescribe them, and so general neurologists that do not work in specialized clinics can do it much easier than in Spain, I think, for example. And then you have countries, I think like Italy, where actually, these drugs are only prescribed in specialized clinics. So, it depends. Every country has their ways, so I would say: Learn how it's done in your country, and just, kind of, fight for getting access, because the guardian angel? You have to be your own guardian angel.

Amy Mowbray (28:11): And finally, what advice do you have for patients who are struggling to access a headache specialist doctor or clinic and are just desperately trying to access these new medications?

Dr. Pozo-Rosich (28:22): No, I would say: Find your — the way of arriving there in your own country. There are patient associations. There's a European Migraine and — or Headache and Migraine Alliance — but then each country usually has their own association that might help you, kind of understand the pathway, what we call the patient pathway, to get where the treatments are. And just kind of — yeah, fight for it.

Amy Mowbray (28:52): Where can we learn more about what you are doing or follow your work?

Dr. Pozo-Rosich (28:55): I'm actually in the process of developing the website of our research group. We do have a Twitter and an Instagram, so social network accounts, where we actually publish and share every paper and interesting findings that we do. And we also developed a little while ago a website in Spanish, although it's only in Spanish, called midolordecabeza.org — so, "my headache" in Spanish — where we actually give tools for patients to understand — so educate — to understand their headache and monitor it through an easy headache diary, and so on. So, that's a tool also, to be known.

Amy Mowbray (29:43): That sounds really useful. What's the name of the social handle for people to follow?

Dr. Pozo-Rosich (29:48): Yeah; so it's either @ —my last name, so — @ppozorosich, or @AdaptiveBrain, we call it.

Amy Mowbray (29:59): OK, lovely. Dr. Pozo-Rosich, it's been an absolute pleasure to speak with you. On behalf of all the patients in Europe who are waiting hopefully for new treatments, thank you for taking the time to share what these new treatments are, and crucially, how and when we'll be able to access them. Thank you.

Dr. Pozo-Rosich (30:16): Thank you. It's a pleasure to be back at the Migraine World Summit.