



MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD LEADING EXPERTS

TRANSCRIPT



PROS AND CONS OF BLOCKING CGRP

ANTOINETTE MAASSEN VAN DEN BRINK, PhD



Introduction (00:04): The antibodies by definition, are for preventive treatment, because a drug always has a plasma half-life: It's the time until its concentration declines in the blood of a patient — and this time is very long for antibodies. So, if you give it, after a month you will still have about the same amount — the same order of magnitude — in your blood. So thereby, by definition, you have it in your body for a very long time, so it's not just an acute treatment. So these are preventives. And then the gepants: most of them up to now have been tested as acute treatments. They also have a rather short half-life compared to the antibodies, but there's also a gepant that is now tested as a prophylactic drug. So, it can be both.

Carl Cincinnato (00:56): Treatment for migraine has been adequate for a long time, but the emergence of a new treatment — the first specifically designed to prevent migraine — has revealed that CGRPs release during migraine attacks, and may even play a causative role in migraine. Today we review the pros and cons of blocking CGRP access, across several different migraine treatment classes, with Professor Antoinette Maassen van den Brink. She's an associate professor of the Erasmus University Center Department of Pharmacology and has been studying migraine for more than 20 years. Professor van den Brink, welcome back to the Migraine World Summit.

Professor Maassen van den Brink (01:29): Thank you very much.

Carl Cincinnato (01:31): Now for those who may be hearing about CGRPs for the first time, why is it so significant?

Professor Maassen van den Brink (01:36): Yes, maybe it's good first to explain what CGRP is. Its full name is calcitonin gene-related peptide. It's a difficult name, but the last word, "peptide," means, in fact, that it's a very small protein. It's a molecule that is built from building blocks — amino acids — and it's 37 amino acids. And what's so peculiar about this peptide, is that it has been found that it is increased during migraine attacks, and after treatment with triptans, this decrease was normalized. So this is suggestive of a role in migraine. And also, if CGRP is infused in migraine patients, but not in healthy volunteers, it may induce a migraine-like attack. So that was the reason to further look for the role of CGRP in migraine.

Carl Cincinnato (02:25): In a recent research study of yours, you mentioned that CGRP is found in both the peripheral and the central nervous system. Can you explain what those are and why that might be significant?

Professor Maassen van den Brink (02:35): The central nervous system is in fact the brain in the spinal cord, and it's protected by a so-called blood-brain barrier. So that is, in fact, very tight connections between cells in the blood vessels. And the peripheral nervous system is all parts of the nervous system outside the central nervous system. And these are nerves that go from the central nervous system to organs, lots of vessels, or anywhere in the body to convey signals from the central nervous system to the periphery, and from the periphery to the central nervous system.

Carl Cincinnato (03:11): Is CGRP a bad peptide?

Professor Maassen van den Brink (03:14): No, not necessarily. Of course from the context of migraine, it may be considered a bad peptide, because increases are related to getting migraine attacks. There are also other tasks in the human body: It may be helpful in



protecting against hypertension/high blood pressure; and also in case of a threat of ischemia — for example, a threat of myocardial infarction or a brain infarction — CGRP may be released, and this may be helpful in preventing such an event. So yes, that brings us also to a possible side effect that needs to be explored for medication that inhibits the effects of CGRP.

Carl Cincinnato (03:58): So CGRP, calcitonin gene-related peptides — we'll just say CGRP because it's a lot easier — it's in everyone. It's not just people that have migraine.

Professor Maassen van den Brink (04:07): No, definitely not. No, it's part of everyone's body.

Carl Cincinnato (04:10): And what is a CGRP receptor?

Professor Maassen van den Brink (04:14): What you can imagine for CGRP: it's that small peptide that we have described, but ... its action should be mediated at some place, and that point of action is called the receptor. So, it's something that is receptive, so it receives the molecules of CGRP that bind to this receptor. And when CGRP is bound to the receptor, then there are several processes downstream in the cell that mediate all the effects of CGRP that may differ.

Carl Cincinnato (04:52): How does CGRP link between the triptans, the antibodies and gepants?

Professor Maassen van den Brink (04:59): Yes, it may be involved in actions from several classes. To start with, the triptans: it's the oldest medication that's available; it was developed as a vasoconstricting drug. At that time, it was thought that vasoconstriction should be the primary action of antimigraine drugs and it may still contribute to the therapeutic action. But later on it was found that the so called triptan receptors — these are subtypes of serotonin receptors — they are also on nerve endings, and if these are stimulated, this inhibits the release of CGRP. So triptans influence the amount of CGRP: They decrease the amount of CGRP that is released, and that may be one of the mechanisms of actions in migraine treatment. So yes, triptans may act via inhibition of CGRP released.

Professor Maassen van den Brink (06:02): And the second one you asked about is the gepants. Maybe we should first explain what the gepants are. Yes, it's a novel class of drugs and they are antagonists for the receptor of CGRP that we have been discussing. And they are molecules that are almost the same size as a triptan. It's like a lot of traditional drugs — small molecules — and they bind to the CGRP receptor, at the place where CGRP would normally bind. So then when CGRP comes around, it cannot bind anymore if the receptor is occupied by a gepant, and therefore CGRP cannot perform its actions. So yes, again, a link between a drug and CGRP.

Carl Cincinnato (06:47): Now, you mentioned — in that explanation of those different types of treatments and how CGRP is one thing that they have in common, or they have an effect on CGRP in different ways — you mentioned CGRP "antagonist."

Professor Maassen van den Brink (07:00): Yes.

Carl Cincinnato (07:00): What does that refer to — an "antagonist?"



Professor Maassen van den Brink (07:04): An antagonist is a molecule that occupies ... it's not an antagonist for CGRP, by the way, but it's an antagonist for the CGRP receptor. So, antagonists are not antagonists for a certain compound, but for a receptor, and it binds to the receptor. And the gepants are — not all of them, but most of them — competitive antagonists: That means that they bind to the receptor and they will only be removed by large quantities of CGRP. So, they inhibit binding. And then you were also asking about antibodies? Yes. So we had triptans and the gepants, and then the antibodies that are now coming — it's a third class. And in fact, this class should be divided into two classes, because there are three antibodies in development. It's eptinezumab, galcanezumab, fremanezumab, that bind the molecule CGRP itself — so the peptides and delta receptor. And there's one antibody, it's erenumab, and that binds to the CGRP receptor. So in fact, a little bit like the gepant antagonist, but then it's a totally different molecule — it's much larger.

Carl Cincinnato (08:17): So let's talk about the size of these molecules. CGRP is known to be a large molecule. And how is that significant, or why is that significant?

Professor Maassen van den Brink (08:27): I think you are alluding more to the antibodies?

Carl Cincinnato (08:30): Yes.

Professor Maassen van den Brink (08:30): Yes, so these are indeed large, and that is relevant because one of the determinants that decides whether a drug penetrates into the brain or not is the size of the molecule. I mentioned earlier the blood brain barrier: the tight connections between the endothelial cells in the blood vessels of the brain. And of course there are other factors such as whether a drug has a high degree of lipophilicity, whether it can penetrate through membranes. But I think anyone can just imagine that if you have a very huge molecule, and it has to penetrate through some very small pores, this is difficult. So we know for antibodies — these are 150 kilodaltons in size, which is really large — that they hardly penetrate into the brain. And because they are effective for migraine, then we can learn from that. And we know that giving a drug to the periphery — so that may be trigeminal ganglion or the dura mater — it's sufficient to have an anti-migraine action. And maybe an effect in the brain would also be helpful but, yes, this hypothesis is not tested with the antibodies.

Carl Cincinnato (09:48): So the gepants are known to be smaller molecules that are affecting the CGRP. Does that mean they penetrate the blood brain barrier?

Professor Maassen van den Brink (09:56): Not necessarily, no. There was a trial, many years ago, with telcagepant and there it was found that it only penetrated into the brain at levels that were suprathreshold — so higher levels than were needed to inhibit the migraine attack. And there is still discussion about whether the technique in that study was proper and whether it was all definite, but it seems that maybe even the smaller molecules work more in the periphery than in the brain. But now there are novel gepants coming and we don't know, exactly yet, whether they penetrate or not.

Carl Cincinnato (10:38): So there was a study done decades ago, when gepants were first being explored, and they weren't successful and they didn't proceed. And now there's a new generation of gepants, which have been renewed that show promise and effects.



Professor Maassen van den Brink (10:55): Yes, in the beginning of the century, the first gepant, olcegepant, was tested and it was effective in the treatment of migraine. But yes, the shape of its molecule caused it to be very difficult to give it orally or via a well-accepted route of administration; it was administered intravenously, which is not convenient — but it was a proof of concept. And yes, this drug was not proceeded further and backup drugs also didn't work, unfortunately. And then there was telcagepant, that I was just mentioning, and it was also effective in the treatment of migraine, but unfortunately in trials where it was tested in way higher doses than needed in clinic, it induced an elevation of some liver enzymes, and therefore this molecule was stopped. But it doesn't say that the target CGRP is not a good target. So it's good that there are now new compounds in the pipeline.

Carl Cincinnato (11:54): So we've talked about triptans, the CGRP antibodies and gepants and how they all relate to CGRP. Which are preventive, and which are for the acute treatment of a migraine attack?

Professor Maassen van den Brink (12:06): Triptans are for the acute treatment of a migraine attack. They are also not suitable for preventive treatments because if you give them too often, they may induce medication overuse headache; so they should be used as acute treatment. The antibodies by definition, are for preventive treatment, because a drug always has a plasma half-life: It's the time until its concentration declines in the blood of a patient — and this time is very long for antibodies. So, if you give it, after a month you will still have about the same amount — the same order of magnitude — in your blood. So thereby, by definition, you have it in your body for a very long time, so it's not just an acute treatment. So these are preventives. And then the gepants: most of them up to now have been tested as acute treatments. They also have a rather short half-life compared to the antibodies, but there's also a gepant that is now tested as a prophylactic drug. So, it can be both.

Carl Cincinnato (13:14): So that's very interesting, because in the past it's usually been, if something's for an acute treatment, it's for acute only, and overusing it can cause rebound or medication overuse headache. And preventives have always been used for the prevention of migraine, or to stop a migraine before it actually starts. And now we're seeing with the gepants, a treatment, potentially, that could be used both for acute and for prevention.

Professor Maassen van den Brink (13:40): Yes, indeed.

Carl Cincinnato (13:40): And so does that mean with that gepant that you can't overuse it?

Professor Maassen van den Brink (13:46): Now I'm speculating, because [these are] questions that all need to be answered. But if I may speculate, then there's a difference ... We have been discussing that gepants, they are receptor antagonists: So this means they are occupying the receptor, but further downstream they don't do anything — they don't have their own intrinsic activity. If you compare that to the triptans, these are agonists: it's serotonin receptors at the 5HT1B and D and maybe 1F receptor. And that means if they bind to the receptor for the triptans, they will induce lots of actions intracellularly downstream. And what might be possible is that if you use the triptans frequently, because they are giving lots of actions downstream, this changes the whole system, and this leads to medication overuse. While the gepants, not doing anything on their own, just sitting on the CGRP receptor — maybe that effect is not there. But it still has to be explored deeper because obviously they are lacking the effect of CGRP, so you could also argue, if CGRP cannot bind to CGRP receptors, maybe then there will be an upregulation of CGRP receptors; in that



sense then more CGRP receptors will be active. So it's still an open question, but there are pharmacological differences between these classes, so it may be imaginable.

Carl Cincinnato (15:21): So it sounds like CGRP is the only thing that the triptans and the gepants have in common in that sense, but they act very differently in the body. So I have to ask, which is better?

Professor Maassen van den Brink (15:32): I won't give you an answer because I don't know. If you look in clinical trials, their efficacy is quite similar. And, of course, what's very interesting: If a patient doesn't respond to a triptan, how will that particular patient respond to a gepant? Can we predict whether a patient will be more responsive to a triptan or to a gepant? But then follow up questions are: which triptan and which gepant? So, I really don't know. I think nobody knows at the moment.

Carl Cincinnato (16:07): Sounds like a very exciting area for research.

Professor Maassen van den Brink (16:09): Definitely. Yes. And it's very gratifying for a researcher now to have all these tools around to be able to investigate further, the mechanisms involved.

Carl Cincinnato (16:18): And that raises also an interesting point. If you don't respond to a triptan, which is obviously affecting CGRP, does that mean that you won't respond to a CGRP antibody?

Professor Maassen van den Brink (16:28): No, I think, that does not mean it. We have to be honest and concede that we don't understand, still, a lot of it. First of all, a triptan: It inhibits CGRP release but it does not totally block CGRP. But, even more simple, there are patients that are not responsive to one triptan but responsive to another triptan, while looking pharmacologically, they are quite similar. So you can't say.

Carl Cincinnato (16:58): Many people only have a limited amount of triptans that they are given each month because they don't want to have medication overuse. Will gepants be the same?

Professor Maassen van den Brink (17:08): Not necessarily, because one of the gepants is now also being tested as a prophylactic drug. So, maybe that's not the case.

Carl Cincinnato (17:17): Can you explain what medication overuse headache or rebound headache is?

Professor Maassen van den Brink (17:21): We don't know exactly what mechanism is underlying this kind of headache. But what may happen if a patient has frequent headaches — and often these are not responsive enough to triptans — then the patient takes more triptans, and this will initiate intracellular mechanisms that will only end up in a vicious cycle. So, the migraine mechanisms get reinforced, and therefore the patient will get chronic headache. So then the remedy that is applied in Europe is to stop with all medication.

Carl Cincinnato (17:57): Is blocking CGRP more effective than other preventive treatments?

Professor Maassen van den Brink (18:02): No. If you look at the clinical trials, on average it's the same, although it's very difficult ... there are no direct comparative trials. And as you



know, many of the older prophylactics, they are more based on anecdotal observations — there are no really good placebo-controlled trials. So we don't have all the appropriate data. But, if you look throughout, they seem to be similar. So, I think the real question is how to identify those patients that respond very well to a particular drug.

Carl Cincinnato (18:38): So, it's not a miracle cure, but it is an effective treatment for a lot of people.

Professor Maassen van den Brink (18:43): Yes. It's definitely not a miracle cure, and I think the lesson we can learn from this is that probably CGRP is not the only important molecule in migraine. But yes, it's a big step that there is now a specific treatment available. And yes, we definitely need research to identify and understand why some patients respond, and some others don't. And also to look at the long-term safety of these types of drugs.

Carl Cincinnato (19:12): And, if we're honest about the effectiveness of other treatments out there, there are other treatments that are very effective, but often the side effects are what stop someone being able to continue using them. What are the side effects of CGRP antibodies?

Professor Maassen van den Brink (19:26): If you look in clinical trials, the effects are virtually none. In the clinical trials they are very similar to placebo; so that's very good and positive. And the only concern that one can have, is whether the long-term cardiovascular safety is really very well established — I think it's not established enough. So, that should be considered. And you won't find it in a clinical trial because luckily, if such events happen, it's not very frequent. And yes, statistically in a clinical trial, you don't have the statistical power to detect very rare side effects. So yes, work has to be done there.

Carl Cincinnato (20:10): Have you seen any information about what is seen in clinical practice, in terms of side effects?

Professor Maassen van den Brink (20:16): Yes. Also very mild. There are now some data about longer treatment, and patients are really quite satisfied. And sometimes there's injection pain, site pain ... but the side effects are generally minor. There have been reports about constipation, because CGRP is also present in the gastrointestinal system. But it's not coming out consistently in clinical trials. I think for the long term, it's still a bit early to conclude about it, but definitely compared to the other prophylactics, a very favorable side effect profile.

Carl Cincinnato (20:58): So we've talked theoretically about what could be side effects with long-term use. Does that mean that CGRP is safe to use, or is there a risk, in terms of long-term use?

Professor Maassen van den Brink (21:07): Yes, I think you don't mean using CGRP — of course it's the peptides that are the drugs that are blocking CGRP. Yes, the answer is that, I don't know yet. Of course we have to be realistic, and every drug has side effects. So, I really want to promote investigating this better, because we need to know. If you look at scientific literature, then potentially there could be this concern. If you look now at recent literature, there are some case reports of patients suffering from ischemia after the use of these antibodies. And no one yet can tell whether it's just coincidence, because anyone may get a stroke, or myocardial infarction, whether or not they are using these antibodies. So, I think we have two options: either now we say we don't know and we will wait for five or 10 years,



and then the numbers are big enough to draw conclusions; or if we do basic research — and I'm terribly in favor of that because I think we are obliged to do some homework. If we think theoretically this may be the case, it needs to be explored because we are giving these drugs to human beings.

Carl Cincinnato (22:26): Is it common that there can be so many unknown factors with the long-term use, but the treatment is still approved? Does this happen with other treatments, or was this just a special case for the antibodies?

Professor Maassen van den Brink (22:39): No, I think it may happen with many treatments, because we have to be realistic. There are lots ... I have a concern about long-term safety, but right now these drugs are changing the lives of many migraine patients, and really improving their lives. So, we can say we first need to do trials in so many patients for 10 years, and then we will see whether they are approved, but I think that would be stopping medicine. And also, you should see all the side effects in perspective to currently used medication. If you look at aspirin, every year several hundreds of people die because of gastric bleedings after aspirin, but no one cares. And you can buy it at a drugstore for almost no money, and you can use it however you want. And so we should not be focusing only on these novel drugs; we should see it in perspective. And I think it's a fantastic step that these drugs are coming. I think they are very helpful for a lot of people. But we should not only say, "Oh, this is wonderful," and look at the sunny side; we should be honest and also look at potential downsides. And more knowledge should not be negative, because maybe this research will turn out that there's no increased risk — that would be very wonderful. And if the research would show that there is an increased risk, but we can identify the patients that would have this increased risk, that would be very helpful. Or maybe, we can find some switch to mitigate this risk — that would also be very helpful. So, I don't see it as going after these drugs to find something very negative and shocking, but just to look globally over the whole picture. And I think, looking at the whole, it's definitely a very positive story.

Carl Cincinnato (24:31): So for someone who is looking at the five to 10-year horizon, we don't have all the information yet; more research is needed. But for someone who perhaps is thinking about trying CGRP, should they have any reason to be concerned about this?

Professor Maassen van den Brink (24:47): I wouldn't be too concerned. If you know that the patient has lots of cardiovascular risk factors, this may be an issue. On the other hand, we don't know how this mechanism is mediated, so what factors should we ask for? So that's the reason that we should do more research. But I'm definitely not against this type of drug and I think it may help lots of patients. And also, these patients are probably currently using triptans, and these induce direct vasoconstriction, so it also has a cardiovascular side effect potential. However, we know from clinical practice that the triptans don't often cause problems. So, no, I think it's definitely a very positive step forward. You should use it, but we should do the homework on all parts of the drug.

Carl Cincinnato (25:40): And that makes sense from a researcher's perspective, but also from a responsibility and appropriate use of treatment. So let's recap: What would you say are some of the pros for CGRP treatments?

Professor Maassen van den Brink (25:53): I think a big pro is that there's finally a drug that is designed really with the pathophysiology of migraine in mind. And you could say it's not important how it was designed, as long as it's effective. But if you look at the other prophylactics, they really have lots of side effects, and this is less for the antibodies against



CGRP, or the gepants. So that is definitely a big pro. If you hear stories of patients, in real life, these drugs seem to be much better than what comes out from clinical trials, because we can all be skeptics and say, "It doesn't matter so much, these headache days per month," but there are patients who report that their life has drastically changed in a good direction. So that's very important. And then you will also ask about cons, I guess. And of course one con is — we haven't discussed yet — but these novel drugs are expensive. So, it differs from country to country, but most likely they won't be reimbursed for every single patient that wants them. So it makes sense that patients should have tried some other prophylactics first. And secondly, my careful con would be that we should study the long-term safety in a better way.

Carl Cincinnato (27:21): Would you say the safety profile of the antibodies is a pro or a con?

Professor Maassen van den Brink (27:28): I would like to split it; and I would say that tolerability is definitely a very big pro and with tolerability, I mean the way it performed up to now in clinical trials, with side effect profiles being similar to placebo. And it's really excellent and exciting and incomparable to the currently available prophylactics. So tolerability is a big, big pro. And the con would be that we need to know more about the long-term safety.

Carl Cincinnato (28:02): OK. So to recap: the effectiveness, the fact that it's the first medicine designed to prevent migraine attacks, and the tolerability — particularly in the short term — are big pros.

Professor Maassen van den Brink (28:13): Definitely.

Carl Cincinnato (28:13): And then the cons may be things like getting access to the treatment because you have to fail other preventives, the long-term questions that haven't quite been answered yet for using the medication ...

Professor Maassen van den Brink (28:23): Yes. And the fact that they don't help everyone.

Carl Cincinnato (28:26): Yes. The fact that it's not a cure is a con.

Carl Cincinnato (28:31): Well, thank you very much for taking us through the pros and cons of blocking CGRP. It's been a pleasure to have you at the Migraine World Summit.

Professor Maassen van den Brink (28:38): Thanks.