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info@reachmd.com

(866) 423-7849

Advancing Acromegaly Care: Diving Deeper Into Diagnosis, Guideline Application, and Emerging Therapies—A Fireside Chat With Expert Perspectives

Opening:

This is GLC Live! Today's program titled Advancing Acromegaly Care: Diving Deeper Into Diagnosis, Guideline Application, and Emerging Therapies—A Fireside Chat With Expert Perspectives is provided by Global Learning Collaborative and supported by an independent educational grant from Crinetics Pharmaceuticals. This program is no longer live, so the polling and Q&A is now closed.

Please welcome your host, Dr. Maria Fleseriu.

Introduction

Dr. Maria Fleseriu:

I'm officially starting the program called *Advancing Acromegaly Care: Diving Deeper Into Diagnosis, Guideline Application, and Emerging Therapies*, and it's going to be a discussion between me and my colleagues, and you'll hear from all of us soon.

I'm Maria Fleseriu from Portland, Oregon. So yes, I'm not on this time zone, and it's a delight to have with me collaborators and friends, and between the world experts for more than 20 years. Probably I shouldn't say that, but Professor Beverly Biller from Mass General Brigham Pediatric Center in Boston, Massachusetts, and Professor Mark Gurnell from University of Cambridge, Cambridge, UK.

These are our disclosures related to acromegaly, clinical trials, scientific consulting. And, also, I wanted to remind you, as always, in rare diseases, we are going to talk about investigational medications, especially in US, if they are non-FDA approved, but it's going to be mentioned on each slide if they are non-FDA approved. And I'm sorry for the international audience that I know several of you are here, but we still have to mention FDA in particular, but where, if possible, we're going to mention other countries too.

Okay. So learning objectives. We have a little bit over an hour, and we are going to give you a landscape of everything from diagnosis, but we are not going to talk about all the details how to make the diagnosis, and we'll be happy to answer questions, and we left on purpose a lot of time for questions at the end.

We're going to talk about some pitfalls in diagnosis through specific cases, and especially if the features are atypical, and also what to do with the GH and IGF-1 when they are discordant, which we all love.

Then we're going to switch to talk about informed care from guidelines and how to select medical therapies, and especially when it's partial biochemical control, because if it's complete biochemical resistance, that's a different story. And even more, what's the definition of resistance?

And then we'll talk about the evaluate emerging medical management, not in this particular order. You'll hear to see if you are all awake, and we switch on you, but we will give you again details on emerging medical therapies, some of them recently approved, some of them not approved in US, but approved in Europe, approved in UK, and also how to integrate them into the individualized acromegaly treatment plans, which are very important, and I think we should all switch to that.

Addressing Disease and Treatment Burden

I wanted to start first by addressing the disease and treatment burden. I don't know if there are patients here. I guess we'll find at the end, but we all know by talking to patients for many years in our clinic that acromegaly has a high disease burden for them.

So let's talk about the case. Thirty-nine-year-old woman with newly diagnosed acromegaly. As you can see clearly late diagnosis by the time you see increased shoe size and the rings no longer fitting, we know this patient had acromegaly for a long time. And we'll see—and Mark is going to show later—why sometimes it's harder to make a diagnosis, but most of the time is the physician awareness not thinking in busy clinics, 10 minutes in primary care clinics, that a corollary of symptoms should be important. And this patient had already enlarged tongue. Denies any cardiovascular history that we know of, though when I did an echo, clearly already had mild left ventricular hypertrophy. Luckily, the normal ejection fraction. Family history notable for colon cancer in her father, and we'll talk more about comorbidities.

And the MRI, as you can see very large pituitary tumor, abutting the optic chiasm and pushing it up significantly, with invasion of cavernous sinus on both sides, on one even more. So we know from the beginning this patient is not going to have biochemical remission.

These are her labs. As you can see, that's not everybody that has such a high IGF-1, and you see the normal range. Very interestingly, for a tumor so large, the patient had normal pituitary function, which sometimes we see with acromegaly more than with other large tumors, which is very interesting, and especially for cortisol and some direct effects on the GH, but for the others, I don't think we have an explanation.

She had pituitary surgery at an outside institution. The IGF-1 decreased, but not too much, 3 months postoperatively. But again, this is a patient that, if who had been in our clinic, I would not wait 3 months. This is a patient that you know just looking at this tumor, where you don't need a super sophisticated imaging that they have in UK, and Mark is going to talk to you about, that this patient will have tumor.

So actually, the MRI looked even better than I thought, but regardless, the patient was not in remission.

She still had large residual tumor, and of course she should have been sent to a pituitary center of excellence to begin with, but that's a different story. And you know the US history of referrals and insurances.

So with residual tumor, we know that the patient will need medical treatment. So the key is what type of tumor? And it's not a surprise if I tell you that if the patient was not in a specialized center, their pathology report sometimes comes as pituitary adenoma and not even a GH, which is very interesting.

But what I wanted to highlight is if you have a patient that had surgery somewhere else, if you get a pathology slide, they can be reread at the center. So what we do for most of the slides, that depends how they are prepared, then we can at least tell. Receptors are sometimes more complicated, but if it's a densely granulated tumor, which is the tumor that responds the best to octreotide and lanreotide, and most likely paltusotine too, we don't have all the predictors, it's clearly better for medical treatment response. If it's a sparsely granulated tumor, then the likelihood of response is to octreotide, lanreotide, and again probably paltusotine too. It's significantly lower, and we know that.

And of course, if we had receptors, and if a patient didn't have surgery, we can look at imaging on MRI. And of course, if it's hyperintense on T2, it's not a good sign, though it's a huge variability. We did a study at some point comparing what we thought is T2 hyperintense and what the neuroradiologist—and it wasn't just me; it was my colleagues that has more patients—and still the neuroradiologist was better. Surprised. But it's very important to discuss with pathologists, but also the neuroradiologist at the same time.

And I wanted to remind you that sometimes there are even more aggressive tumors, which they don't have good response, most likely the one that I had, but it's not enough data to talk about.

So this patient had acromegaly. We already missed it for years. The delay in diagnosis, it moved down from 11 years to between 5 and 10, so we're not doing great. But once we have a pituitary MRI and then an adenoma is identified, the patient should go to surgery for the large majority of cases, and this was a patient that had optic chiasm compression, so it's almost no discussion unless the patient has contraindication. Surgery is first line, and if not, even surgical debulking.

Now, if nothing gets on the MRI, which again, unfortunately, most of the time it is, with exception of subadenohypophysis that had hemorrhage, then we'll go to either exploratory surgery, which some centers are doing, or medical therapy. But I have to say, right now we're using more medical therapy if we don't see the tumor, and again, we do not have the very sophisticated imaging. And in our practice, we're using radiation therapy either for inadequate medical response or for tumor enlargement. We're not using as preventive to use less medications in the future.

So the latest consensus guideline was a true shift for all of us because we kept talking about biochemical disease model, which again is still very, very important. So we want to normalize IGF-1. We still look at GH in some patients, and you will see later on, but now we are looking because we have more data. And thanks for several of you that have published the data to look at, so we can actually discuss that in addition to tumor control, the clinical symptom burden is controlled, the ancillary phenotype, and of course the

patient-specific metabolic risk.

So what we have available right now, we have several groups, so somatostatin receptor ligands. I'm going to go through all of them, so these are all the ones that are available. And if we're talking first about octreotide—and you'll hear later on about the emerging therapies and move on and talking about the newer therapies, the oral octreotide.

I'm not going to show you all the studies. I'm going to show you the one where we looked at patients controlled on injections, controlled on oral, so controlled on both, switched then and randomized to either injections, and you see on the left, and you can see was very clear, similar, and the mean IGF-1 values were the same.

Furthermore, when we looked at the extension for these patients, once they were either on octreotide or on injectable, when they were switched after the randomized control, you see on the right that these were patients on injection, and when they switched to oral octreotide, the patient-reporting outcomes, they said 67% increase from baseline that they were feeling better. And this was a specific Acro-TSQ that we have validated many years ago: treatment satisfaction, treatment convenience, symptoms interference.

And I want you to remember that the more we ask our patients, the more they will tell us, so some of them were our patients that they were on injections for a long time. Again, as you've seen in a lot of the studies, this is also a bias of patients that will go into a particular study. So I want you to think about that.

How about lanreotide? We're using it for many, many years. We have now more data on extension to every 6 to 8 weeks, and it still works. I want you to bring the idea of primary therapy, especially for the international audience. We rarely use it, but this was a study where they use lanreotide as primary therapy, so no surgery. And as you can see, I want you to look at the purple, and the purple showed percentage of normalized IGF-1 over time, not too high. But again, I told you that surgical debulking actually works. And if you see for tumor decrease, we always say yes, you can have tumor shrinkage, and this is the same with octreotide too, but if you look at this graph, you see that some of them will decrease significantly, and some of them will actually increase but very few.

But you can see significant shrinkage. This is a patient from that study, and as you can see from baseline to week 48, the tumor is decreased more than half. So keep in mind, when we need tumor shrinkage, we need drugs that work at the pituitary level.

How about pasireotide? This is a multiligand receptor, which is a little bit more recent. Though now that the main papers were published more than 10 years ago, has high affinity also on type 5 receptors. It's associated with tumor volume reduction. I'm going to show you some long-term data that we have now available from Netherlands, and in the study that compared pasireotide with octreotide, the tumor shrinkage was similar. But here you see patients that were uncontrolled for a long time, and then they were switched to pasireotide, and you should expect another 20% to 25% of patients controlled with significant hyperglycemia in a large percent of patients.

This is the long-term tumor control, and as you can see, these were 44 patients for up to 8 years, and we

know now that it's possible again, looking at T2 that there are some specific changes in tumor, because this was also related to the fact that patients, longer term—and I've seen in some of my patients too, but this was a larger study—27% actually had reduced doses, and the decline in IGF-1 continues. So that's very important to think about adjusting doses, not just up-titration, but down-titration also.

We know that pasireotide causes hyperglycemia and diabetes. I wanted to point out the risk factors that we know in advance: older age, impaired glucose tolerance, elevated A1c, and of course obesity and metabolic syndrome in general. But I want you to also point out that otherwise the tolerability is similar to the other drugs. And there are some studies that a combination that I'm going to show you soon may improve metabolic outcomes despite the hyperglycemia overall.

So this is the ACROSTUDY that we have published few years ago, and there are many iterations, and several of you have participated in that. The problem was that the increase in doses was not done appropriately for various reasons, including cost and availability of the drug. So if you see that dose frequency was mostly daily, which now we don't use, but look at the daily doses also between low, mid, and high. So it took years to actually get to probably the right dose for the patients, with probably explaining the difference with other studies.

Combination therapy, I don't know how many of you are using it. We'll be happy to talk more in detail. There are several of them for patients with resistance who are using either octreotide or lanreotide or paltusotine with pegvisomant. Again, this is off label of the off label, but we are using in patients if needed.

I rarely, rarely use cabergoline and pegvisomant, and I'm sure you've seen our poster yesterday, but for patients that have resistance to medical treatment, pasireotide and pegvisomant can be used as a combination again off label for FDA, and it's not approved in other countries either for specific patients.

How do we monitor adenoma progression? And you'll see more details again on what to look for the MRI, but I just wanted to bring up to you that this is part of the monitoring for the disease. Most of patients have to have MRI. Some of them cannot, but we need to look, what is progression, and we have a lot of problems. Expert review, we should make friends with a neuroradiologist.

Post-op MRI, again, imaging alone, I have many patients all the time coming back as a second opinion. I was told that they don't see anything on the MRI, so that IGF-1 should be falsely elevated. Nothing on MRI does not mean surgical remission, and of course we have to wait for post-op changes, and if not, again, we have to have different imaging, which is not available in US. So if you're asking, it's not available.

How do we define resistance? I think that's very important, and we have covered in the latest consensus guidelines, but I think I just wanted to briefly, because I'm not going to have time to talk about everything, but the key is biochemical control still. But it's also when do you check it? So for injections, and this is one part of the treatment inertia—for injection, we used to check everything after 3 months.

For the oral medications, either octreotide or paltusotine, keep in mind that we can make decisions much, much faster because the IGF-1 is declining, and we know from the study that you will see. So 2 to 4

weeks, nobody should wait more than that to actually have, and I do at 2 weeks, because by then I get it, the 3 weeks, and then at 4 weeks I can make a decision.

Rapid tumor growth, that's resistance to me, and that's when I panic. And of course clinical features that we should all think about as part of the resistance. Now, the symptoms could be different, and you'll see a lot of decision-making related to comorbidities also a little bit later on.

So with this, I wanted to remind everybody that patient preference and route of administration and frequency of administrations, this is very important for the patient, degree of biochemical control, residual tumor burden, of course glycemia, comorbidities, and adenoma characteristics also. So we should all look at everything, and I know it's a 10 minutes visit or 15 minutes visit, but we should all, when we prep the chart, I usually, when I go into the room, I want to have an idea immediately of what's the next step, thinking of all these factors at once.

And with this we'll switch to hear about new treatment. Thank you.

Integrating Emerging Medical Options in the Management of Patients With Acromegaly

Dr. Beverly Biller:

Thank you so much, Maria. Good morning, everyone. As I am not a morning person, I am very impressed that this many people are up and awake and alert, so thank you for coming.

I have the fun of talking about some new medical therapies, and here's what I will do. I'm going to focus on 4 of the new medications that have either completed phase 3 and in some cases been approved or are in phase 3 or phase 2 trials. And so we'll talk about paltusotine, which is FDA approved, as well as EMA approved. We'll talk about CAM2029, which is also approved on the other side of the Atlantic so far. And then I'll mention briefly 2 new medications under investigation, so you know that there's even more coming in the future.

But I'd like to start by telling you about this patient. He was a 66-year-old male lawyer who had been diagnosed a decade earlier when his existing diabetes became uncontrolled, and he noticed that his hands were getting bigger, his ring was not fitting. He was diagnosed with an IGF-1 3 times the upper limit of normal and a 1.6-cm lesion seen on MRI. So he had transsphenoidal surgery by an expert pituitary surgeon, and his IGF-1 was better, but he was not in remission because of cavernous sinus residual.

He was initially started on cabergoline, but that did not normalize his IGF-1, and so then he was started on and up-titrated with octreotide, and at 30 mg per month he was well controlled. However, he did not like the inconvenience and pain of the IM injections, and so when the oral octreotide study was available, he immediately volunteered for it, and he was well controlled on oral octreotide. And when this was FDA approved in 2020, he switched to taking commercial oral octreotide.

However, he had a new assignment at work, which involved taking clients out to dinner several times a week, and he found that he couldn't figure out when to take the afternoon or evening dose of oral octreotide. Should he take it earlier in the afternoon? Should he try to take it after dinner? He couldn't

figure out how to fit the fasting around the second dose, and so when the paltusotine trial became available, he decided to enroll in that because it's just once-a-day oral dosing.

So what is paltusotine? It's a nonpeptide selective somatostatin subtype 2 receptor agonist that has been developed as a once-daily oral treatment for patients with acromegaly. It's very potent. It's highly selective for the SST2 receptor compared to the other receptors. Its half-life is over a full day, and it's available orally.

So what I'm going to show you now are the two phase 3 trials that led to FDA and EMA approval. The first of these studies, which is called PATHFND-1, was a 36-week, double-blind, randomized, placebo-controlled trial in biochemically-controlled acromegaly patients. In order to be enrolled, they had to have been well controlled on either octreotide or lanreotide, and then they were randomized after screening to either take paltusotine or placebo in a 1:1 randomization. They were up-titrated if needed from 40 mg to 60 mg, and the primary endpoint was the mean of IGF-1 levels at weeks 34 and 36. The patients took the pill in the morning with water after an overnight fast, and then they had to fast for another hour before eating or drinking. Following this study, there is an open-label extension as well where everyone was able to take paltusotine.

And so here are the results from the primary endpoint. You can see in blue the patients who had been randomized to paltusotine, and you can see that as they switched from their control on octreotide or lanreotide, most of them maintained control as well on pasireotide, over 80%. In contrast, the patients who were switched off their previous treatment to placebo, most of them were not controlled. Only one of them, or 3.6%, remained controlled.

And this shows you the time-course curve over the 36 weeks, where again the paltusotine-treated patients are in blue, and you can see them below that 1.0 upper limit of normal IGF-1 line, whereas the placebo-treated patients immediately rise to be uncontrolled.

In this study, there are a couple of other parameters I'll show you. One of them is growth hormone. So patients had a mean of 5 samples of growth hormone collected at least 30 minutes apart over a 3-hour period at week 34. And again you see in blue that the vast majority of patients who had been randomized to paltusotine maintained control with a growth hormone less than 1, whereas the patients randomized to placebo had higher mean growth hormone levels.

And another parameter that was investigated was something called an Acromegaly Symptom Diary, a tool that's been validated for patients to say how they are feeling. And you can see that when patients were randomized to pasireotide and maintained good control of IGF-1, their symptoms did not worsen. But the patients who were randomized to placebo, shown in the gray box, had worsening of their symptoms as they lost control biochemically.

I'm going to switch gears now to tell you about the second study called PATHFND-2. This was a 24-week, double-blind, randomized, placebo-controlled trial, this time in patients who were not medically treated at the time that they enrolled in the study. They had active acromegaly. They had abnormal IGF-1

levels.

There are 2 groups called Stratum 1 and Stratum 2 that I'll explain now because it's actually 3 groups. So the first stratum, Stratum 1, which will be shown in the red boxes here, were patients who were not medically treated at the time they enrolled, and they needed to have an IGF-1 at least 1.3 times the upper limit of normal. Now, many of these patients are what you might think when you hear not medically treated, that is medically naive. They have never been treated with medical therapy. But there was also a subset within this stratum of patients who had been previously treated, but for some reason had not been on any medical therapy for at least 4 months, and sometimes longer.

The second category, shown here in the orangey-yellow color, were patients who washed out. They had been well controlled on octreotide and lanreotide for at least 3 months, but they were interested in being in a clinical trial and agreed to stop their injections and switch over to the new medication, so they were washed out. So before washout, they had to be controlled, and after washout, their IGF-1 needed to be at least 1.1 times the upper limit of normal, and that had to represent at least a 30% increase compared to the screening period.

And so then all of these patients in these sort of 3 different categories were randomized again 1:1 to either paltusotine in the blue or placebo in the gray. There was again a titration period where patients could be titrated up from 20 to 40 to 60 if needed based on IGF-1. And in this case the primary endpoint was the average IGF-1 from weeks 22 and 24. And then there was also an open-label extension where patients all got to take the new study drug.

And here are the primary results. The primary endpoint was met with over 1/2 of patients who had not been treated at the time of enrollment controlled by week 24. In contrast, you can see that only 3 of the placebo-treated patients achieved that.

Breaking down the results by Stratum, on the left here you see the not medically treated patients, where 42.5% of them were controlled, and again very few placebo patients. And on the right side, you can see that the patients who had very recently been on medical therapy had even higher rates of control at almost 93%, again very different from a placebo group.

I'm not, in the interest of time, going to show you in this case the growth hormone and Acromegaly Symptom Diary scores, but just to say that it was very similar to what was seen in PATHFND-1, that is, the patients treated with paltusotine had lower growth hormones as a mean and better ASD improvement than the placebo-treated patients.

What about safety? This grid shows you the summary of adverse events that occurred in more than 5% of patients. And we're not surprised to see things like diarrhea, the things like abdominal pain we're used to seeing in this class of drugs. Over 200 patients have taken paltusotine in phase 2 and 3 studies, and there are very low rates of treatment discontinuation. And I would say there are no surprises. There are no new safety signals compared to other drugs that we have used that attach to the somatostatin receptors.

What about pituitary tumor volume on MRI? It was either stable or reduced overall, and in PATHFND-2

there was a decrease in tumor size in 4 patients, whereas 4 of the placebo-treated patients had an increase in size. So that's encouraging, but remember these are relatively short-term studies, and really to know about effect on tumor size we need more patients and longer-term studies.

So to conclude about this particular medication, in two phase 3, placebo-controlled studies, paltusotine was effective in both biochemical and symptom control and was well tolerated. One of the things I think says a lot about a new medication is whether patients taking it in a trial elect to continue in an open-label extension. They're voting with their feet if they want to stay on the medication for a longer-term study. And in fact over 90% of patients in both of these trials chose to continue into the open-label extensions, which are showing continued biochemical and symptom control. As I mentioned, this has been approved on both sides of the Atlantic.

So now I'd like to switch gears to talking about another medication that has had two phase 3 studies conducted, CAM2029. This is a novel octreotide subcutaneous depot product. What's different about it is that patients or their partners can give it to themselves at home once a month using a smaller needle and a lower volume than the currently available intramuscular somatostatin receptor ligands. It's stored at room temperature, doesn't require refrigeration, and [is] ready to use, meaning it doesn't need to be mixed the way some of the older somatostatin receptor ligands do. And here you see that it comes with a pre-filled auto-injector pen with a hidden needle. And now that so many of our patients are taking, or have friends who are taking, GLP-1-related medications, it's not so intimidating to have a pen and to give yourself an injection once a month.

So patients with acromegaly were studied in two phase 3 trials, and these led to EMA approval in 2025.

What is this product? It has a FluidCrystal prolonged-release technology that's lipid based with an immediate onset of drug release after injection. So the patient injects the medication, and then gradually it degrades, and as it does, the drug is released into the circulation over hours and then weeks to months.

I'll show you the two phase 3 trials. The first was called ACROINNOVA 1. This was a 24-week, double-blind, randomized placebo-controlled trial, again in patients who were already biochemically controlled on octreotide or lanreotide for at least 3 months. The IGF-1 levels, we needed to be normal to show that they were controlled, as well as mean growth hormone levels, and then they were randomized 2:1 to CAM2029 or placebo.

The primary endpoint was to look at the proportion of patients who maintained control after switching from their previous standard of care, looking at the mean of week 22 and 24.

So here are the results for ACROINNOVA 1, and once again we see that the primary endpoint was met with a higher proportion of patients on CAM2029, shown in blue, than those on placebo who maintained control after the switch. These patients also completed an Acromegaly Index of Severity score, and that improved from baseline. They also had higher levels of treatment satisfaction compared to baseline.

Now I'll turn to tell you about ACROINNOVA 2. This is a study that looked at longer-term treatment with

CAM2029 in the patients I just talked about in ACROINNOVA 1 and also a new subset. So who were the patients in this particular trial? Well, a lot of them were patients who had been in ACROINNOVA 1. Either, across the top bars, had been randomized to CAM2029 originally, or across the bottom bars, the people who had previously been randomized to placebo and now were switched to CAM2029. And there was another subset of patients called the directly enrolled group, who were patients who had not been in ACROINNOVA 1 and needed to have IGF-1 levels that were less than or equal to 2 at the screening time point. And so these patients enrolled directly into ACROINNOVA, representing another subset of patients who had not taken the medication before, and then there is an open-label extension.

So let's focus first on the far-left set of patients. These are patients who had originally been on CAM2029 in the ACROINNOVA 1 study, and when they continued into this ACROINNOVA 2, nothing changed. In other words, their control was sustained. They continued to have normal IGF-1 levels at a very high rate.

Let's look at the second set of bars now. These are the people who had previously been randomized to placebo, and now in this ACROINNOVA 2 phase, they were switched to the study drug CAM2029, and you can see that the vast majority of them regained control, with 94.4% of them having an IGF-1 within the normal range.

Finally, let's look at the directly enrolled group. Remember, these are patients who were not in ACROINNOVA 1, and we can see that they had improved control, even though they were not controlled on other drug treatments. And the far right just shows you the average overall.

What about tolerance? This was well tolerated with really no unexpected adverse events compared to other monthly intramuscular somatostatin receptor ligands. Most of the adverse events were mild or moderate and often included injection site reactions. There was COVID as well because this study was being done during that time period.

So in conclusion about this drug before I tell you about the investigational drugs, in two phase 3 studies CAM2029 was effective in biochemical and symptom control. It was well tolerated with no safety surprises. Patients reported improved treatment satisfaction. They liked that they could give themselves this injection at home, and as I mentioned, it's EMA approved and available now in several countries.

Finally, I want to tell you about 2 drugs that are under investigation. I'll start with Debio 4126. This is a 12-week octreotide formulation for patients with acromegaly that's being developed. And here I show you data from ENEA [European Neuroendocrine Association] in 2024, but actually there was a poster 2 days ago, so you may have seen the poster. And what we're showing here, what this poster had shown, is the IGF-1 times the upper limit of normal, so of course we want it below that 1 line. And after these 4 shots that were given at the points of the green arrows, and what you can see is that the IGF-1 was maintained very steadily. The mean is represented by the red diamonds across this period of time, showing that if you give it every 3 weeks, the IGF-1 remains controlled with no safety surprises.

So there is now a phase 3 study that is ongoing. It is underway at 9 US sites and in 20 other countries for adults, again the same sort of population controlled on octreotide or lanreotide, and patients will be taking

this injection every 12 weeks, a total of 3 shots, followed by an open-label extension.

The other drug that I want to mention to you is MAR002. That's another investigational drug, which is a monoclonal antibody that's an allosteric inhibitor to the growth hormone receptor. It lasts longer than the growth hormone receptor antagonist we're familiar with, pegvisomant. And here you see some data from a normal volunteer study where they were given an injection, and you can see that it lowers IGF-1 in these healthy volunteers for up to 42 days with a reduction in IGF-1 up to 64%.

So this compound is being investigated this year, starting this year, in a phase 2 trial. The plan is to enroll 72 patients starting this year with a large group of patients in terms of different categories, like some of the studies I've been describing to you: untreated or controlled on therapy or uncontrolled on therapy, and they will be randomized to 1 of 3 active doses in a dose-finding way, and then there'll be an open-label extension available thereafter.

So I'd like to finish by telling you what happened to my patient. Remember the 66-year-old lawyer who enrolled in the paltusotine trial. Well, he was very happy that he could go to his work dinners without having to think about when to fast and how to take the pill because he only needed to take it in the morning. He achieved a normal IGF-1 on 60 mg a day with no side effects, and his MRI has been stable. When this drug was approved in the United States in December, he switched to commercial product, and he's doing very well.

And I think he is an example of how the availability of new medications that work in different ways or use different delivery systems really allows us to offer our patients a treatment which is specifically tailored to their needs.

And I will stop there. Thank you.

Dr. Maria Fleseriu:

Great, thank you, Beverly, for this nice review. And now we'll hear from Mark.

Challenges & Consequences of Delays In Timely Diagnosis & Management

Dr. Mark Gurnell:

So good morning, everybody. Thank you very much for coming along to join us today.

So we've just heard very nicely from both Maria and Beverly that actually, for a patient who now arrives in the clinic with newly diagnosed acromegaly, I think we can be pretty positive that actually we should be able to achieve good outcomes for them. But of course, if we're going to get to the point where we can actually give them access to these number of different agents, then we actually have to make that diagnosis in the first place. And that's actually what I'm going to focus on for the next few minutes, is trying to just remind us of the sorts of things we should be looking out for, but in particular, things that could put us off the trail and where we might just need to pause for a moment and think again about whether we need to revisit our diagnostics.

So there's a lot of different things that could trigger somebody being referred in for potential screening for acromegaly. The problem is many of the features that we see here are common in the general population, and it's often only when some of these come together and cluster together that we start to recognize that this might indicate that the patient has acromegaly. Not everybody walks through the door with the very coarse features. Earlier diagnosed acromegaly often is milder, and it may take a little bit of time to recognize. But what, of course, this does is remind us that patients with acromegaly are subject to a true multisystem disorder with lots of potential complications, and making this diagnosis can indeed be life changing for them.

This is actually taken from a very nice review that Maria and Andrea Giustina have recently published, and this just reminds us that this condition, par excellence, is associated with many, many different complications and comorbidities, all of which independently can affect the outcome in terms of the quality of life of those individuals, but it presents increased morbidity and, I'm afraid, if not recognized, potentially increased mortality. And we'll come back to this a little bit later on, but many of the patients with acromegaly, by the time we see them, have already acquired a number of these different complications and are already struggling and taking a number of medicines.

So what are the barriers to the effective, timely management? And I think this helps just to think about them in the different categories. There are truly patient factors that might influence the speed at which we actually get to meet these. It's interesting when you talk to patients that anecdotally many patients, for example, have avoided having their photographs taken over time, and they've recognized that something has changed, but nobody has really clicked. And the classic example, of course, is that there's a medic somewhere in the family who hasn't seen them for a number of years and then comes to a family event or sees a photo and says, 'Oh my goodness, you have acromegaly.'

The problem is that the changes, even for a clinician who is seeing the patient, like a primary care clinician maybe on a regular basis, are often very subtle and come on gradually. So if you were to look back and see an appearance from 5 years ago, you may recognize it, as we know, but you might not notice it when it creeps up on you slowly. It's amazing how often I hear that term, 'Well, I just thought it was all part of that natural aging process, all those aches and pains I had. These were all parts of the things that people encounter.' And comorbidities often take quite some time to be diagnosed and are often missed in the first instance.

But then the clinicians also have a potential role in why we don't make this diagnosis so early. The first thing is, of course, although we are starting to recognize and diagnose more patients, it's still a rare condition. So if you're in primary care, you may literally see 1 or 2 patients with acromegaly during your career, so that takes a bit of time sometimes before the penny drops. But also because we haven't got the message out there as well as we need to, what are those symptoms and signs that should make you pause and think, could this patient have acromegaly? The comorbidities, I think, are really important here. Once you start to see clustering of comorbidities, certain endocrine conditions should come to pass. This is not just acromegaly. We see this in Cushing's, where you see people who, at a young age, have had, for example, hypertension, diabetes, diagnosed with sleep apnea, diagnosed with carpal tunnel syndrome, and still the penny hasn't dropped that this is a lot of things coming together. And then, of course, there's

incidental findings on CT or MRI, which are sometimes, unfortunately, dismissed.

Then, even if we've thought about it, we can sometimes run into difficulties and challenges with the tests we have available to us. So we know that assay performance varies enormously. You really do need to talk to your laboratory. So Maria encouraged you to talk to your neuroradiologist. I would definitely say before you do that, make a friend with your laboratory, because you will need to talk to them when you don't see the result that you're expecting. Don't just accept that. Every good laboratory will say to you, 'Well, if you provide me with more context, more information, I may be able to help you. We may need to look again.'

The apparent disconnect between growth hormone and IGF-1 is almost legendary in this field. Think about where you're working geographically because it may be the other way around. So we know that in certain assay combinations it's likely to be the IGF-1 which is high when the GH is looking a little bit better, but the reverse is also potentially true. And then, as we'll see with some cases, there are potential false results from confounding factors.

So I'm going to use a series of cases. I'm going to allow you to interact. I'm not going to come around each asking people for an answer from their table, but we'll give you a little bit of time just to think about the cases and about what you might have done in the circumstance.

So this was a gentleman referred into our service who'd actually just moved location within the UK, a middle-aged man, and actually he'd had a really tough time. He'd been in hospital for a long time after having revision surgery for a prior knee replacement, and unfortunately, the antibiotic combination that he'd had was a pretty heavy-duty one, and at one point there were some visual concerns, and an MRI of the orbits was arranged because they were considering the possibility of toxic optic neuropathy. And as often happens, something is actually in the sellar region. When you do that incidental scan, the question is whether you see it, and whether you notice it, and whether your neuroradiologist chooses to mention that.

So this is axial imaging. It's T2 imaging, and it's got the sella caught within it. Typically, it's thick slices at this point. You might have 5-mm sections, so you might not get many views through the sella, but there is a lesion highlighted there, and of course, what should happen is that patient should then move on. And when this patient actually has imaging, and this type of imaging you're seeing here may look a little different to something that you normally look at, this is what's commonly known as a volumetric MRI. So these are very thin slices, very few gaps between the slices, gives us a lot more detail. There is clearly a left-sided lesion sitting within the sella.

So the question is, does that trigger anything? Does that do anything? Does anybody think about that? And fortunately, in this case, people did. The patient was referred on for an endocrine assessment, and wow, the IGF-1 is more than 7.5 times the upper limit of normal, and you can see that the patient not only has diabetes to go with his acromegaly, with that complete failure of suppression of growth hormone.

But the reason for emphasizing this case is that the diagnosis is made now when an MRI is done looking for a side effect of treatment, and yet this guy has had hypertension, type 2 diabetes, known cardiac

enlargement documented on echo, sleep apnea diagnosed, had his colonoscopy and found his colon polyps, had his large joint arthropathy. So he's got his hand up in the air saying, 'I've got all these different conditions,' and yet it's the MRI, thank goodness, which eventually triggers the diagnosis being made.

And actually, this raises a really important point around the imaging, which was highlighted in the Pituitary Society incidentaloma guidance that was published last year, which strongly encourages everybody who has an incidentaloma to be referred on for appropriate investigation, and in that, obviously, is the endocrine assessment. And there are 2 parts to that. There's a general endocrine assessment for patients with sellar and parasellar lesions, but you will see that there was a very specific recommendation for making sure we check the easy things, the prolactin and the IGF-1 level, which will give us a clue that this exists. And this is consistent with the latest consensus group work for acromegaly in terms of talking about diagnosis and remission, published in *Pituitary* in 2024, which also made the same point, which is that all patients with a newly diagnosed pituitary mass should undergo IGF-1 measurement. This is an opportunity not to miss the diagnosis, so please go back, please spread the word. We don't want to miss this, because this is a chance to pick this up, and it may be the only chance to pick it up if we've managed to unfortunately overlook many of the other common complications the patient already has.

Why is diagnostic delay really critical? We tried to assess this in this latest document to just remind people that prolonged GH excess, don't need to tell people here I'm sure, is associated with increased morbidity and mortality, as we've just seen. It seriously impacts quality of life, and it may mean that when we come to treat it, we actually have more challenges than we would have had, and we may need to use different agents or combinations of agents, and may achieve unsuccessful results, or results which are not as optimal as they could have been. So we're really looking to reduce that delay so that we reduce short-term and long-term morbidity, and we improve that quality of life.

Now, at the moment, we are not at the point where clearly we can argue that there should be wholesale screening for this condition, but we should be trying to remind colleagues, spreading the word that when that conglomeration of symptoms or comorbidities comes together, or when there is a newly identified pituitary mass, take the opportunity to check, is there a possibility this patient could have acromegaly? They may not look like a classic textbook presentation.

And we speculated a little bit in the group about how this might move forward in terms of reducing delay and raising awareness. It's tricky if you're a primary care clinician; you are constantly bombarded with every specialty telling you why you shouldn't miss this. A lot of the electronic patient record systems now spring pop-ups telling you this combination, that combination, have you thought of. There is almost the sort of overload in that, and sometimes we can overlook that. But I'm sure that, as this points out at the bottom, liaising with patient advocacy groups is also an important way forward.

Could AI be part of the solution? I put this in because it's very interesting and potentially provocative. I don't know quite what is happening in your geographical location, but in the UK, we have a huge amount of CCTV coverage now when you're out and about. So here's an idea. Shall we introduce the facial recognition software to the general CCTV analysis which is happening? I don't know if you want to receive a message through the clinic saying, 'Hello, we think you have acromegaly because we saw you walking

down the high street,' but it's an interesting concept.

And this is just one paper from Manel Puig-Domingo's group actually putting together—and this software is called AcroFace. It is capitalizing on the options for deep learning and various techniques that can bring this together. And actually, when they tested this out in subjects with acromegaly, in healthy individuals, so they had a training set, they also had a validation set in 14 subjects with acromegaly, and they tested it then in 24 subjects with acromegaly and 57 healthy individuals. It actually returned pretty impressive results.

The problem is, tongue in cheek, unless you go back and you really are going to roll this out into places where nobody has a pretest suspicion about it. If you deploy software like this at the point where you've thought about the diagnosis, with due respect, I would suggest measuring IGF-1 is going to be probably the better option at that point. But it's interesting. It gives us just something to think about, and who knows where we will land up.

So I'm going to come back to another case, and this is a very interesting case referred by a colleague, Miles Levy, based in Leicester, and other colleagues down at the Royal National Hospital in Queen Square. This was a patient who'd been really struggling with tricky headaches and been sent to the UK Specialist Headache Clinic, where actually Peter Goadsby, who's been doing headache management for a long time, very attuned and switched on, clicked into the fact that perhaps there could just be some evidence here that a patient who is not responding to the gamut of conventional therapies, perhaps there might be some indicators, but it was pretty subtle.

And in his letter, he said, 'I just wonder, when you ask her, she says her rings are a little bit tighter, she's still wearing them, she's complaining that she's actually experiencing more sweating episodes. Is there a possibility?' And, in fact, IGF-1 had been measured, and in the first assay, which I'll refer to as Assay A, it was 1.24 times the upper limit, so tantalizingly there or thereabouts, but the IGF-1 in the second assay was a little higher. Nothing in terms of high prolactin to support that. So the journey looks as if it's now moving towards the fact that somebody may have picked a patient up with acromegaly earlier on, but we always need to be a little bit careful and be sure.

And in actual fact, what had happened is the patient was then moved on to the next investigation as a confirmatory investigation, and that was a standard oral glucose tolerance test. And here you can see a very profound reduction in the growth hormone in response to the glucose challenge. You can see the glucose is given. You can see the growth hormone starts at a fairly modest level and pretty much at the first hint of glucose, the growth hormone is disappearing rapidly down to 0.2.

So you've had your food, you're sitting there comfortably, you're ready to go. I'm not going to come around and ask everybody individually, but I'm going to give you just a few seconds to think about what would you do with this patient next. Would you write back to the neurologist and say it was a good thought, but actually I'm afraid probably not? Would you say actually that was a really good thought, and I think you're right, I think the patient has acromegaly? Or would you say I'm not sure, I'm going to phone a friend, I'm going to send the patient to somebody else, they can sort that all out. Portland, Oregon, here comes a

patient. So what would you do?

Be interesting to know whether any of you would have moved on at this point and actually gone on to do imaging. Because when you go on to do imaging, you need to be careful here, because we also need to bear in mind the incidentalomas. But then we're in that circle. We've already said if you have an incidentaloma, you measure the IGF-1. So now we have a patient who's had some imaging, and you can probably see that there is a small abnormality, probably best appreciated actually on the T2 sequences sitting in the right-hand side of the gland. You really don't appreciate this very well on the T1 without contrast. The contrast is really crucial. Gadolinium is a mainstay of imaging still. Yes, we had some concerns about gadolinium a few years ago. We do need to be judicious with use, but there is something likely sitting there, seen on the T2. And then actually, if we add some of the other sequences that I've previously mentioned, FSPGR and Cube are volume sequences, ie, you are getting a very, very fine slice through the sella.

Now, you have to be careful at this point, because the better the imaging, the more detailed the imaging, the likelihood is that, of course, you might find something incidental that isn't the cause. But now you have something, so now the patient is sitting in front of you in clinic and says, 'Right, I've been reading about this condition, acromegaly. I think I've got acromegaly. The IGF-1 result tells me I've got acromegaly, but then you did this other test, and you told me maybe I don't have acromegaly, but then I persuaded you to do a scan, and you've done a scan, and I've got something on the scan. What are you going to do? Are you going to send me to the surgeon? Are you going to give me some treatment? Are you going to make me go away?'

So what would you do next? And the option to send the patient to somebody else still remains there. And if you want to do that, the question is who do you want to send to?

Well, this patient actually was quite keen to be sent to a surgeon, so what else could you do? Well, Maria allowed me to do this, so I'm going to do this. I know this is not widely available everywhere, but I think it just illustrates where some of the advances that we're getting are coming, and some of these are available in other centers now, especially in Europe, where we're getting more molecular imaging. We can now move from just looking at anatomy and structure and looking to see whether a lesion that we see within the gland is active. So this is functional imaging. This is looking specifically to see whether a lesion is active.

What this does, and the review is there that you're welcome to go and have a look at, is it summarizes all the different ligands that we could use. Unfortunately, the ligands that many of us have access to, such as fluorodeoxyglucose, 68Ga-DOTATATE, for reasons I won't spend too long discussing, are not, I'm afraid, ideal ligands for trying to identify whether a lesion is potentially a causative pituitary lesion.

So years ago we got very interested in looking at amino acid transport that is sitting over there on that left-hand side, and in particular using 11-carbon methionine, but you can use 18-fluoroethyltyrosine, which is an amino acid analog of tyrosine, of course, and all pituitary adenomas are essentially making peptides. And so our strategy was to try and develop imaging that would allow us to image whether it's acromegaly, Cushing's, prolactinoma, TSH-secreting tumor, etc.

So not widely available, but is becoming more used, as I say, especially across the UK and Europe. And in that situation, sometimes you get this very nice picture, of course, where you see on this axial image that where the lesion is visible on the Cube on its own, there is also, the best part, the way to describe this is a hotspot on the PET/MRI.

So I can see Michael is sitting over there in the corner, and at this point, Michael, you're the person I will be referring to, because I think this is the person who now should be potentially considered for surgery. And this patient did go on to surgery, and the lesion was identified and came back to clinic feeling much better. The IGF-1 was now, within a short space of time, within the first 3 months, was actually coming down nicely, and by 6 months was down to 1.07. Still, perhaps a little way to go.

When you go back to the GTT, it looks very different now to that original GTT. And this is a really important point. And actually, the term micromegaly was coined to potentially describe this entity, and this was mentioned yesterday. So look at the area under the curve, as it were, originally before the surgical intervention and then afterwards. So this patient's pathological GH secretion is pretty subtle, but it's there, and there is the pathology which confirms that this was indeed a sparsely granulated somatotroph tumor.

So this case illustrates that don't give up, the patient didn't give up, and we shouldn't give up. And remember, with all our tests, every test is changing the probability that the patient has a diagnosis, but rarely does a single test on its own dictate the answer yes or no.

Okay, so just briefly, a little bit more about molecular imaging in acromegaly. There's a lot of interest in molecular imaging for Cushing's, but actually, there's also really quite nice evidence, I think, emerging that it potentially has a role in acromegaly. Less so in de novo acromegaly at diagnosis, such as the case, I've just shown you, because most patients have an obvious tumor, they have an obvious clinical phenotype. You really don't need functional imaging to confirm.

But we have seen patients, as Maria alluded to earlier, where the MRI scan is completely normal, but molecular imaging may allow you to find that lesion.

So you've seen this picture before. There's a whole menu of different tracers that, if you went to talk to your nuclear medicine colleagues, they might flag to you and say you could try. We've been working on these amino acid tracers, and one of the first things that intrigued us was whether patients who we were seeing in our center and being asked to consider redo surgery, where other specialist MDTs had said there was no option for repeat surgery, in particular patients with lateral disease in the cavernous sinus, whether the molecular imaging could help us to be more confident. Now, this was a small case series, as you can see, just 9 patients, but all 9 had disease that was deemed not to be resectable. But using molecular imaging and demonstrating that the lesion was actually within the scope of field for the surgeon to interact resulted in patients getting potentially positive outcomes off treatment.

So with that in mind, Linus Haberbosch, who came to spend some time with us, went back and looked at all 189 patients referred to our center with acromegaly over around about a decade. Many of the patients had had previous heavy-duty treatment. You can see that might involve surgery, medical therapy, a small

number with radiation therapy. And what we were able to demonstrate was that actually of the 61 patients, some of whom were truly de novo with small tumors that hadn't been seen, we were able to identify a target in 52. And of that 52, 33 patients agreed or said they would like to go through with further surgery, and more than 70% of those patients who were deemed not to have a surgical option actually went into full biochemical remission, and then a small number also achieved an improvement in their IGF-1. And here are the IGF-1 results in this group.

So I just want to plant a seed there that actually, if you are lucky to have access to this, this may be something that could make a difference for select patients. This is not everybody needing molecular imaging; this is a small group of patients and then being looked at with a specialist MDT, with the expertise of the surgeon behind it to be able to act on those findings.

And in fact, if you're interested in this, again, in this special supplement that's just been published in *JCM* in parallel with this meeting, you could read more about why I would like you all to become imaging enthusiasts for acromegaly, because you should be challenging your radiologists in a nice way. You should ask them to look again if you think that something might not be there, and there are some other options.

Okay, so we're coming towards the end. Just one more case, so hopefully you can bring this all together.

This is a patient with retro-orbital headaches, no visual disturbance, and an incidental finding of a pituitary lesion on MRI brain. And now goes on to have a dedicated pituitary MRI, and I don't think there's too much doubt about that. You can see a lesion. This almost has those features of acromegalic tumors. It wants to go inferiorly into the sphenoid sinus. It's more common with acro tumors than it is with, for example, non-secretory adenomas. But the IGF-1 is just under the upper limit of normal. There's not a lot else going on in the biochemistry. What would you do next at this point? Would you be comfortable in just saying, okay, you've got no visual compromise here, the biochemistry shows that you're pretty eupituitary, and we don't really need to worry about anything else for the moment? Or would you do anything else? Now, you're sitting in a meeting where the answer is unlikely to be do nothing, so hopefully you would do something else.

So something else was done, and that was to determine the IGF-1 again and also to perform a GTT. And this time the IGF-1 is unequivocally raised, and this time the growth hormones in the GTT are definitely abnormal.

What happened in between? Did we just send the patient somewhere else? Did we get lucky? Or did we do something in between? If you go back for a moment and just have a look at that first set of investigations where the IGF-1 is 0.96, the cortisol is 28.1, and the LH and the FSH are measurable. Anybody know what happened? What was going on? What was the patient taking that actually confounded the results?

And there we go. So this is actually 6 weeks after discontinuing the combined oral contraceptive pill. So we need to make sure we don't miss out on this, because there are a whole host of factors, both growth

hormone, but here I'm just going to refer to IGF-1, that potentially can either push your IGF-1 up when you don't have acromegaly or, importantly, could hide that raised IGF-1 when you do have acromegaly. And you can see within there oral estrogen-containing therapies, such as a combined oral contraceptive preparation.

There are a lot of other conditions here, and this is a couple of lists which actually are really quite important to keep in your mind when things are at the borderline, and things are difficult to be sure about.

And I just really want to now come towards the last piece of this around the biochemistry and just direct you to this beautiful piece of work by Katharina Schilbach and colleagues, really starting to look at where GH nadir should sit in adults, and just highlighting now that they almost certainly—having a one-size-fits-all threshold isn't what we should be doing.

So you can see in A, males, in B, females without oral estrogen-containing contraceptives, and then in C, those with. And you can see the effect of body mass index on the nadir and just how low growth hormone really does go in normal individuals. And again, nicely showing the GH nadir concentrations in men, in females who are premenopausal, females who are premenopausal on a combined contraceptive pill, and also postmenopausal females. A one size does not fit all. I think that's pretty clear.

And then I just want to return and finish with this, which is the reason this is really important. The reason it's really crucial that we get this diagnosis right is because if we don't, the patients are at risk of all of these comorbidities. And as I say, this comes from this very nice article that Maria and Andrea published recently, and it reminds us that actually in that clinic, as Maria said, when you go into that clinic room, the patient will have some expectations of what they want, but we also need within that constrained time to try to make sure we have covered all these different areas, so that we're not overlooking something, because some of these persist even when the patient has good control of their acromegaly.

And just to show you one example from a piece of work that we published recently: this was a group of patients with de novo acromegaly who were having assessments for obstructive sleep apnea, and actually what it does is confirm what everybody else has said, which is 4 in 5 patients with acromegaly at diagnosis have obstructive sleep apnea. Interestingly, depending on the technique you use to diagnose the sleep apnea, you may or may not make that diagnosis, or you may or you may not estimate the severity. Apnea-hypopnea index is the gold standard here, and you can see that in both the men and the women, the average scores indicating more severe disease are higher if you use the gold standard for assessment than, for example, if you just measure oxygen desaturation, or worse than that, if you use a binary scoring system like the Epworth Sleepiness Score, where if you score above 11, you have sleep apnea. If you score below, you don't.

And actually, many of the patients, as you can see, didn't even know they had quite significant sleep apnea.

And with that, thank you very much for your attention, and we look forward to discussing more.

Dr. Maria Fleseriu:

Thank you. Thank you to my colleagues for wonderful presentations.

Closing:

Thank you for joining us for this special GLC live broadcast! This program is provided by Global Learning Collaborative and supported by an independent educational grant from Crinetics Pharmaceuticals. Thank you for listening!