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A Q-Challenge™ Replay: Advancing Precision Diagnosis and Treatment Strategies in Acromegaly

Chapter 1: Spot the Signs: Early Recognition of Acromegaly

Dr. Fleseriu:
Good evening, everyone. We're going to talk about advancing precision, diagnosing, and treatment strategies in acromegaly.

It's a delight for me to chair this session, and I have with me 2 colleagues, international expert and a mentor to all of us for many years, but if I say for how many, that makes me old too. Professor Shlomo Melmed, he's an executive vice president and dean of the medical faculty from Cedars-Sinai in Los Angeles. And we have with us Dr. Elise Brett, she's an associate clinical professor at the Division of Endocrinology, Diabetes, and Bone Disease in Mount Sinai in New York. And I'm Maria Fleseriu, professor of medicine and neurological surgery and director of the Pituitary Center in Portland, Oregon. So West Coast wins for now, but we'll see.

Learning objectives, you have them in the paperwork. We're going to talk about diagnosis, we're going to talk about using the consensus guidelines to select and adjust therapeutic strategies, so to fight against the treatment inertia, and then we're going to talk about several new therapies. And we're going to compare results from studies for efficacy, safety, and then also show you some real-world applicability of new therapies and how to use it. And then we leave time for your questions.

Spot the signs, early recognition. A 52-year-old woman presents with fatigue, frequent headaches, joint pain, excessive sweating. Wedding ring no longer fits. She has hypertension, carpal tunnel, type 2 diabetes. On exam, clinical features of acromegaly. What is the most appropriate next step?

Okay. A 45-year-old man with sleep apnea, carpal tunnel syndrome, hypertension undergoes screening for acromegaly. His age-adjusted IGF-1 serum level is 1.25 upper limit of normal. What is the most appropriate confirmatory test?

40-year-old man with acral enlargement and progressive coarsening of facial features, has an IGF-1 level 1.2 upper limit of normal. Baseline GH is 1.2. Following OGTT, nadir growth hormone level is 0.4. What is the most appropriate interpretation of these results?

Okay. A 58-year-old woman presents with progressive arthralgia affecting multiple joints over the past 8 years. She has hypertension and type 2 diabetes. Shoe size increased from 7 to 9 over the past decade, and unfortunately this is a very frequent case. Coarse facial features on exam and enlarged hands. What factor most likely contributed to the diagnostic delay in this patient?

Okay. A 32-year-old woman with suspected acromegaly undergoes biochemical testing. She takes combined oral contraceptive. On exam, acral enlargement, coarse facial features, but age-adjusted IGF-1 is 1.2 upper limit of normal. Which factor most likely explains the discordance between the biochemical and the clinical findings in this case?

A primary care physician considers implementing routine IGF-1 screening for all patients with type 2 diabetes in his practice, given the association between acromegaly and diabetes. Which statement best describes the appropriate screening strategy?

Okay. A 44-year-old man underwent resection of a growth hormone-secreting macroadenoma. At 3 months, IGF-1 is normal. Nadir GH on OGTT is 0.3. MRI shows stable 3-mm residual lesion in the cavernous sinus, reports markedly improved headaches and soft tissue swelling. Blood pressure and glucose well controlled. Which of the following best describes the recommended approach to ongoing monitoring of disease control in this patient?

Dr. Melmed:
Cool. Congratulations to our winners. And now let me just review with you some of the causes of acromegaly, and hopefully the answers will come out in what didactic slides we can discuss together.

If you have a patient with acromegaly, there are basically 3 causes, and it doesn't matter which cause the patient has, because the end result will be a high IGF-1 and a high growth hormone. And growth hormone and IGF-1 being elevated act dependently and independently to cause the somatic growth dysfunction and the metabolic dysfunction of these patients.

So our patients could have primary growth hormone excess, usually from a pituitary lesion. They could have extrapituitary growth hormone excess, extremely rare—extremely rare—from an ectopic production of growth hormone. Or a little bit more common, but still very rare, they could have ectopic growth hormone-releasing hormone production from an ectopic tumor, stimulating the growth hormone to hypersecrete growth hormone.

Now, the pituitary adenoma is the most common pituitary cause of primary growth hormone excess, and there are many types of pituitary adenomas arising within the somatotroph cell or adjacent to the somatotroph cell, which can give rise to acromegaly. By far and away, the most common are the densely and sparsely granulated adenomas and the mixed growth hormone and prolactin adenomas, and the others are relatively rare. Pituitary carcinomas and the familial syndromes listed on the right are extremely rare, and it's unlikely that many of us will see more than 1 or 2 patients every few years in a busy endocrine practice.

Extrapituitary growth hormone excess may occur, ectopic production of growth hormone from a pancreatic tumor, lymphoma, or it could be iatrogenic from inappropriate taking of growth hormone for all sorts of inappropriate reasons.

And then ectopic GHRH—growth hormone-releasing hormone—production, again rare, but could usually be caused by a carcinoid pancreatic adenoma tumor or a malignant pancreatic tumor, adrenal adenomas, medullary thyroid carcinoma, and very rarely a pheochromocytoma.

And this is just one example of an iatrogenic acromegaly. This gentleman, at the age of 30, decided for body building reasons that he needed hormone replacement, and by the age of 56 he has clear features of acromegaly. And when he comes to see his endocrinologist at the age of 60, he has self-induced iatrogenic acromegaly.

Now, diagnostic delays are important, and one of the questions related to that, because diagnostic delays cause higher morbidities and more disease burden because of the exposure, the long—sometimes decade-long—exposure of the peripheral tissues to growth hormone and IGF-1.

And unfortunately diagnostic delay has not improved in the past 2 decades. In fact, if you look at the original description of growth hormone hypersecretion in the 1920s and 1930s, they had a similar diagnostic delay. Women have a longer delay than men. And if you look at the 603 patients in the Swedish National Registry, you can see that the delay was more than 10 years in one-quarter of all patients with acromegaly, and Sweden has a very well-controlled public health system for medical care.

Now, it's very easy for an endocrinologist or an internist or even a busy general practitioner to make a diagnosis of acromegaly when he sees one of these images. If a patient walks into your office and they have macroglossia or they have the jaw mandibular dysfunction or the intestinal hyperproduction of polyps, it's easy for you to make the diagnosis. The problem is that by the time these patients get to you, they've already had the disease, sometimes for 10 years.

And all these textbook features of acromegaly, the respiratory features, gastrointestinal, musculoskeletal, the local mass effects of the

adenoma giving rise to headache and visual impairment, hyperprolactinemia sometimes, all the cardiovascular side effects of high growth hormone, metabolic and endocrine effects, especially type 2 diabetes, reproductive effects—these are the textbook features which we all learn to pass our boards. And these are the features which you all know and which you all in retrospect say, “Wow, my patient has many of these.” How do we alert ourselves to be able to make the diagnosis earlier than currently is the practice?

And I would like to just emphasize some red flags for you in terms of understanding the constellation of symptoms rather than the symptoms themselves. And we spoke about it in one of the questions. So for example, recent-onset hyperglycemia in an otherwise healthy man or woman should be an alert to you. Snoring, daytime sleepiness, and a constellation of a suspected OSA—that patient should alert in your mind the possibility of acromegaly. Multiple uterine fibroids in a woman, colon polyps or cancer occurring inappropriately in a family, impaired vision clearly should be a trigger for you, and especially in a younger patient with left ventricular hypertrophy, valvular insufficiency on echo, and blood pressure monitoring dysfunction should be a trigger for you.

And headache and depression are extremely important because headache, regardless of the size of the adenoma, is a major determinant of acromegalic symptomatology. Even tiny microadenomas, hypersecreting growth hormone can in fact present with very severe headache.

So how do we make the diagnosis after you've thought of that constellation of symptoms rather than 1 or 2 of the symptoms? So if you suspect acromegaly—and this again was an earlier question a few minutes ago—the best screening test is measure the IGF-1 level. If the IGF-1 level is normal, it is highly unlikely that your patient has acromegaly. You can consider pseudoacromegaly. You could consider a previous adenoma which was present, caused acromegaly, and then self-infarcted. And the patient could have undergone previous acromegaly surgery without telling you, the physician. And you should re-treat these patients as needed.

But if the IGF-1 level is below the normal level of 1.0, you should not be concerned about acromegaly. If there's mild elevation of the IGF-1, you should then proceed to perform a glucose load and measure growth hormone during the oral glucose load. And if it is not suppressed, you have really made the diagnosis through the mildly elevated IGF-1 level, and the patient has all the clinical features, this is in fact acromegaly.

If the growth hormone is fully suppressed after a glucose load, it's almost certain that the patient does not have acromegaly, but like everything in medicine, there are exceptions. And at least 30% of patients with true acromegaly may in fact give you a false sense of hope because they do suppress on glucose. So the very elevated and high clinical suspicion accompanied by a high IGF-1 and a non-suppressed growth hormone is invariably acromegaly, and at that point you can proceed to the MRI.

Don't waste money on an MRI until you've been through that earlier, much more cost-effective biochemical evaluation. And if the adenoma is present, then if a patient is a suitable candidate for surgery, you'll proceed to surgery, and we'll talk about that momentarily. And if the patient is not a candidate for surgery, or declines surgery, then we have medical options.

In the very, very rare circumstance that there is no pituitary adenoma that is clear cut, you should assess the patient for ectopic acromegaly, one of those rare syndromes that I showed you on an earlier slide.

But there are pitfalls for IGF-1: anorexia, liver disease, kidney disease, uncontrolled diabetes, oral estrogens, and severe obesity will all lead to lower IGF-1. In fact, one of the questions which you had was oral estrogen. And oral estrogens will give you a decreased IGF-1 level, because estrogens—and that's why women have lower IGF-1 than men—because estrogens block growth hormone action on the liver to produce a lower IGF-1 level than an age-matched male.

But I want to point out on the slide the 2 conditions which increase IGF-1, and these are the only 2 exceptions to a high IGF-1 that's not acromegaly. So to all intents and purposes, if you're screening for acromegaly and the IGF-1 is high, your patient has acromegaly unless they're pregnant or unless the patient is in the late spurt of late pubertal growth, 17-18 years old. So those are the increases in IGF-1, and this is an important list to remember, because it helps you interpret that lab test before you embark on a long, expensive, and time-consuming assessment and also engender unnecessary anxiety in your patient.

Morbidity is high in acromegaly. And looking at age-matched controls, you can see in the solid blue lines as compared to the green lines, there are high levels of cardiovascular disease, hypopituitarism, sleep apnea, malignant neoplasms, arthritis, type 2 diabetes, and bone disorders. And these are control studies from big population groups, so there is a high morbidity from this condition leading to a

high mortality.

And this is just one example of several rigorous population studies that have now recently been published, in fact several since 2022, which confirm the study, that there is an increased mortality in these patients. And if you look at the standardized overall survival, and this is 700 patients who were published 3 years ago, you can see there's a marked distinction between those patients who are biochemically controlled in the top right solid curve versus those who are not controlled or in whom the control was unknown.

So clearly, biochemical control is one of the levers which we can apply to prevent this high mortality in these patients. And now I'm going to hand it over back to our chairperson.

Dr. Fleseriu:
Thank you.

Chapter 2: Translating Guidelines Into Real-World Practice

Dr. Fleseriu:
Let's switch gears a little bit to talk about how to translate guidelines into real-world practice. And you have more questions. So hopefully you have more glucose now—

Dr. Melmed:
Your growth hormones will be suppressed.

Dr. Fleseriu:
A 45-year-old woman is diagnosed with acromegaly, with a 15-mm pituitary macroadenoma. The IGF-1 is very high, 5 times upper limit of normal, no cavernous sinus invasion. Which of the following is the most appropriate first-line treatment? And I know it depends, but still you have to choose one, and the right one if you want to be on the leaderboard.

48-year-old patient with acromegaly undergoes resection of a densely granulated growth hormone–secreting pituitary adenoma. Three months after surgery, IGF-1 level is twice upper limit of normal, and repeat MRI demonstrates 1-cm residual tumor. Which of the following is the most appropriate first-line medical therapy? Four options.

Okay. 48-year-old man with acromegaly has an IGF-1 1.8 upper limit of normal despite 12 months of maximum dose injectable octreotide. A1c 7.4, fasting blood sugar 95. You are considering switching to pasireotide LAR. Which of the following is correct regarding pasireotide? So the correct option out of the 5.

38-year-old man with acromegaly underwent surgery with incomplete resection due to cavernous sinus invasion. Postoperatively, IGF-1 is 2.8 upper limit of normal and growth hormone still high. Then 2.5-cm residual adenoma with T2 hyperintense signal and cavernous sinus extension. Immunohistochemistry: sparsely granulated adenoma with predominant 5 expressions and low 2 receptor expression. No history of diabetes, blood sugar 92 fasting, and A1c 5.4. Which of the following is the most appropriate medical therapy?

35-year-old woman with acromegaly has persistently elevated IGF-1 and is intolerant to octreotide due to severe gastrointestinal side effects. She has poorly controlled type 2 diabetes. MRI still shows small residual adenoma. She declines repeat surgery, so you don't have this option. Pituitary function is intact, and she desires future pregnancies. What is the most appropriate next treatment for this patient?

55-year-old woman with acromegaly has persistent disease after surgery and is intolerant to SRLs due to severe gastrointestinal side effects. She also has diabetes. You initiate pegvisomant therapy. Which of the following monitoring strategies is most appropriate for this patient?

We'll talk first about the conceptual shift between consensus guidelines, and then you'll actually hear how these are applied in clinical practice.

As you all remember, in 2018 the consensus guideline meetings published at that time looked at primarily a biochemical model. So we

all discussed for days what's more important to control, IGF-1 or GH, with different types of medications. Of course, we're talking about comorbidities in context. Many years after and many studies after, because when we meet, we discuss about the studies that actually have been published, not just our opinion, we looked at patient-specific metabolic risk, cellular phenotype, clinical symptom burden, adenoma control. So that's why there are some changes, because without data and with the participation of all of you sending patients to clinical trials, and the patients, we were not going to have and were not going to advance the field.

So how do we personalize the post-op medical treatment? And we had in the other talks several questions. It's very hard, because each patient is different. But in general, the somatostatin receptor ligands, and now we have more approved, are first line for the large majority of patients in US. Pegvisomant is also approved as first line. It's not approved in other countries. Cabergoline, it's only for very mild elevation. This is not FDA-approved for this, but it has been used. I don't use it as first line, but this was an international consensus.

Second line, though, some of these drugs I'm using as first line when we need to, is patients that are inadequately controlled or they don't tolerate well. And then we also look at specific cases, how big the tumor is. And I'm going to show you the data for tumor shrinkage. For example, what type of tumor? Is it sparsely granulated? You've seen earlier, in Dr. Melmed's presentation, the importance of the type of pathology. Does the patient have uncontrolled diabetes? And then we use a lot of combinations, and by the way, none of the combinations are FDA-approved. We had some studies for few of them, but they are not FDA-approved.

And then extremely rare in more aggressive cases, which, depending on the center, I have many patients on this type of combination and also a few on temozolomide, but this is because it's a referring center. But however, with what we have available right now and what's coming, we should be able to control all patients with acromegaly.

So these are the drugs that are targeting the somatostatin receptors that are available right now. I'm not going to go through the doses. You all have AI available when you need to prescribe it, and Epic is doing it for us anyway. We have several, and then the insurance will say what they want anyway, and I'm sure you've all went through that. But it's important, and I'm going to focus more today on some of the newer drugs, where we have more recent information then maybe not so much experience.

But I wanted to highlight that biochemical—when we talk about efficacy and we talk about biochemical efficacy, the data in naive patients, even for octreotide and lanreotide, which initially we thought it's controlling everybody because they were prescreened for control, and it was 100% in some of the studies initially, it's actually 50% to 60%, depending. And on the study design, as you go, it goes from 17% to 80%. Octreotide and lanreotide, if somebody is asking me, they are pretty much the same.

Control-wise, the oral octreotide we have shown in studies where they were tried on both drugs, that it's comparable efficacy. When it was with placebo, it was a little bit different but definitely favor patient-reported symptoms. Pasireotide LAR, more favorable biochemical control, and this was one of the questions. However, significant hypoglycemia in more than 50% of the patients.

And paltusotine, which was newly approved, and some of you I'm sure have used it already, it's an oral non-peptide SSTR2 agonist approved for patients with inadequate response to surgery or where surgery is not an option. And I will show you some of the studies. After switching, patients previously controlled maintained stable IGF-1 and GH, and I'm going to show you the data that has been published and some of the posters that are coming. I'm not going to show you, so we just have to go and see the posters.

So when we're talking about oral octreotide, keep in mind that there were several studies, large studies. One was against placebo, so you need to know the design of the study when you look at the data. So this was patients controlled on injectable switched to, in blue, oral octreotide, in dark gray was placebo. And left is IGF-1, and on the right is GH response.

When we look at patient-reported outcomes, so this was from a different study, which in the interest of time I'm not going to show you all the design, but these were patients controlled on both that I mentioned earlier. In longer term, the patients had stable IGF-1, almost the same. You would see the graphs, and you are done.

However, the most important thing, because we expected that, was how the patients were feeling when they were switched. And these were patients—on the left you see that they were on oral octreotide in the main study, and then when they were continuing on oral octreotide over time, the 26% increase from baseline was good symptom control declared by the patients, not the physicians. And we have patients here in the room, and they agree that clearly what the physician says is not always what the patient says.

On the right, you see patients that were switched in the randomized to injection and then switched to oral after that. And as you can see, it was 67% increase from baseline. And I want you to look: the upper and the lower are the same; they're just different groups. Treatment satisfaction, treatment convenience, symptoms, interference, GI interference, and emotional reactions—all of them were improved when patients were switched. So these were patients with biochemical control. The IGF-1 was in some even a little bit higher, because here was 1.3, so I wanted to highlight that it's not just biochemical control. It's also symptoms.

How about pasireotide? So in the study that compared pasireotide with octreotide, different doses, different designs, was complete lack of up-titration, 30% were not up-titrated. However, if you look at the overall, both normal IGF-1 and GH, pasireotide was better than octreotide but not as much as we have expected.

However, when we looked at other studies where there was resistance, pasireotide adds additional benefit. In aggressive or invasive adenomas you see sometimes more shrinkage, but sometimes it's key for sparsely granulated with more receptors type 5. And actually, we look at lack of type 2, or I use it, however, with hyperglycemia, as I mentioned earlier, and the cost is an issue for all the drugs.

So how do we use as predictors for shrinkage? And again, for paltusotine, we don't have a lot of data yet, but I'm looking to see, because it was a study where some patients were naive to medical treatment, and that would be very important to look for predictors. How much the IGF-1 decreases, and with oral medications, you find out pretty fast. You know if it's a densely granulated, it's going to respond more. It's not 100%. In our data, it was 80 even for densely, so it's something post-receptor. And of course, if you have type 2 receptors, high expression, which is debatable, and hypointensity on T2. And for pasireotide, it's less IGF-1 reduction after octreotide than lanreotide, and it's not a cutoff, but sometimes I switch immediately to pasireotide.

How about pegvisomant? So it's a lot of data. Pegvisomant now has been approved for many, many years. I'm going to show you here the most recent published data where we look at over 2,000 patients. Several of them were also in combination, so take this with a grain of salt. But what we're looking for safety in this data was initially, because of the mechanism of action, was an idea that this is maybe going to increase tumor. As you see, out of more than 2,000 patients, 7 increased and no change in that had measurable tumor. The IGF-1 normalization clearly increased, but the doses also increased, and few treatment-related AE and drug discontinuation due to AE was very low.

So when do we use pegvisomant? I use it more in combination, but in uncontrolled disease, unacceptable AEs with SRLs, the patients with hyperglycemia that require higher doses, though if you look at the meta-analysis, there was minimal improvement in A1c per se, but I think each patient is different. And of course, monitor LFTs, which are rarely a problem, but we have to monitor.

And then what's important, I think, that those especially for single therapy—for combination it's different, but if you look at the dose frequency, this was a study done all over the world—I don't think I have anybody on daily—but if you look at the study, because this is how it's approved in the US also, label says every day, but even if they are on single therapy, I don't use it every day. And for combination, I use it twice a week. Dr. Melmed is using—and he showed in a study—even weekly will work. But if you look at the doses, that's why some of this control was not higher as an initial study. If you look over the years, the high dose slowly increased, but still I don't think we're doing a good job in optimization therapy for any of the therapies that I have presented you.

So I want to briefly show you, and it's going to be looking at colors. So if you have mild increase in GH and IGF-1, maybe consider cabergoline. But this is the guideline consensus, which was with international participation. I have to say, I extremely rarely start cabergoline because we have other oral therapies that are approved. So that's, of course, if you are—and I don't want to single out countries, because I'm also from Eastern Europe—but if you don't have any other medication, yes, don't leave the patient untreated. But if you have a lot of options, you do not get a lot of control with cabergoline, and that has been proven.

If you look in blue, all these features that I mentioned earlier, either injectable SRL or, again, at that time, we said consider the oral or possibly paltusotine that we added later. We had no studies on this published yet and with longer-term data. So right now, especially if it's approved or the insurance will let you use it, it's clear now that there is no difference in between injectable and orals. Elevated IGF-1 and GH, adenoma mass, gross clinical impairment—if these are an issue, then definitely we have to look at inadequate dose control. And I'm not going to go over all the details, but if you have particular questions, not for a specific case, in general how to deal with inadequate disease control, I would be happy to answer questions with my colleagues.

Now this was very hard for pegvisomant because there's no data. We're just assuming that if they have diabetes, they will do a little bit better, especially considering pasireotide. And also the no adenoma mass, because we don't want shrinkage. So all of these were actually more double negatives. So that's why this would be a drug that will work first.

But again, this is complicated. But the key thing is, with what we have now available, we have no reason to leave patients uncontrolled. And the IGF-1 should be normal, and also the patient has to have all their symptoms controlled.

Thank you.

Dr. Brett:
Thank you. So I was invited to be part of this panel to give the perspective of the community endocrinologist. So I'm a general endocrinologist in solo private practice. I have 9 acromegaly patients in my practice, and I don't work in a big referral center. So how did these patients come to be under my care? So obviously, most of them I diagnosed myself. Either I was seeing them for diabetes or hyperparathyroidism, or maybe they were sent to me to evaluate for hyperprolactinemia, amenorrhea, and I had to have a high index of suspicion, either because of a constellation of symptoms or because of classic features, but I diagnosed them myself.

What else is different about how I manage my patients from my esteemed colleagues? Besides managing the acromegaly, I'm also taking care of all the associated endocrine problems. So I myself am also managing the diabetes, the dyslipidemia, the hypertension. I'm screening them for osteoporosis and managing the osteoporosis. I'm diagnosing and managing the hyperparathyroidism. And if they have a palpable thyroid abnormality, I'm doing the thyroid ultrasound in the office, and I've diagnosed at least one of them also with thyroid cancer and managing the thyroid cancer.

How am I able to do all this? I do have some resources. I am able to do blood testing in the office and send the blood out to good commercial labs. I do have a good radiologist right down the block who will do MRIs for my patients within a day or two. And I'm lucky to be in New York City, and I've got four world-class pituitary surgeons on speed dial who will answer my texts within minutes, as long as they're not in the OR, and they're very happy to see my patients right away.

I do have familiarity and experience with all the FDA-approved drugs. What I don't have experience with is treating aggressive or malignant disease. I've never prescribed temozolomide. If I had one of those patients, I would refer them out to a colleague. I've used cabergoline, of course, but I don't have experience with off-label dosing of other FDA-approved drugs. I was thinking recently that I did want to start a patient currently on pegvisomant once a week, and I wasn't quite sure how to do that. I'm not an investigator in any clinical trials. I also haven't recently had access to send my patients to any clinical trials, and I don’t have a nurse in my office to administer injections. So I did have a patient in the past couple years who needed monthly lanreotide injections, and I had to do that myself, which was a pain in the butt for both of us.

Chapter 3: Addressing Disease and Treatment Burden

Dr. Brett:
Okay, so we have a few more questions now.

A 38-year-old woman is newly diagnosed with acromegaly. She has no family history of colorectal cancer and no cardiac or GI symptoms. Thyroid is not palpable. According to current guidelines, which of the following screening strategies is most appropriate?

Okay, next. A 45-year-old woman with acromegaly states she has poor sleep, morning headaches, and daytime somnolence. Which pathophysiologic mechanism best explains a key comorbid condition contributing to these symptoms?

Which of the following metabolic comorbidities is most commonly associated with acromegaly?

A 52-year-old woman with acromegaly has been on monthly injectable octreotide LAR 30 mg for 3 years following transsphenoidal surgery. IGF-1 is 0.95 times the upper limit of normal. Growth hormone is 0.8. She reports persistent fatigue, joint pain, frequent headaches, and depressed mood. She rates her quality of life as poor. Which of the following statements best reflects current understanding of this clinical scenario?

Which statement best describes the relationship between acromegaly disease control and major comorbidities?

So let's talk a little bit about morbidities. So the leading cause of premature mortality in acromegaly, clear-cut in all the studies, is cardiovascular disease. High growth hormone levels are associated with hypertension, cardiomyocyte growth with cardiomyopathy, left ventricular hypertrophy, valvulopathy, and arrhythmias. And what's not on the list is atherosclerosis. There is no clear-cut evidence that patients with acromegaly have accelerated atherosclerotic heart disease.

So the cardiomyopathy is usually a left ventricular hypertrophy, valvular dysfunction, and leading to a distal dilated usually left ventricle. And you can see the cardiac ultrasound, which is classic at the bottom of the slide over here. And if there is any colleague who you need in order to manage your patients long term with acromegaly, it's a good cardiologist and a cardiac imager.

Respiratory complications are important because snoring—new-onset snoring—can be a very important trigger to the doctor to make a diagnosis. Sleep apnea occurs in up to 70% of patients in some series because the high levels of growth hormone, as you saw in some of your questions, were associated with swollen pharyngeal tissues, macroglossia, and pulmonary tissue hypertrophy. And the duration of growth hormone excess and obesity are directly proportional to the degree of sleep apnea. And males are more prone to develop sleep apnea than females, and that is the classic case of macroglossia. And this patient came to see us after his spouse had complained that suddenly, at the age of 60, he started snoring.

Skeletal comorbidities are important, and we highlight just one important one here, which is vertebral fractures. And that is why you should always try and do vertebral morphometry on your patients, because most of the vertebral fractures in acromegaly are asymptomatic and will only come to attention of the orthopedic surgeon or the neurosurgeon after it is too late.

And you should really, when part of your initial screening and certainly your ongoing follow-up, you should assure yourself that you have excluded vertebral fractures, and you should be performing a TBS and vertebral morphometry on all these patients.

There is a lot of evidence now that malignancy is increased, both in acromegaly as well as in the long-term follow-up of patients with acromegaly. And this is just one example of several recent studies from the Swedish nationwide population showing a very high level of increased mortality, with a standardized incidence ratio for some conditions being well over 2. And you can see that the time from acromegaly diagnosis to malignancy persists for many years, and the median time from diagnosis to cancer diagnosis in this Swedish study was 6.5 years. So it's incumbent upon us as endocrinologists to make sure that we initiate appropriate cancer screening programs for our patients.

So how do we put it all together? How do we follow these patients? We've made the diagnosis, we may have sent them to a surgeon, we put them on all those wonderful treatments which Dr. Fleseriu spoke about, we have the infrastructure which you heard from a very experienced community physician. How do we put it all together for managing comorbidities?

So every 6 months, we should do our cardiovascular screening. Our endocrine and metabolic disorders should be screened for. And then every year at least, we should add to that vertebral morphometry. And I want to emphasize that, because these fractures are usually asymptomatic. And we should start considering quality of life measures—objective quality of life measures for our patients. And then every 2 years, to add dual-energy X-ray absorptiometry. Once again, bone disease is a very silent contributor to morbidity in these patients.

And then every 10 years, we should be repeating a colonoscopy. And if we didn't mention, we should mention it here: at diagnosis every patient should have a colonoscopy. I know that in a lot of countries outside the USA, that isn't the practice, but at diagnosis, especially for young patients, we perform colonoscopies on all patients.

Dr. Fleseriu.

Dr. Fleseriu:
Okay. And talking about complications in general, before we move to treatment, each patient is different. So yes, we said for a colonoscopy in that guideline 10 years, assuming it was normal. But if it's abnormal, the GI doctor that's doing the colonoscopy should know that the patient has acromegaly. And we talk to all our colleagues, that if they don't know it's a high-risk disease, as Dr. Melmed was saying, that's very important for the cardiologist to know that that patient has acromegaly. And now it's getting a little bit better with

Epic, but sometimes you just need to pick up the phone and say, I have a patient with acromegaly. This is a high risk. What's next?

Because every time I do that, the treatment differs, including from cardiologists, what they do and how frequently they do it. For GI, at least we know if they find colonic polyps.

Chapter 4: Integrating Newly Approved and Emerging Therapies

Dr. Fleseriu:
So now, questions again.

48-year-old woman with acromegaly, well controlled on lanreotide depot injections for 4 years, IGF-1 0.9 upper limit of normal, reports significant injection site discomfort and asks about switching to oral paltusotine. She has type 2 diabetes, hypertension, GERD, prior cholecystectomy for gallstones. Which of the following is the most important consideration when initiating paltusotine in this patient?

Okay. 44-year-old woman with acromegaly has achieved stable biochemical control on long-acting injectable octreotide. She reports significant injection-related adverse events, including bruising, pain lasting several days, and led to missed injections. She also reports difficulty attending clinic visits due to transportation barriers. She has poor adherence to frequent doses and requests a simplified, low-frequency regimen. Which of the following is the most appropriate next step in management?

52-year-old man presents for follow-up 3 months after transsphenoidal surgery for a GH-secreting macroadenoma. GH post-op is 8.2. IGF-1 is still high. Abdominal ultrasound is normal. MRI shows 1-cm residual adenoma in the cavernous sinus. Pathology is sparsely granulated growth hormone adenoma. Well-controlled diabetes type 2, no gallstones. After 6 months of octreotide 30 mg every 28 days, IGF-1 is 360. Patient declines radiation. Surgeon is concerned about residual adenoma in the cavernous sinus. What is the most appropriate next step in the management of this patient?

Okay. 52-year-old woman with acromegaly status post transsphenoidal surgery, has been on lanreotide autogel for 2 years with good biochemical control. She takes multiple medications for comorbidities. She switches to paltusotine to reduce treatment burden, but later reports difficulty managing doses with meals and prefers to return to monthly injections. Which of the following is the most appropriate next step in management?

48-year-old woman with acromegaly has been on paltusotine for 8 months with good control on IGF-1. She presents with a 2-week history of intermittent right upper quadrant pain, occurs 30 to 60 minutes after eating fatty meals, occasionally radiates to right shoulder. She denies fever or jaundice. Her initial GI symptoms resolved after 6 weeks of treatment. Mild upper right quadrant tenderness, no rebound or guarding, normal liver enzymes. Which of the following is the most likely complication of paltusotine therapy in this patient?

When counseling the patient about expected adverse effects, which of the following is the most common category of adverse events reported with CAM2029 in clinical trials? This is not approved in US yet, but this is an international meeting, and this drug is approved in Europe and in the UK. And I'm going to show you some data.

Okay, so before I move on, and I'm going to show you some recent data that was published, I wanted to remind everybody if they want to send questions, then we'll have time to look over and combine some of them. We already got some for discussion but keep it going.

So I'm going to present you, so for paltusotine, there have been several papers published. I'm going to show you the most recent one, because I think this is very interesting. It was in *JCM* earlier this year, where the study included patients that were either completely naive to medical treatment or semi-naive, meaning they were—and you'll see in the paper—they're called washed out. But what we meant in the study as washout is actually they were on therapy and then the therapy was discontinued, so they were not on medication at the time, and they were uncontrolled at the time of entering the study.

So I want you to look at colors, because I can't show you otherwise. So blue and going down, because we're talking about IGF-1, and that's what we're tracking in acromegaly. All patients you see on the left with the drug versus placebo in gray.

So blue is the drug; gray is placebo. And as you can see, it's a significant decrease in all patients. And again, these were naive or washout. So this was not a switch. I'm not showing you the switch study.

And then if you look for the not medically treated, so the pure naive and naive to medical treatment, because most of these patients actually had surgery, and then washout, also it was significant improvement. But I was more impressed by the not medically treated, because we know, comparing with octreotide studies or the head-to-head with the pasireotide study, the control rate was significantly lower there. Again, different type of patients, so we don't have any head-to-head yet.

So when we're looking now of the changes in IGF-1 with the least mean changes, again, blue is good, and these were patients not medically treated, either naive on the left or previously treated. So if you see, it's a significant decrease in IGF-1 in both groups of these patients, and you see the placebo, the gray, is a very low number of patients, and we can have a discussion on the placebo probably for an hour, and still we do not have an explanation.

As I showed you for the oral octreotide, this study includes patients, keep in mind, that were not switched from medications, so we're looking at different data. In the other, patients were controlled, and then they were switched and they saw improvement. So these were patients that some of them were uncontrolled at baseline. So if you look again, blue is the drug, gray is the placebo, and coming down is good, because we're talking about improvement in symptoms. And this was a different type of scoring but includes the same type of symptoms, and I'm going to show you soon, and this is usually what we ask in clinic. And I think I did so many trials that now even my clinic note includes almost the same questions.

So both for the washout and for the not medically treated, was significant improvement in symptoms. And I think that for the washout was even worsening because they knew what it means to actually feel controlled, but that's my opinion. I have no data for that.

So look again, blue is the drug, and it's good because it's coming down: headache, joint pain, sweating, fatigue, leg weakness, swelling, and numbness and tingling. Now do you see 100% improvement? No, and you don't see this with any of the drugs. And we were expecting significant improvement when we did other trials also, because we thought if we can control the patients—and this is clear, more drug, because it's every day, and I will show you for the injectable subq, it's also higher concentration of the drug.

However, the duration of the disease and some of the complications that Dr. Melmed showed you are not reversible. But the sweating and the fatigue here, and including the headache, so this is one of the things that sometimes I'm switching patients for, thinking about that.

How about this is a new drug. So I'm going to give you some details. This is a study. I can tell you that overall, based on my experience in clinic, or—and it makes sense because it's a type 2 receptor, it's just more selective—we see gastrointestinal, and they are the most common. Keep in mind, this was—especially the study I was showing you earlier—was a study done in naive patients. Almost everybody has some GI symptoms when they start a somatostatin receptor ligand agonist, or targeted how we're going to call them now, may occur within the first 2 months and last 6 to 18 days.

Sinus bradycardia was seen. We see this with all the receptor ligands, palpitations, glucose changes, decreased TSH potentially—that's why we're using TSHoma SRLs—vitamin B12 deficiency, and then cholelithiasis was 6%.

Now, a new study was more of a systematic review, but a little bit of meta-analysis, because it's not a lot of data. I presented you half of the study that exists on prospective clinical trials. So it wasn't super hard to select. I selected few for each drug. But this looked—which I think is very important—tells us not so much about the efficacy, which is we need comparative studies, but it tells us what's the probability with the data we have. And I'm not saying this is reality. It's like if you have other cases, you should all publish it. The idea is, with available data, what's the probability of discontinuing because of an adverse effect?

So looking at this, if you see the probability of ranking the best for discontinuation was paltusotine. It's interesting; it was the octreotide subq, then, of course, it's the placebo, which, again, people didn't know they are on placebo, so this is funny. And then oral octreotide and then the combinations.

The type of patients in each study were very different. So I think until—and this is never going to happen—we have a study where you look prospectively at several drugs and do comparative, I'm waiting for a study like that for Cushing's for 15 years, and we couldn't do it, so that's not going to happen. But I just wanted to show you, because that's a very good question to ask the patients when they're coming to clinic on each of these drugs, is you have adverse effects. And sometimes, if they want to stop it, I ask to see if they're

thinking of it, because I prefer to find out in advance than the patient discontinuing. As you've seen, the adherence is very low overall, or it has been with other drugs, and we need to know that.

How about CAM2029? Again, approved in Europe and UK. The studies were done—also, there were several studies—this was an octreotide depot. It's a subcutaneous autoinjector. It's self-administered with a pen.

So compared with the octreotide that's intramuscular, and it has to be injected in—for us it's in the infusion center; we don't even do it in the clinic. The release profile is different than the octreotide LAR. It's immediate onset with sustained 4-week release, and the concentration seems to be a little bit higher. The data has not been published, but we have presented in posters where the IGF-1 stability, even with extended doses, not at every 4 weeks for some of these patients, they had better control, both biochemical and symptoms. And it makes sense, because the bioavailability is much, much higher than the LAR. And the visit burden, imagine—and I have talked to some of my colleagues in Europe that the patients, though, as Dr. Melmed said earlier in the other talk, the patients in Europe like injections more than our patients in US. Which our patients in US, they all want oral, and some of them, as you've seen in some of the questions, switch back, and then they go back. But again, patient preference is very important.

So the data for the study that has been published by several of our colleagues last year in *JCM*, this was, again, a different design. Each of these studies were different designs, and I didn't choose them. I'm like, this is how they were. So I wanted to see if you're awake, but that's a different story.

So these were patients that were on injectable and they were controlled. They all started at the same dose of 20 mg, which this is the dose approved in Europe, every 4 weeks. Again, this is not FDA-approved. This is a CME program. This is not FDA-approved yet, but it was approved by EMA.

And then you see on the right the placebo that some patients stayed, because the duration of the study wasn't long enough probably; we have seen this with oral octreotide, but several of the patients went significantly higher.

So key points: not approved here, self-inject with a pen, it's every 4 weeks, subcutaneous self-injectable, as I said earlier. It's octreotide, and common AEs were GI disorders. And when the drug would be approved, we'll have a label with more detail.

What was also very important, and shows us that maybe with the new drugs available, we'll be able—you've seen the data for oral octreotide, we've seen the data for paltusotine, we have seen the data with this drug—when it will be available. Again, the same thing that I said: no patient should be left uncontrolled. Also, patients have options. We cannot decide for patients what they could be on. We have to tell the patients what's available and what we think is best for them, but we cannot make the decision.

I usually tell the patients, for the drugs that have the same efficacy, you can decide. If we're talking about which one for sparsely, because sometimes they hear about a drug and they want that, that's a different story.

So this is the mean IGF-1 in the study that I have shown you, and this is the time to loss of response. So again, these were patients that were poorly controlled. And this was a switch study, and then this was the mean change. But I will show you other details too. This is the mean change in symptoms overall from baseline over time. So as you can see, again, blue is drug. So the mean change in overall symptoms, these were patients that were controlled before. That's why they were switched. This was a switch study versus placebo. So with higher concentration, maybe with LAR or lanreotide, we didn't get to the right dose. And there are studies showing that you can get better efficacy with higher doses, but those were more adverse effects. Here was not the case.

I would like you to think about what we have discussed. We don't have all the answers, but we have more answers than before.