Acromegaly Research Highlights at ENDO 2023; Wenyu Huang, MD, PhD

Hello everyone. Welcome to this CME presentation. We're going to discuss acromegaly highlights that were presented at the Endocrine Society meeting in Chicago in 2023. My name's Wenyu Huang. I'm associate professor at Northwestern University at Feinberg School of Medicine. So these are my disclosures. So first, I'll start out of what is acromegaly. As you know, acromegaly is a very rare endocrine disorder that was caused by excessive level of growth hormone production and secretion. So with the recent epidemiological data, so the prevalence of the disease is about two to 13 per 100,000 patients where the incidence is somewhere between 0.2 to one patient per 100,000 people. In many case, growth hormone excess is caused by a benign tumor of the pituitary gland, which in turn causes overproduction of IGF-1 as we're all familiar with. So below, you can see the common symptoms and signs of acromegaly.

Most of our patient complaining about fatigue, excessive sweating, joint pain, soft tissue swelling including their hands and feet and tongues and they snore, have sleep apnea. They also experience neuropathy most commonly present as carpal tunnel syndrome, but other neuropathy can be seen as well and brain fog, which is forgetfulness and short-term memory loss. And some patients, because the tumor is big, they also can have headaches and visual disturbance as well. Now, if you examine the patient, oftentimes we see there are some characteristic features of acromegaly which include prominent forehead, protruding lower jaws, overbite and skin thickening.

Now, these here listed are the current therapies for acromegaly, and you can either target the pituitary growth hormone secretion where you target the growth hormone action. So for the pituitary target therapy, we have dopamine agonist, mostly is cabergoline is off-label use and occasionally we use bromocriptine but very rarely. And mainstay of treatment is actually called somatostatin analog or we call somatostatin receptor ligand. And there are first generation somatostatin analog which include octreotide injection, lanreotide injection and octreotide oral capsule. And there's also a second generation somatostatin analog which here shows this pasireotide injection or you can target the growth hormone action and we use Pegvisomant to block the growth hormone receptor. So these are the mainstay and currently FDA approved therapy, of course not including dopamine agonist which is off label use but very commonly used in our field.

So again, I'm going to review some interesting abstract that was published and presented at the Endocrine Society Meeting in Chicago this June. And due to time limitation, I was only able to present a few of them, and so sorry that I cannot include everything related to acromegaly that were presented. It was a very interesting meeting. So let's go on.

First, I'd like to talk about clinical trials that are related to acromegaly. So first, I would like to bring to your attention is paltusotine. They reported a phase 2B trial data looking at the long-term effect. So paltusotine is an investigation drug. It's orally used once daily, is non-peptide compared to the other somatostatin receptor ligand. It actually is targeted to the somatostatin receptor two specifically. So they're using that to try to treat acromegaly and neuroendocrine tumor. So there are two active phase 2B trial that was there, is called ACROBAT Edge and ACROBAT Evolve.

So the Edge involved patient with IGF-1 level is more than higher than the one times upper limit normal where the Evolve trials involve patient with adjuvant well controlled, which is less than or equal to the one upper limit of normal. Though when these two study ends, they were eligible to enroll in the Advance trial. So they actually had an interim analysis for patient treated with paltusotine for more than two years in the ACROBAT Advance trial, which is the ongoing four-year single arm open label extension study. So total their 43 patients enrolled in the Advance trial that include 32 patients on the Edge and 11 patients from the Evolve trial which is about 88% of eligible patients. So as you can see, I'll bring your attention to the right.

On the table, you can see that at baseline, the meaning IGF-1 level is about 1.15 times the upper limit of normal. And at week 51, 52 the median IGF-1 level is about 1.08 and then times the upper limit of normal. At week 77, the IGF-1 level is about 1.01 times the upper limit of normal. And again, about two years mark, the IGF-1 level would stay stable at 1.1 times the upper limit normal.

So they also in the study looking at the acromegaly symptoms, so they use a Acromegaly Symptom Diary for the patient. As you can see at baseline, the symptom score is 8.57, and about week 77, the symptom score is similar at 8.0. The patient was also asked about their preference in terms of whether they like the injections or the paltusotine. You can see at about one year mark, 88.9% patient prefer paltusotine, 5.6 prefer the previous injection and 5.6% of patient have no preferences. So here, the study at this point shows the once daily oral paltusotine treatment was well tolerated associated with stable IGF-1 and symptom control relative to that achievable by the injectable SRLs and was preferred over injectable therapy.

The most common treatment emerged adverse factor reported here including headaches, arthralgia, fatigue, no serious drug-related treatment emergent AEs were reported. Six patient discontinued the therapy and 2.1 of them was due to this headache. Now, the glycemic control was also looked at in this study and it was stable during the paltusotine treatment. So these are the phase 2B trials and I believe that paltusotine, there are two phase three trials around the same compound. Hopefully they will report the result in the next few months. So we stay tuned.

Now, the other important medication we often use is pasireotide, which is second generation somatostatin analog which mostly target the somatostatin receptor five. So this study looking at a long-term safety of this medication in an eight-year period of time. So it is the interim analysis evaluate the long-term safety of this in patient with acromegaly and Cushing's. Because this medication has been approved for both indications and other endocrine disorders, this is the open label multi-standard study and so they're able to allow continual treatment for patients who were previously on pasireotide in a clinical trial.

The primary objective of studies I mentioned earlier to evaluate long-term safety and was determined by frequency of the adverse effect and the severe serious adverse effects. So overall, 341 patients from 29 countries enter study from 14 parallel study parent studies and 228 patients had acromegaly, so majority of them, two-third of them have acromegaly.

So you can see the median exposure to all pasireotide formulation which include both intramuscular injection and subcutaneous injection, which here is a short-acting pasireotide. So at the time of the data cut off is close to four years, so 45.3 months. The median dose from the rollover at baseline was 45.4 milligram per month with pasireotide LAR, which is the monthly injection or 1,200 microgram per day with the short-acting injection subcutaneous pasireotide. And 26% of the patient discontinue the treatment. The most common reason is withdraw of consent, and here listed are the most common adverse effect.

You can see listed here only in the patient with acromegaly because this is the focus of this talk. You can see nasopharyngitis, hyperglycemia, back pain, headache are the most commonly reported. Overall, 5.3% of the patient discontinue treatment because the adverse effect, and the severe serious adverse effect was reported in about 25.5% of the patient. The most common one is cholelithiasis and COVID-19 during the study period. As you can expect, hyperglycemia is unexpected AE during the pasireotide treatment which often occurred in the first three months of therapy. An incidence of new hyperglycemia related adverse effect during the rollover study was low, so no new safety signal was identified.

So I like this study because it gave us an idea over eight-year period of time how people fare in terms of pasireotide safety, and of course, hyperglycemia is picked up as the one of the adverse effects. Now, knowing that back for the question, are there risk factors with pasireotide in terms of hyperglycemia

adverse effects? So this study is trying to answer that question. So Samson et al looked at a post-hoc analysis from a phase four study which is trying to assess predictor of hyperglycemia in patients receiving pasireotide.

So in this study about 190 patients with acromegaly and 59 patients with Cushing disease were given pasireotide. So at the start of the study, none of the patient needed treatment with hyperglycemia or only managed with metformin alone. So this is the enrollment criteria. So during the study, 88 patients with acromegaly with 15 patients with Cushing disease did not require anti-hyperglycemia medication, and hyperglycemia and diabetes mellitus occurred in 21% and 14% of patients with acromegaly or in the group of Cushing's 28% and in 12% of patients reported these adverse outcomes.

Now, looking at the common characteristics of patients who did not develop hyperglycemia, you can see while in the table. So in patients specific with acromegaly, so if the patient's less than 40 years old, 63%, almost two third of them did not develop hyperglycemia. If the patient have the baseline A1C less than 6.5, very likely they would not develop hyperglycemia in the trial. And also looking at the fasting plasma glucose, if it's less than 100 milligram per deciliter in about three quarters of a patient with acromegaly did not develop hyperglycemia during the time of this trial.

So they were able to identify statistically different risk factors associated with pasireotide-induced hyperglycemia in the acromegaly. So these are the common ones listed here, age based on A1C and based on pre-diabetes or diabetes status. So it probably gives some idea if you were to start pasireotide and if you're concerned of hyperglycemia, those are the factors you will have to keep in your mind before you start patient on this medication.

Now, there's another FDA approved drug is oral octreotide capsule. And so the study trying to look at what are the predictors that a patient may respond to this oral octreotide versus the injectable octreotide and/or the injectable lanreotide. So they're actually using the data from the global study MPOWERED trial. That trial alone showed that the oral octreotide were non-inferior to injectable SRLs in the maintenance of biochemical response in those previously responded to both the oral octreotide and also the injectable SRLs. So you can look at the bottom for the design of the trial.

So the patient and they were all controlled with injectable SRLs, then they entered into run-in phase and they were started on the oral octreotide capsule and then depending on their control, biochemical and symptomatically, they're titrated up, the highest dose is 80 milligrams. So at the end of the run-in phase and the patient, if they meet the criteria for randomization, they will be randomized into either the oral octreotide and/or the injectable SRLs and then they will be compared in terms of accuracy. So the main objective that specific trial was looking at the efficacy and safety of that track.

For this specific study that we're talking about, the objective of study is to identify patients or disease characteristic to predict what is the likelihood that patient responded to the oral octreotide capsule. So again, those include the patient that was in the MPOWERED study and all the patient actually receive the octreotide during the 26 weeks when in phase. And so responders at week 24 are randomized as mentioned earlier to those two trials. So this study specifically looking at the response at the end of run-in and so looking at those patients who responded or actually were randomized, which means they are well controlled during the run-in versus the group who's not randomized, which also called non-responders. So basically comparing to those who we know that they were responders to the injectables and then they put in the run-in phase, some of them will maintain the response, some of them will not. So looking at the characteristics of those two and hopefully try to identify who may be the candidate for this medication being still responders.

If you look at the table on the right, you can see there are 92 patients randomized. There are 54 did not randomize after the end of the run-in phase. So you look at the IGF-1 level prior to the OOC or oral octreotide capsule initiation. So there was a 0.8 in the randomized patient and 1.0 times the upper limit

of normal and then also the reached significance but not so for the growth hormone and also not so for the excess of growth hormone excess symptoms. And also, the prior injectable SRL dose was looking at either they're low dose or medium dose or high dose, there's no difference between them. So the conclusion of the study is that the baseline IGF-1 level on the injectable SRLs but not other acromegaly baseline characteristics was the only predictor of subsequent response to the oral octreotide capsule.

All right. So there's also some interesting retrospective studies looking at, so Maria Fleseriu et al looking at the treatment patterns in this insurance claim database. They're trying to see what about the demographic characteristics, the treatment frequency by line of treatment and how many of them need changes and the treatment persistence for the first line of treatment monotherapy and how the medication would titrate up and down. These are again from an insurance claim database. There's some interesting findings of the study. So looking at the table on the right, the first column, you see that about almost 60% of patients was using only one line of treatment. About 23% of patients are on two lines of treatment is about 17.5% of patients on three lines of treatment.

Now, looking at the patient only on monotherapy, you can see a different distribution. So the dopamine agonist is the highest used one, which is about 34.5% followed by the first generation injectable SRLs with octreotide and lanreotide and then also followed later by the growth hormone receptor antagonist which is Pegvisomant is only 10.5% of patients are using this according to the claim data.

Now, it is a little surprising that the dopamine agonist is one of the main ones which is almost a third of the patients are using this dopamine agonist. Now, looking at persistence of monotherapy and actually you can see that the dopamine agonist does not last long. It lasts about 14.4 months where the injectable SRLs lasts for 20 months versus the Pegvisomant lasts a little more than two years, and about two-third of the patient has some form of increase in the SRL during that trial. And also there's about 45% of the patient needs dose reduction. As I mentioned earlier, one-third of the patient initially with dopamine agonist, but they're the shortest persistence in this study which is quite interesting to know.

You can see the real world experience and how these medications are used in our patient with acromegaly. The guideline actually does not usually recommend dopamine agonist at the first line and they only recommend dopamine agonist in those patients who actually have a mild elevation of IGF-1. But in real life, the data as I said is showing out the difference.

Now, I also like this study which is actually from a UK registry study. We're trying to look at the question whether or not remission matters in terms of survival. So this is again is the UK registry study. They're looking at the first remission. So which was defined here is between the difference between the date of diagnosis and date when the growth hormone is less than two or equal to two microgram per liter followed either by surgery and/or medical therapy. So in this registry, they studied 37 and 50 patients in this registry. So 65% of them achieved remission.

So if you look at the mean time to remission with somatostatin analogs which was 4.5 years and the mean time to remission with dopamine agonist which was longer at 7.3 years, which compared to the somatostatin analogs. The mean survival in those who do achieve remission was 25.5 years. The means survival in those who did not achieve remission was 21.9 years, and they're statistically different.

If you look at the inpatient who achieved remission within one year, so over about the followup 24 years or so, they have 15% mortality rate. In patient who achieve remission after one year, the mortality rate is much higher at 23%. So I think it's an interesting conclusion from the studies. So after adjustment for age, diagnosis, baseline growth hormone, gender, shorter times remission is associated with improved survival. So that pose a very interesting clinical question, should we be very aggressive in trying to put patient in remission either using surgery or medical therapy? So the sooner probably the better in terms of their survival rate over long term.

And then pre-op treatment. So this is not currently recommend by the guidelines because there's a big debate about whether we should pre-treatment before surgery. So this study, the small study looking at try to answer some of the questions. So they actually enrolled 10 patients given neoadjuvant pre-treatment with somatostatin analogs prior to pituitary surgery is a retrospective study. They compare radiographic and long-term biochemical control and also compare to historical data who underwent resection only without pre-treatment.

As you can see that in the group that are treated with neoadjuvant therapy before surgery, there is a 30% reduction in the total volume of the tumor and volume of tumor in the cavernous sinus also shrink by about 48% reduction. If you look at the biochemical remission, they're very actually similar to the historical control, but if you delve into a little deeper to looking at growth total resections based on the Knosp criteria. So Knosp criteria for those who don't know is basically looking at the invasion of the tumor into the cavernous sinus. So the higher the number, the more the invasion.

So if you look at a grade three, so they start with one and all the way to grade four. So four is the highest invasion, the tumor is wrapping around the internal carotid artery. So you can look at the difference. So if it is a grade three Knosp criteria tumor, there is no difference at least in their study. But for a more aggressive tumor, grade four as mentioned earlier said there is the new adjuvant therapy, at least in this most retrospective study seemed to offer some benefit. I think there's some controversy about this, probably at least from this study. Maybe for the most aggressive tumor, the pre-treatment may be helpful but I think more studies are needed to try to answer this question.

Now biomarkers for growth hormone, this is another interesting topic because we all probably face some dilemmas if we are treating our patient with acromegaly. So the things we often see that there is discrepancy between the growth hormone and IGF-1 level. Sometimes you see IGF-1 level high if growth hormone is controlled versus IGF-1 level normal but growth hormone is high. So there's some discrepancy of that. And also there's discrepancy between the growth hormone action because some patients they're very well controlled biochemically but they're not symptomatic control. So we're trying to bagging for a good biomarkers for growth hormone action. So this may shed some light on that.

So this is something called serum soluble alpha klotho. So in some earlier studies that was published in 2021, this group showed the serum concentration of this soluble alpha klotho is elevated in acromegaly patient and then decrease after disease is in control. But the big question that we have is, what is normal, right? So as endocrinology, we're looking at a normal range before we even say is normal, abnormal and we use that data. So this study is trying to salvage a normal range of this molecule.

So this study "890 healthy Caucasian subject to attend the reference range." So they also have IGF-1 level, IGFBP-3 as comparators and also they throw in some other patient with non-functioning pituitary adenoma and prolactinoma and try to see whether there's any differences.

So the main finding is on the left side of the table. You can see total patients, so the average range. They use something called IQR, interquartile range, which means the range for the middle 50% of the data. So 672 picogram per mL is the total range, but there is some difference between male and female subjects. Female subjects tend to have a little higher level of this alpha klotho. And then the non-functioning adenoma patient very similar to control but for some reason interesting note is here the prolactinoma patient have higher level of alpha klotho compared to the control group.

A couple of interesting findings on the study not listed in the table. They actually looking at ... as we know, growth hormone and IGF-1 level, they varies when people age, right? So when you look at the IGF-1, IGFBP-3, they vary by decade. If you only look at this marker of alpha klotho differ only between the younger adults, you're defined as less than 40 years old versus the older one, which is more than 70 years old. And also oral estrogen also reduce alpha klotho as it does with IGF-1, as we all know. And then the alpha klotho also correlates with IGF-1 but not with IGFBP-3. And interestingly as I mentioned

earlier, age, gender and BMI all correlate with IGF-1 level but the alpha klotho concentration showed weaker negative correlation to age and BMI as compared to IGF-1. So this could be potentially a marker for growth hormone action. I think more studying to be done looking at physiology, possibly zoology and how they correlate with disease control and whether or not this molecule is associated with symptoms of the patients. So more to be done.

And then a couple more slides about a disease monitoring. So this group develop a Acro-TIME score and try to include clinical, pathological and immune markers to identify and who are the candidates that can be resistant to first-generation somatostatin receptor ligand, which in those patients most of them will need a second line treatment. So in this study, they enrolled 43 acromegaly patient. So the first line treatment has to be surgery and they also receive post surgical first-generation SRLs and they also have tissue samples for experiment so they can do immunostaining. They look at 18 clinical, pathological and immune features that analyze the possible predictors to the first generation SRLs and the score assigned to each covariate proportion to its beta coefficient. So these are more statistical analysis.

The score interesting range between 18.5 to 24 in those cases responsive to the first generation SRLs versus minus 5.5 to 21.5 in those who were resistant to the first generation SRLs. As you can see on the right side here listed a few of those parameters that I looked at. So the age diagnosis ... so here with the coefficient, so the lower coefficient means more resistance to the first generation, and you can see the age cavernous sinus invasion are assigned a negative factor which makes sense and a Ki 67 more than 1.5, which is coefficient markers. We usually look at pathology of the pituitary tumor, also has a negative marker.

Interesting also laid the somatostatin receptor to a immunostaining and they use a score called volante score is basically scoring system for expression of receptor in the pituitary tumor. So which as you know that first generation somatostatin receptor analogs or somatostatin ligands are targeting mostly the receptor two. So of course the higher which they listed here was actually the highest score in all the scores they assigned to all the different markers. They also looking at CD68 versus CD8 markers with immune markers. They're also looking at residual tumor size. Of course, that's a negative factor here.

So in this study, a score of less than 19 was chosen as a cut point to identify the first generation SRL resistance. A score less than 18, as I said, if the patient has a score less than 19, so there's about 84.6% of chance that the patient will be resistant to the first-generation somatostatin receptor ligand, which is actually quite interesting as we know the first-generation SRLs are usually our first choice to treat patient. Hopefully if the study is confirmed with a bigger population of patient with acromegaly while at least having some scoring system we can identify who may or not responded to. So if they didn't respond, we can switch them to a different therapy quicker and we don't have to wait for long to do on the same therapy knowing that it may not be controlled.

So lastly, I'll talk a little bit about patient reported outcome. So this is a MACRO Registry study. Basically, it's prospective observation cohort study of patient with active acromegaly on medical therapy or eligible for medical therapy, but basically having questionnaires for both the patient and physicians. And so they complete the questionnaire at enrollment every three months after up to three years. And then the parameters were asked during the survey including their demographic features, disease activity, their treatment information including their rating of symptoms, whether they're biochemical control and of course the patient reported outcomes.

Interesting if we look at the data, well-controlled symptoms as reported by patients were associated with significant higher AcroQOL. This is acro quality of life score across all skills and five out six of Acro-TSQ is treatment satisfaction questionnaire with five out six domains have significance. So except the injection site interference and also less impairment in three out four WPAI score, which is work productivity activity improvement questionnaire and except absenteeism.

Now, on the right side you see here listed the biochemically controlled patient and how many of them report symptoms. You can see here the joint pain, more than half of the patient reported a joint pain and also more than 50% of the patient report fatigue. You can see the frequency of symptom the report despite the fact that they're all biochemically controlled. So if you look at this group though, about 73% of patient and 72% of physician report symptoms are well controlled.

Then later on looking at the pairs of physician and patient, meaning that the same patient, their physician have data in terms of their rating for symptomatic control versus the patient rating of symptomatic control. And Geer et al. and Strasburger group also published there. There's some sort of discrepancy between the patient reported outcome versus the physician reported outcome. But I think it's confirmed in this study as well. If you look at the readings, I wanted to look at a diagonal line from the upper left to the lower right. You can see those are the ones that actually are concordant. So the concordance rate is about 60%, but the most concordant rate is on the upper right corner and in the lower left corner about 0.5% patient says well controlled, the physician says not sure and what the well controlled well physician feel like 3% is well controlled where the unsure is about 3%.

So there is definitely some discrepancy between what the physician perception of symptomatic control versus the patient perception of symptomatic control. And as you also at the end of the study looking at all data and overall the memory problem, fatigue and joint pain were the most frequently reported symptoms at baseline even in those biochemically controlled patients that was not reported by their match physician. So there's a lot for us to learn about why there is discordance between the physician reported outcome versus the patient reported outcome.

So in a nutshell, these are the clinical pros we get from the Endo 2023 about acromegaly. Once daily oral paltusotine treatment was well tolerated associated with stable IGF-1 and symptom control relative to that achievable by the injectable SRLs was preferred over injectable therapy. Pasireotide is a well-tolerated long-term treatment with a low discontinuation rate over eight years.

Risk factors for hyperglycemia at baseline including age, baseline A1C and also the status of prediabetes with diabetes and their baseline. And also in those who want to be switched to the oral octreotide, so the baseline IGF-1 level with the injectable SRLs were the only predictor of subsequent response to the oral octreotide capsule. Patient who achieved remission quicker in the UK's registration study showed a slightly better survival rate over time. The soluble alpha klotho may prove to be a valuable biomarker for activity of growth hormone action acromegaly. So more to be seen.

Acro-TIME score which integrated clinical, pathological and immunological data so they have a scoring system. And using those scoring symptom, we may be able to predict the patient response to the first generation SRLs. So for those who have predictor have resistance, maybe we can switch them quicker to the second line therapy. An adequate symptom control and physician-patient agreement on extent of symptomatic control continue to be under-recognized in the field of acromegaly and constitute an unmet need in acromegaly patients. So that's the end of my presentation. Thank you very much for your attention.