National Government Services, Inc.

Moderator: Dr. Ola Awodele

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Dr. Awodele: Uh, usually the way these things work is we have you present, it's for you to make comments on our draft LCD that we have out there.

We listen to your presentation and if we have any questions we ask you and we're also going to be recording this particular presentation so that it can be a part of the official record of the open meeting as if you had presented at the open meeting.

So we do apologize for the change in dates and everything.

Dr. O'Rourke: No, no, that's I actually appreciate you letting me present at a time that's convenient for me. I had clinical issues that I think kept me from the prior weeks.

Dr. Awodele: Great and I think Stephanie is going to advance the slides for me so this is just my background. Before coming to Portland where I've been out for the last five years I was at Wake Forest for 25 years and was a professor of medicine there and ran the fellowship program and I'm currently a chair of the approval committee that runs the American Board of Internal Medicine Rheumatology certifying exam. Next slide.

And I don't really have any conflicts. The only outside work I do is with the ABIM. I'm presenting this morning in relation to an issue that came up in reference to one of my patients that I currently follow, but actually affects two additional patients who have the same diagnosis and I probably anticipate will probably come under the same sort of questions as regards to coverage of IVIG for their underlying condition. Next slide.

So these patients have a condition that has been broadly called immune mediated necrotizing myositis. Like a lot of the newer myositis syndromes, it is a subset of polymyositis that in the literature first was differentiated in about 2011 or 2012. This is a slowly progressive to sub-acute onset inflammatory muscle disease. Who that it's really characterized by its refractory and severe nature over time. It's similar to many inflammatory muscle diseases. It affects primarily, proximal extremity muscle groups in the arms and legs, but can also lead to involvement of other sites of skeletal muscle, including in the upper esophagus, and that's usually manifested by dysphasia symptoms. These patients typically have very high markers of muscle inflammation. Their CK levels are generally quite high and the largest subset of these patients have a specific autoantibody. One that is called anti-HMGCR or HMG-CoA reductase, and the other is an antibody against SRP.

I should point out there is a subset of immune mediated necrotizing myositis that actually is antibody negative, and so these patients don't have to have these antibodies, but the vast majority of them do.

Technically, one makes the diagnosis by muscle biopsy. There's a very characteristic finding as I've listed of this very necrotizing muscle inflammation and muscle

degeneration that is noted. And even though a good proportion of these patients have antibodies to HMG-CoA reductase which is the same enzyme that is inhibited by statin therapy. One does not require prior exposure to the statin drug per se, to get this kind of myositis. One can develop this syndrome even in the absence of any prior statin exposure. And I should also mention that it is very distinct from the toxicities of statin therapy. So in general, statins can cause a host of muscle symptoms. They can cause elevations of CK with no symptoms. They can cause muscle aching with or without elevation of CK. There is a form that is a very toxic myopathy that presents very similar to rhabdomyolysis. What we're talking about, though, in terms of my presentation and the patients affected, is actually a completely different syndrome in which patients get a true autoimmune disease. That, like I mentioned in some patients, can be the byproduct of prior statin drug exposure, but in other patients can occur spontaneously without prior statin therapy. Next slide.

So like a lot of the myositis syndromes, it's very rare. I gave you the global prevalence. If you calculated these numbers to the state of Maine, the prevalence would be anywhere from 26 to 400 patients at any one time. The problem with any rare disease is that it doesn't really afford itself therefore too easy clinical trial evaluation. It's very difficult to get individuals with this syndrome sufficiently in one or more clinical centers in order to do the kind of randomized double blind placebo controlled trial that is really required, generally of an FDA approval. And thus coverage under Medicare for the use of the drug in that specific disease. And thus we are really limited as we are with the majority of the muscle disease syndromes that we see to guidance through reports in the literature of individual patients, small case reports, supplemented by expert consensus. But what I'll just go over with you briefly in the next final slides are really the literature that I tried to summarize. That's been more recent. That supports the use of IVIG in this syndrome. I will note that the FDA has approved IVIG for dermatomyositis. It's really the only FDA approved other diagnosis that I'm aware of in the in the M coding group of the myositis syndromes. Next slide.

So like I mentioned in the remaining slides - these are a combination of a couple of recent case series as well as a couple of recent reviews by international experts. So this study came out this year looking at the role of IVIG in this syndrome. They were able to look back in their own patient database over the prior six years of 20 adult patients and evaluated them by a rigorous set of myositis core set measures. So this was done at the University of Pittsburgh. This is one of the institutions in the United States that has a well-defined, internationally recognized myositis center. And clearly from their evaluation over time and these limited number of patients, they clearly pointed out that the use of IVIG was really the thing that led to significant improvement in these patients; who up until that point really had not responded significantly to the usual sorts of immune suppressing medication options used to treat this disease. Next slide.

This is a recent review in current treatments and in rheumatology. I pulled the line from it that reflects that there are international treatment guidelines out there that have recommended IVIG in this syndrome. They predominantly though come from Europe at this point. This review article noted that the European Neuromuscular Center Working Group did recommend IVIG for individuals, particularly those that have the HMG-CoA reductase antibody. Next slide.

This is a review from Nature Reviews Disease Primary from 2021. This was more of a global overview of the inflammatory myopathies, but did have comments within it; reflective of individual syndromes including immune mediated necrotizing myositis. Noting that at that time, it really was a case report literature basis for which we have used this medication. And clearly noting that it and or rituximab tended to be the medications that do provide the majority of patients the significant degree of improvement that we need to see and need to see relatively rapidly, either with or after the initiation of standard therapy, which in this review reflected case reports of individuals who had been on either methotrexate or azathioprine, which are two of the standard immune suppressing drugs that are used across many myositis syndromes. Next slide.

This is taken from that article, noting from a therapeutic standpoint, yes methotrexate and azathioprine do tend to be first line therapies in combination with high dose steroids, but IVIG can be used along the course of disease either as part of first line therapy or as sort of a rescue medication for individuals who have more refractory disease to standard initial treatment. Next slide.

And I think this might be the last review that I have. Again, this review, now two years old in Nature Reviews Rheumatology summarized again the literature to that data and again made reference to the European Neuromuscular Center guidelines. I will say that I don't have in the slides, but came out online last month is an article from Rheumatology which is a one of the British journals, in which the British Society for Rheumatology came out with their treatment guidelines for the management of this broad group of inflammatory muscle diseases. And in it they do recommend again that IVIG should be considered as treatment of severe and or refractory muscle inflammation. And gave it a grade one recommendation as well. Very similar to the guideline recommendations that I've showed in the slides so far. Next slide.

And I think this might be the last slide I have that references a specific group of patients. This is again a small study, but this is what we have for this disease that is relatively rare. Thirteen patients, well defined, immune mediated necrotizing myositis, evaluated over seven years. And so again, seven years - 13 patients. The prior study I showed you six years, 20 patients. Again, with very rigorous protocols for evaluation, including MRI imaging, noting that it really was IVIG that was the medication that ultimately led to the marked improvement of these patients over time.

So I think that's the last slide I have, and according to the time it looks like we have a enough time for questions. I'd be happy to answer. Or, what I could also do is I can give you some generic comments regarding the patients I currently have for whom I'm requesting IVIG.

I currently have three patients who I follow regularly with this condition, all of whom were initially treated with standard high-dose steroids and either methotrexate or azathioprine. All of whom had less than adequate responses to treatment, following which the initiation of IVIG was the one thing that actually provoked these patients into remission. The most recent patient I can give you an example. I first saw last June of 202. Was placed on methotrexate. Did not do very well over the first month to two as treatment with that and high dose steroids and then IVIG was added, and his CK level subsequently came down from about the 2000 range with an upper norm of about 200. Most recently down to about 142, and it was this patient that prompted this request because his IVIG, which up until that point had been approved, was then denied for subsequent ongoing treatment and over the last couple months now that

I've seen him. While waiting for this committee meeting to try and get it approved for his diagnosis, his CK level has again started to climb. It's near 500. I've had to go up on his methotrexate and transiently treat him with steroids again. And so I mean he, I think more than the other patients that I have really exemplifies how well this medication works for this underlying disease.

Dr. Awodele: So, Dr. O'Rourke you're saying that you have a patient who had prior gotten IVIG approved? I mean not approved but paid basically.

Dr. O'Rourke: Yes.

Dr. Awodele: And recently has not been because of the old LCD? The old LCD is still effective until the new LCD comes up.

Dr. O'Rourke: Well, because I think the issue in regards to this specific patient, it was a question about what their condition should be coded under. And so, I have always coded these patients as M60.9 which is myositis unspecified. Because that's my understanding medically as to how this disease has evolved out of polymyositis, which is under the M codes, not the G codes. So I think, and correct me if I'm wrong in terms of the information you may have received during the meeting when it was scheduled last week or the week prior are local individual at Maine Med Center is not allowing me any longer to code it under M60.9; but states instead it should be coded under one of the G72.xx codes, which I disagree with on medical grounds. Which I feel are first of all, they those are neurology codes to begin with, and second of all the one that I think it was recommended that he be coded under with G72.49, which is other inflammatory and immune myopathies, which includes potentially muscle diseases that could be paraneoplastic can be infectious, et cetera. It's an incredibly broad category of muscle diseases. And I think if the outcome is to approve IVIG under a specific diagnostic code, then I do not think it's appropriate to do so under G72.49 because that is way too broad a code and includes conditions for which IVIG has not shown efficacy, even in the case report literature. Whereas, I had always coded these patients as M,60.9. That was the code under which it actually, I believe was covered for this patient up until recently.

Dr. Awodele: Still covered.

Dr. O'Rourke: Well, not according to the people at our local Medical Center who...

Dr. Awodele: OK, so that's them. So that's what I wanted to point out. Is that up until our new LCD, it is valid to for you to make this presentation and to make this request to have it continue to be right. It is still currently covered with our LCD that is currently in effect, so the issue with getting it out the door and it processing and getting paid is really an in-house issue that you have with your folks.

Dr. O'Rourke: Right. But I was advised that this was my only avenue to ensure coverage for this patient and actually for the other two patients who are under similar constraints.

Dr. Awodele: And I'm going to kind of push back a little bit and say when this new one takes effect, yes, this is your way to ask us to include the diagnosis, which would then have the M60.9 that should we decide to do that to continue to be covered? This push would not make the G72.49 be included because your people feel that that's the correct code; because like you have said it's too broad a code and includes too many other things that are not going to be covered.

That's what I wanted to kind of just bring out to you. That technically, the old or the current/soon to be old LCD covers the condition. That you are discussing right now.

Now that's the first thing I wanted to say. The second thing I wanted to say is that these documents are really for what we call first pass, right? In terms of with the coverage, they help to make sure that things are paid based on what we've reviewed and felt were medically reasonable and necessary on 1st pass, right? If it's denied, there's always the appeals process, which I hope you will avail yourself of for your current patients. You know to kind of get them through the system and we would be able to review with the records and make the appropriate decision, but so I just wanted to this/is different from/there are two separate things going on here. I just wanted to point that out to you and what just brought that to my attention is your statement that it had been paid before.

Dr. O'Rourke: So is the new LCD that is being proposed...would that include immune mediated necrotizing myositis then?

Dr. Awodele: This is the meeting we're having now, right? So you are saying could you please? Or - here's my reasons why I feel that you should continue to pay for this.

Now, a big thing too is when we create the LCD's and we write these policies as you know, it's more of a common things what is usually paid for? What are the you know, it's not really for the exception. A lot of times it's more for the more common and things that in order to process that we would be able to get through the system and have them get paid, uh, because hey, here's what the literature says. And all of that.

So I we appreciate you presenting to us and bringing this up that OK we would like for this to continue to be paid and continue to be in the policy; in the new policy. And here's the reasons why. So we'll take this information, we'll go dig deeper and see how that comes out, which you will be able to see when the material, when it finalizes, and when the policy finalizes and we have an accompanying response to comment article that comes along with the final document. But I just wanted to point out to you that should it even be that we decide to continue this, your claims will probably still continue to be denied, because it certainly will not be [paid] under G72.49.

So I just wanted to let you know that ahead of time because right now your current issue that you have is the code that's being chosen to use as opposed to whether it's actually covered or not.

Dr. O'Rourke: Actually have already have and we're not getting anywhere so.

Dr. Awodele: With the appeals process?

Dr. O'Rourke: Well, at least locally, yes.

Dr. Awodele: Locally?

Dr. O'Rourke: Right, and so the issue we're having is that the patient is being forced to sign an ABN form stating that if it gets denied, he will be responsible for paying the entire cost of IVIG, which is 9 to $10,000 per dose. Something that he cannot afford to take a chance on, should it be denied and he'd be forced to cover the cost as opposed to the drug being approved upfront. But, I understand that this is out of the realm of what your committee is addressing in the context of this issue, yeah?

Dr. Awodele: So I just I just wanted to clarify and I just wanted to...since you brought it up to kind of give you let you know that there's a process. So when I say appeal, I mean the claim being appealed to NGS; not in terms of locally within maybe an appeals process to change the ICD-10 that it's going out with, so that's what I just wanted to clarify to

you to avail yourself of and make sure that they avail themselves of that process; for your patients, so I'm gonna ask if anybody on the anybody else on the call has any questions for Dr. O'Rourke? Or comments?

Dr. Gina Mullin: Hey Dr. O'Rourke, this is Gina Mullin. I do have a question about slide three and I did want to say just thanks for all of your work. I have a few friends that went to Wake Forest for medical school and [it's] a great place that I got a chance to visit. But on slide three you have; about the biopsy. I wanted to see - it's a twofold question where the/what muscle specifically you guys target for this biopsy and #2, if you are highly suspicious that a patient does have IMNM and the biopsy, for some reason is negative or not convincing, what route do you go next? Do you do another biopsy or do you just try and initiate treatment to see if the patient improves and that's it?

Dr. O'Rourke: Yeah, so the biopsy that's chosen is really reflective of what is most symptomatic in that individual patient. I think most biopsies are done in the upper outer thigh in the vastus lateralis because it's usually involved. It's superficial, it's not fraught with any neurovascular bundles that are near to it and can be done as an outpatient. But there are some patients for whom perhaps the proximal lower extremity muscles may not be as severely involved as other proximal muscles like the deltoid or others, and so there really is no one particular site that we always do. Irrespective of the patient, I think the patient tells us essentially through their evaluation where to go. Technically if I don't get an answer on one biopsy, it's always good to biopsy another site because essentially, we are committing individuals with this disease to potentially life long treatment of one kind or another. And I think before you make that step in an individual, you want to be as certain as you can about the diagnosis. So it's not often, but yes, there are patients for whom sometimes we require more than one biopsy to make a diagnosis.

Dr. Gina Mullin: And if that because I'm sure there are some patients who you are concerned have IMNM. If that second biopsy is negative, but they do have still elevated CK plus or minus the autoantibodies. Are you, I guess, where does the management go?

Dr. O'Rourke: Well, so in the absence of the biopsy, which is really the defining thing, because, as I mentioned, the autoantibodies don't necessarily have to be present. And so, if you don't have the characteristic biopsy findings, then those patients are probably treated as polymyositis, and so their initial therapy tends to be high dose steroids; plus, an immune suppressing agent such as methotrexate, mycophenolate or azathioprine. IVIG is used in those patients, but typically not as frequently early in the course of disease other than individuals who present with dysphasia symptoms where it is well known and well accepted across various myositis syndromes to use IVIG early in the course of disease that involves the upper esophagus. And so if I don't have the characteristic muscle biopsy findings, it's hard to otherwise suspect this disease, so to speak, particularly in the absence of an autoantibody, in which case they are therefore treated, and probably appropriately coded as just having polymyositis.

Dr. Gina Mullin: Perfect, thanks so much.

Dr. Awodele: Thanks Dr. Mullen. Does anybody else have any questions? Any last questions for Dr. O'Rourke? OK, so Dr. O'Rourke, I just wanted to thank you very much for taking the time to come.

Dr. O'Rourke: No, I appreciate you having me come on this extra session and for all of you making the time to hear me, I very much appreciate that.

Dr. Awodele: Our pleasure. So basically we have something called a comment period on every draft that we put out. The comment period is the time. It's usually 45 days from when we posted it online, which that means for this particular draft LCD, it started on the 9th of June 2022 and will end on the 23rd of July 2022. So if you could send stuff in in writing. Anything else that you think could help us would be really appreciated. And then we then take all the comments that we get after the comment period ends and we respond to them, we make any adjustments or changes to the draft and then it shows up in the final with a notice period before it becomes effective. And there's also an accompanying response to comment document where we write all the comments we got and what our response is. Whether we adjusted the policy based on those responses or what our own answer is to that comment. So thank you very much and if you could just send those to it's at/it's on....if you go online and look at the draft LCD you'll see at the end the actual e-mail address. I'm going to give you so you don't have to memorize it or write it down, but it's it's called PartBLCDcomments@anthem.com. And if you choose to use snail mail, it's

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Again, this information is at the end of the/is in any of our draft document documents. If you go towards the last pages, you'll be able to see that information. All right, so I thank you very much.

Dr. O'Rourke: Alright, thank you all very much.

Dr. Awodele: Thank you. thanks everyone. Bye bye.

Dr. O'Rourke: Bye bye.

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