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Reviewing the Treatment Landscape for Duchenne Muscular Dystrophy

Dr. Turck:
Duchenne muscular dystrophy, or DMD, is a genetic disorder characterized by the progressive loss of muscle, primarily in young boys. Though there's currently no cure, recent therapeutic advancements are aimed at improving symptoms and patient quality of life.

Welcome to NeuroFrontiers on ReachMD. I'm your host Dr. Charles Turck, and I'm speaking to Dr. Kay Davies, who's Dr Lee's Professor of Anatomy Emeritus at the University of Oxford. Today, we'll be discussing the current treatment landscape for DMD.

Dr. Davies, thanks for joining me today.

Dr. Davies:
You're welcome. Good to meet you.

Dr. Turck:
Well, to start us off, Dr. Davies, would you explain the cause of DMD and what happens in different parts of the body as the condition progresses?

Dr. Davies:
Yes. DMD is caused by the absence of a protein called dystrophin in muscle, and so the first symptoms appear when the boys in their early lives are unable to stand very quickly. They're unable then to go upstairs, and they progressively show this muscle weakness, and they tend to go into a wheelchair in the age group 10 to 12 years of age. The heart is also affected, but that isn't really apparent until later in the disease.

Dr. Turck:
Are there any other symptoms we should be looking for? And what are some diagnostic challenges?

Dr. Davies:
The families usually present to their clinicians between the age of two and five when they have difficulty walking or, as I said, raising themselves from the floor. The diagnostic test is pretty absolute because we can now do DNA tests to demonstrate the absence of the gene coding for the missing protein called dystrophin. Most of these patients, 65 percent of them, have bits of this gene missing, so it's very characteristic and very easy to diagnose now using a DNA test, so you rarely need a muscle biopsy in order to get this diagnosis.

Dr. Turck:
And once the diagnosis is made, what are the primary goals for treatment?

Dr. Davies:
Well, the primary goal is to slow the disease down, first of all, so that the child is able to stay on their feet as long as possible, and that's usually steroid treatment. So for many years it's just been glucocorticoids. There are ones with less side effects that have recently become available. There is something called an HDAC inhibitor, givinostat, which was approved about two weeks ago by the FDA, which actually just suppresses the inflammation in muscle, and again, slows the rate of progression of the disease. So this might keep them ambulant for longer, maybe until they're 16 or 17, but it doesn't have a major impact on the disease.

Dr. Turck:
For those just tuning in, you're listening to NeuroFrontiers on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Kay Davies about the progression and diagnosis of Duchenne muscular dystrophy, or DMD.

So getting back to treatment, Dr. Davies, you had mentioned corticosteroid therapies. Would you still consider them then the cornerstone of treatment? And you had mentioned that some are a little bit more tolerated than others. I'm wondering if you could touch on that a little bit more.

Dr. Davies:
Glucocorticoids are still the standard of care, but vamorolone has recently been approved in the States, and that doesn't have the side effects that corticosteroid does; but givinostat, which is an HDAC inhibitor, just suppresses the inflammation that you get from the regenerating muscle fibers has recently been approved, and that will also slow the progression of the disease because if you decrease the inflammation, then you stop the necrosis; you stop the invasion of connective tissue, which is what's so damaging in the function of the muscle in the early lives of these boys.

The problem with the disease is there's no real cure yet and only treatments that slow down the disease. So there are ways in which you can try and replace dystrophin. You can try and do something called stop codon therapy where there is a mutation that stops the gene before it produces the full-length protein. There's readthroughdrugs, but those only have a minor effect on the progression. And there's exon skipping. And again, theoretically, that should produce a truncated, a smaller protein molecule, that might function in muscle, but they don't work very efficiently. So they slow the progression of the disease, but they don't actually cure the disease.

Dr. Turck:
I was wondering if you could tell us a little bit about which patients are eligible for those different forms of therapy.

Dr. Davies:
Right. So for the stop-codon readthrough, you have to have a single stop-codon mutation, which is only about five percent of patients. For exon skipping, again, it depends which exons that is bits of the gene that are missing, and whether you can skip over them to put the protein back in frame so that you get a shortened but functional protein, and that's applicable to about 13 percent of patients if it's exon 51 skipping, for example. And Sarepta have produced several drugs for skipping exon 45, exon 51, exon 53, and each one of these adds up to about 20 percent of patients overall, but the effect is still only minor. It will slow the progression of the disease. And that's because the exon-skipping oligonucleotides don't target all the muscle and don't target very efficiently. Having said that, there are better exon-skipping drugs within the pipeline currently, so for that, those small percentage of patients, it could be that things will improve dramatically in the next two or three years.

Dr. Turck:
Are there any other advances in gene therapy or any other forms of therapy that we should be aware of and their potential impact on treatment?

Dr. Davies:
Okay, so the big hope is replacing the gene using AAV, adenoviral gene delivery. The problem is the dystrophin gene, which is the one that's missing, is too large to go in a conventional AAV vector. So what they've had to do was shorten that gene, the so-called mini dystrophin gene, and use that to replace the full-length dystrophin gene. The gene therapy is based on a smaller gene, often called

either a micro-dystrophin gene or a mini micro-dystrophin gene, and it's based on a patient I characterized in 1990. The patient that I characterized lived until his early 70s, and he has a distant relative who is currently 59. He's in a wheelchair, but he's still able to get himself out of the wheelchair and into bed, so he's doing very well. In other words, he has a very mild clinical course. So the hope is that by introducing a mini or micro gene based on this patient's dystrophin gene, you might be able to go a long way to curing this disease or alleviating it and translating the very severe Duchenne muscular dystrophy course to a very mild so-called Becker muscular dystrophy course.

Dr. Turck:
What would you say are the next steps needed in our quest to identify effective therapies for DMD?

Dr. Davies:
Well, Sarepta have actually done a clinical trial who have got accelerated approval for one of those micro-dystrophin genes that I was talking about. The problem is that it doesn't work efficiently in all patients, and it's early days yet. We need to be able to understand that. Is it because the virus doesn't stay in the muscle long enough? Is it because the mini gene doesn't work as well as we thought it might? Or is it because the AAV doesn't target enough of the right muscle? I think that will become clear in the next year. There are other companies that are using that micro-gene approach. Pfizer has solid therapeutics that have got different micro-genes. They might work better.

So I think in the near future there's hope that the gene therapy will indeed have a large impact. The problem also, of course, is there's a large price, and gene therapy isn't available, actually, in all clinics. So we are still looking for exon skipping in those patients where it's mostly applicable or trying to get some multi-exon skip, which deals with most of the exon skips and might be applicable to, say, 60 percent of patients instead of 30 percent of patients.

Dr. Turck:
And finally, do you have any other thoughts from a global standpoint on where we are in combating the progression of DMD?

Dr. Davies:
Globally, I think most countries are ready to do exon skipping. We, in my group, and a couple of others now, are trying to increase the levels of a protein that's very closely related to the one that's missing, called utrophin, and we've shown that in the mouse and the dog that if you increase utrophin, you do effectively cure the disease, so maybe globally we could produce a small molecule, which might be able to increase this related protein, which might go some way to treating the disease. So I think it's a combination of therapies; gene therapy, which would be applicable to a small percentage of patients because gene therapy at the moment is not applicable all over the world; exon skipping, which is much more globally applicable; and I think those are the only options. But I think there's hope now for the very first time that sometime in the next five to 10 years we should have an effective treatment for DMD, and therefore, the early diagnosis is very important because the earlier physicians report the patients as having DMD, the earlier they can start on their treatment, and the more effective it's likely to be.

Dr. Turck:
Well, with those considerations in mind, I'd like to thank my guest, Dr. Kay Davies, for sharing her valuable insights on the expanding therapeutic landscape for patients with DMD.

Dr. Davies, it was great speaking with you today.

Dr. Davies:
It's good to speak to you too. Thank you.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit NeuroFrontiers on ReachMD.com, where

you can Be Part of the Knowledge. Thanks for listening.