Transcript Details
This is a transcript of an educational program accessible on the ReachMD network. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/clinicians-roundtable/new-horizons-in-als-insights-on-emerging-treatment-options/14230/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

New Horizons In ALS: Insights on Emerging Treatment Options

Mr. Nacinovich:
Amyotrophic lateral sclerosis, or ALS for short, is a rare neurodegenerative disease that has been challenging to treat, but emerging research may have big impacts for the treatment landscape. What's on the horizon for new treatment options?

Welcome to *Clinician's Roundtable* on ReachMD. I'm your host, Mario Nacinovich, and here with us to share insights on the latest research for ALS is Dr. Walter Koroshetz, who is the Director of the National Institute of Neurological Disorders and Stroke.

Dr. Koroshetz, welcome to the program.

Dr. Koroshetz:
Well, it's a pleasure to be with you, Mario.

Mr. Nacinovich:
Let's start with some background, Dr. Koroshetz. What are the latest clinical testing and developments for ALS? And have there been any notable emerging treatment?

Dr. Koroshetz:
Well, I'm sure everyone listening knows that ALS is a really tragic illness, that it leads to progressive paralysis, average time to death from diagnosis probably around three years or so, so it's been really tough to try and develop highly effective treatments for this disease. There have been, however, a number of agents that have shown some mild to moderate benefit approved by the FDA and heavily used in the patient community, but we're still waiting for the discoveries that can be turned into the kind of high effect size therapies that could stop this illness from causing, you know, its fatal consequences, and we haven't really gotten there yet.

There are a couple of interesting advances that have occurred, I'd say primarily out of the genetic forms of ALS. There are genetic forms that make up maybe 15 percent of ALS cases, and this has given scientists the ability to kind of get into the cell and understand what these mutations do and develop targets for new therapies. And a number of the genetic forms of ALS are now in clinical trials of genomic therapies, and so everyone is hopeful that these might lead to a real change in the course of that illness.

Mr. Nacinovich:
Now, in June 2022, the FDA unveiled a five-year strategy in its action plan for rare neurodegenerative diseases. Can you tell us what the plan details for ALS and what we need to know about the current ALS science strategy?

Dr. Koroshetz:
Well, I couldn't talk to the FDA strategy, but I can talk to the NIH strategy.

And the strategic plan looked at a whole host of areas of research that are thought to be important. First and foremost is to try and understand the disease. I talked a little bit about the genetic forms of the disease, but 85 percent of the people have the nongenetic form. So tremendous need to understand what causes ALS in people who don't inherit these mutations. There has been some progress in that some of the findings from the genetic forms are also seen, what we call the sporadic forms, so some of the targets that are coming out of the genetic forms may actually, in fact, inform treatments of the more common condition.

I think there's a big need to bring data together. So there's NINDS funds, over $100 million, in ALS research. It's given in individual grants, and there's thought to be some efficiencies, and we can bring that data together and coalesce the community more. And that we can actually do with the FDA because the ACT for ALS bill instructs the NIH and the FDA to build a public-private partnership. So that, I

© 2022 ReachMD

think, came out of the strategic plan loud and clear, the importance of that. There's also a component of the plan that focuses on the caregivers and how best to care for persons with ALS. So there are, you know, devices that could be developed to allow communication skills once someone loses the ability to speak or mobilization once one cannot walk anymore. And then there was a discussion of public-private partnerships, bringing in the industry, the academics, and the people who suffer with the disease, so in our strategic plan we actually had patients involved and that was very instructive.

Mr. Nacinovich:
So, if we look at the multistakeholder infrastructure working to accelerate possible therapies, can you tell us a little bit more about this Critical Path Institute and the Critical Path for Rare Neurodegenerative Diseases, or CP-RND for short?

Dr. Koroshetz:
Sure. So as I mentioned, the ACT for ALS bill instructs the FDA and NIH to set up a public-private partnership, and the FDA has a mechanism to do that through what's called the C-Path Institute. And C-Path also has generated a data portal to bring data in from all disparate sources, including industry trials, academic trials, natural history studies.

Mr. Nacinovich:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Mario Nacinovich, and I'm speaking with Dr. Walter Koroshetz about amyotrophic lateral sclerosis, or ALS for short.

Now, Dr. Koroshetz, can you tell us a little bit about the role the NIH plays in working together in development of data analytics with the FDA?

Dr. Koroshetz:
Sure, Mario. So the ACT for ALS bill instructs, as I mentioned, the FDA and NIH to set up a public-private partnership, and through the C-Path Institute, the expectation is that we'll be bringing data in from all different sources into their data portal for analytic, investigation mining the data and working to develop better outcome measures from this data, for instance.

Mr. Nacinovich:
So, recently, you mentioned that experts and key stakeholders convened for a planning workshop specific to ALS. What else can you tell us about specifically what NIH is doing in terms of its strategic planning activities for ALS research?

Dr. Koroshetz:
So, yeah, it's interesting that planning workshop was really the culmination of about a year's worth of work in which we brought in experts from academia and industry and patients, and they worked in different groups over the year coming up with a set of recommendations that then were presented in a public manner. And now the process is open for public comment, and then those public comments will then inform revisions, and the final version will come to the NINDS Council for their review in the first week in February 2023. But importantly, what we heard from this workshop is that there is what is termed the ALS clock, which is people who have ALS have limited time, and also people who have these genetic mutations that will eventually develop ALS, they have limited time, and so the urgency to get at the bottom of ALS and try and develop more effective treatments cannot be overstated. So, the plan is, as I mentioned, we're going to start, you know, as soon as possible to try and make improvements in our funding of ALS research.

Mr. Nacinovich:
You had Tweeted earlier this year, as directed by the accelerating Access to Critical Therapies for the ALS Act, that part of the role for NIH was to also accelerate and expand access to investigational treatments. Can you talk a little bit about how the NIH is helping to implement that with these partnerships, and independent of those partnerships?

Dr. Koroshetz:
Sure thing, Mario. So, yeah, the ACT for ALS bill instructed the NIH to fund research under what's called expanded access. Expanded access is a designation that is given by the FDA to companies so that they can make their drugs available to people who are not in clinical trials. In the bill it asks NIH to fund research using expanded access. It's limited to drugs or treatments coming out from what are called small businesses, and we had a solicitation for grants, and we announced an award to a company and a group to study what's called a drug called Trehalose for ALS. And in this expanded access there was not a control group, so you're looking at treating people who are not eligible for clinical trials or who finished up a clinical trial, and they would be treated over time particularly to look at biomarkers and see how biomarkers of ALS might be influenced by the treatment.

Mr. Nacinovich:
And then, and then there's another recent, company that has approval for a product for the treatment of ALS. That's a product called Exservan. And this product was actually designated for orphan drug designation in January 2018, and that is the generic, or chemical name is riluzole, R-I-L-U-Z-O-L-E, and it received early action from FDA. Can you tell us a little bit about Exservan drug.

© 2022 ReachMD

Dr. Koroshetz:
Well, so riluzole was the first drug approved, and that is a drug that affects sodium channel activation, thought to maybe quiet the nerves, decrease their demand for energy. The more recent drug, the Amylyx drug, it's not entirely clear exactly how it works. It has some effects on improving metabolism in some hands or decreasing or improving what's called autophagy, which is the ability of the cells to get rid of abnormal proteins, and in ALS the signature feature is the aggregate of a protein called TDP-43, so some think that improving metabolism of that protein may be helpful in ALS.

Mr. Nacinovich:
And we certainly know that any time we've got a new tool to slow the progression of this disease that represents a very important milestone in terms of how we battle ALS.

Dr. Koroshetz:
Yes.

Mr. Nacinovich:
As we look to the future of what may happen, are there any initiatives in the works to help accelerate possible therapies for ALS, perhaps things like the HEALEY platform and other opportunities in those collaborations?

Dr. Koroshetz:
Yeah, Mario. Well, I think that at this point in time people are looking at the genetic forms of ALS and genomic therapies so, C9orf72 is a mutation that causes ALS and also frontotemporal dementia, and so it's thought to be, you know, still a little controversial, but it's thought that it may be due to a toxic effect of the mutant, and so using antisense oligonucleotides people are trying to suppress the production of this protein in people who have the mutation, and so there's a lot of hope that this will work. It should work if you can shut off the toxic protein.

Still a couple of assumptions that, you know, that there's not a problem with not enough of the normal protein in these folks. Also, shutting off these proteins using antisense, it's a fairly new technology. It was very successful in spinal muscular atrophy, but it was still working out how to deliver it to the adult spinal cord and motor system and how to do it without any toxicity. So I think those genetic treatments are what look most hopeful now.

As I mentioned, TDP-43 is a protein that aggregates in many of the genetic forms and also in all of the sporadic forms, and that has been tied to a problem, a general problem in splicing of RNA, which would upset a whole bunch of different proteins in the cell, and so treatments that would correct the splicing defect, when TDP-43 is not as active as it should be in the nucleus, that is another avenue that I think should be pursued, not only in the genetic forms but also in the sporadic forms.

Mr. Nacinovich:
Well, with these updates in mind as well as a look towards the future, I want to thank my guest, Dr. Walter Koroshetz, for joining me to share the latest research on ALS as well as the latest multistakeholder collaborations.

Dr. Koroshetz, it was a pleasure speaking with you today.

Dr. Koroshetz:
Well, same here, Mario, and thanks for having me on.

Mr. Nacinovich:
I'm Mario Nacinovich. To access this and other episodes in our series, visit ReachMD.com/CliniciansRoundtable where you can be Part of the Knowledge. Thanks for listening.

© 2022 ReachMD