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AMERICAN ACADEMY OF NEUROLOGY 67TH ANNUAL MEETING

Progress coming in amyotrophic lateral sclerosis, but rigorous studies needed

By Marie Powers, News Editor

The community of individuals living with amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, has endured many false hopes for promising therapies and is still waiting for the first disease-modifying drug. Nevertheless, "we have made huge progress in the last decade in ALS," Merit Cudkowicz, professor of neurology at Harvard Medical School and chief of the neurology service and director of the MDA ALS Clinic at Massachusetts General Hospital, told participants in an integrated neuroscience session on ALS at the American Academy of Neurology (AAN) 67th

See AAN, page 3

IN THIS ISSUE

AAN

Continued from page 1

annual meeting.

Researchers in the field have developed new ideas about what causes the disease and what pathways can be targeted for therapeutic approaches, and people with ALS are living longer, with an improved quality of life, Cudkowicz said. Two drugs are approved in the U.S. targeting symptomatic treatment. Rilutek (riluzole, Sanofi SA), which has been on the market for two decades, is designed to block glutamatergic neurotransmission in the central nervous system and prevent apoptosis of the motor neuron, although the beneficial effects are modest, typically prolonging life of an individual with ALS by only a few months. Nuedexta (dextromethorphan hydrobromide and quinidine sulfate, Avanir Pharmaceuticals Inc.), approved in 2010, is approved to treat pseudobulbar affect. (See *BioWorld Today*, Dec. 13, 1995, and Nov. 2, 2010.)

Those drugs are just the tip of the spear, with nearly two dozen others following behind. Among the candidates Cudkowicz cited were Gilenya (fingolimod, Novartis AG), approved to treat multiple sclerosis, the epilepsy drug retigabine (Potiga/Trobalt, Valeant Pharmaceuticals International Inc./Glaxosmithkline plc), and Actemra (tocilizumab, Genentech/Roche AG), approved to treat rheumatoid arthritis. London-based Glaxosmithkline also is advancing ozanezumab, an immunomodulator now in in a phase II program, and Neuraltus Pharmaceuticals Inc., of Palo Alto, Calif., earlier this week reported the publication of phase II data showing positive trends in its candidate, NP001, for slowing ALS disease progression.

Also on the list was Nurown, from Brainstorm Cell Therapeutics Inc., of Hackensack, N.J., which disclosed data this week that included a piece-wise linear regression analysis of ALS patients who received the bone marrow-derived neurotrophic factor-producing mesenchymal stem cells in a phase IIa study and a prior phase I/II study. The data suggested a statistically significant improvement in the estimated rate of decline in forced vital capacity and a nearly significant improvement in the rate of ALS Functional Rating Score-Revised decline at six months post-treatment.

Benjamin Brooks, medical director, at Carolinas Neuromuscular/ALS-MDA Center and professor of neurology at the University of Wisconsin School of Medicine and Public Health, also presented detailed safety data during the ALS session from an ongoing phase II study of the Medicinova Inc. candidate, ibudilast (MN-166). The La Jolla, Calif.-based company reported this week that ibudilast raised no safety or tolerability concerns compared with placebo after three months of treatment, and the study is continuing as planned.

Cudkowicz admitted that the list of drug prospects is growing faster than her ability to track them. Still, "we're really just at the beginning of learning" how to help ALS patients, she acknowledged.

Like many degenerative neurological diseases, the ALS space has been noteworthy for spectacular failures. In recent years, they included lead compound olesoxime from French biotech Trophos AS – a company acquired earlier this year by Roche AG, of Basel Switzerland – and dexpramipexole, developed by Cambridge, Mass.-based Biogen Inc. in partnership with Knopp Biosciences LLC, of Pittsburgh. (See *BioWorld Today*, Dec. 14, 2011, and Jan. 4, 2013.)

Another that was on the endangered list, tirasemtiv (formerly CK-2017357), a fast skeletal muscle troponin activator from Cytokinetics Inc., of South San Francisco, was given a second chance after a phase IIb failure with a reconfigured phase III trial that impressed analysts with a solid design. (See *BioWorld Today*, April 28, 2014, and Feb. 17, 2015.)

Studying the effect of drugs in ALS remains a tricky business, Cudkowicz said, due to the late stage of many patients at diagnosis, the enormous heterogeneity of the disease and the dearth of validated biomarkers. Those stumbling blocks make study design a challenge – especially studies that are powered sufficiently to predict success in pivotal trials.

Because of the tremendous clinical variability in ALS, "we can't predict efficacy in small studies" that enroll a limited number of patients, Cudkowicz cautioned, because "we don't know if there is also biological variability."

Small, open-label phase II studies may enroll a disproportionate number of slow ALS progressors, which could cause them to make unsubstantiated efficacy claims, she suggested. Others might enroll disproportionate numbers of quick progressors, which could prompt them to mistakenly conclude that the study drug has no effect. Both extremes hurt the ALS field, according to Cudkowicz.

"If we put too much faith in such studies, we might be misled," she said.

'SPEND MORE TIME IN PHASE II'

Although ALS researchers are improving the design of early stage studies as more is learned about potential targets, Cudkowicz suggested that "one lesson for field is to spend more time in phase II," where researchers can take the time to select the appropriate dose and target.

Early trial design in ALS should focus on the intervention and restrict the lessons learned to the targeted biological action, tolerability and the relationship to dosage, she advised. Thoughtful trial design should address whether the study drug reaches the targeted tissue at a sufficient concentration and in a biologically active form. These studies also should inform whether the treatment acts as intended biologically, influences downstream biology or pharmacology and, if so, at what dosage and toxicity level, she added.

That's precisely the beef the FDA appears to have with GM604, an AKT protein kinase stimulator from Genervon Biopharmaceuticals LLC that was another drug on the list of

See AAN, page 11

AAN

Continued from page 3

prospects cited by Cudkowicz. The Pasadena, Calif.-based company approached the agency to request accelerated approval for GM604 on the basis of a randomized, double-blind, placebo-controlled phase IIa trial that enrolled 12 patients with ALS.

The company presented data in April 2014 showing that 10 weeks following completion of dosing without further treatment, clinical measurements of ALS disease progression remained unchanged from baseline in two of eight treated patients, but the rates of degradation in clinical measures slowed in the other six. Genervon subsequently reported additional details, including publication of findings in January that showed improvements from baseline to week 12 in clinical observations after a six-dose treatment of GM-604, including clearer articulation in a patient's speech video and swallow volume compared to baseline.

Although the findings appeared largely observational, Genervon issued a press release last month outlining its regulatory approach and reiterating the findings, which it called statistically significant. The company emphasized the urgency of gaining accelerated approval, noting in its release, "even though the FDA has promised to help Genervon expedite the approval process for a phase III trial, it would still take at least three years for GM604 to reach [new drug application]. This means the majority of this generation of ALS patients would not survive to try GM604."

Last Friday the FDA released a public statement on ALS that called on Genervon "to release all the data from their recently completed trial in order to allow a more informed discussion of the trial findings among ALS stakeholders. Such a release should include the pre-specified clinical outcome measures as assessed by change from baseline observations that were taken just prior to randomization to drug or placebo."

Genervon officials did not attend the AAN and declined additional comment on the matter beyond citing their press releases and a link to the scientific rational and trial data on the company's website.

'WE HAVE TO STAND UP FOR PATIENTS'

Cudkowicz also steered clear of the controversy in her presentation. But prominent ALS researcher Stanley Appel, chairman of neurology at Houston Methodist Hospital and director of the Houston Methodist Neurological Institute and the hospital's MDA/ALS Clinic, echoed many in the ALS community by siding with the FDA.

"Everyone's hanging by their thumbs with this issue," Appel told *BioWorld Today*. "The company is pushing this on Capitol Hill and everywhere else, and there are no data. The FDA has made a logical request: 'Show us the data.'"

A 12-week study with findings in eight patients isn't sufficient to draw conclusions about the efficacy or even the safety of an ALS drug, Appel maintained.

"I fully understand the sense of urgency," he said. "I deal with this every week with our patients. They want access to everything."

But drug companies targeting ALS must meet the same standards as those pursuing therapies in larger indications, despite the challenges outlined by Cudkowicz, Appel maintained, charging that failure to do so could cause physical, financial and/or emotional harm to patients and their families.

"We've been through this so often in ALS," Appel said, citing the laundry list of failures in the space, including some drug candidates that caused more harm to patients than placebo. "At some point, we have to stand up for patients and protect their interests."

In some ways, efforts to treat ALS effectively mirror the rapid evolution of personalized medicine, in which "it is quite clear that dramatic advances have been made in determining mutant genes, and we are learning how we can deal with these individual genes" by down-regulating them, Appel said. "This is very, very exciting."

But the challenge for the scientific community is that multiple genes implicated in ALS can produce the same clinical phenomena, while a single gene can produce multiple clinical manifestations.

"We're getting more evidence that the process is not cell autonomous, but non-cell autonomous," he said, with mutated genes altering the rate at which motor neurons are damaged but not necessarily the mechanics of that process.

For drug development in ALS, that may mean a sharper focus on targeting what's already known about degeneration of the motor neurons, such as down-regulating mutant superoxide dismutase, or SOD, according to Appel. Therapies to target this gene using antisense oligonucleotides or viral vectors with RNAi are on the front burner. (See *BioWorld Insight*, Oct. 20, 2014.)

Efforts to "reprogram" the immune system and tamp down ALS also need more attention, according to Appel, who acknowledged his bias for pursuing this approach rather than seeking to find additional genes of interest.

"I'm all in favor of further genetic exploration," he said. "But it's now been more than 20 years since we knew that mutant SOD causes ALS, and there is not a single therapy for patients. If we couldn't develop a therapy targeting a common gene like SOD, how are we going to target all of these other genes?"

In other AAN news:

Acorda Therapeutics Inc., of Ardsley, N.Y., presented data from a phase I trial of rHIgM22, its remyelinating antibody in development to treat multiple sclerosis (MS), showing the candidate was well tolerated in each of five tested doses and no serious adverse events occurred at any dose level. In its poster presentation, the company also reported that rHIgM22 was detected in cerebrospinal fluid, indicating the drug's access to

See AAN, page 12

AAN

Continued from page 11

the central nervous system. The placebo-controlled, single-dose, escalating study in 72 patients with clinically stable MS was designed to explore dose tolerability for six months following treatment. Acorda plans to advance the drug next into a study in MS patients experiencing acute relapses. On Wednesday, the company's shares (NASDAQ:ACOR) fell $1.33 to close at $33.34. (See *BioWorld Today*, April 21, 2015.)