The “gold standard” for tracking ALS progression in clinical trials is the ALS Functional Rating Scale (ALSFRS), which, as its name implies, focuses on changes in functional activities, such as mobility, feeding, dressing, etc. But in a recent webinar, Ammar Al-Chalabi, M.D., made the case for the benefits of a different rating system, one tied to clinically relevant stages in disease progression, which also reflects the need for interventions and prognosis. A staging system he has developed “corresponds to what we expect to see in the disease; it allows mapping of clinical decisions, and corresponds to functional decline,” he said. Dr. Al-Chalabi is Professor of Neurology and Complex Disease Genetics, and Director of King’s MND Care and Research Centre at King’s College in London.

Staging is widely used in other diseases that progress, especially cancer, Dr. Al-Chalabi noted. There are several staging systems in the development phase of ALS, including Dr. Al-Chalabi’s. His system is clinically based, but reflects ideas of disease pathophysiology, especially the idea that the ALS disease process is self-perpetuating and spreading. ALS begins, he proposes, because of a combination of genetic and environmental factors that may differ among different people. The risk burden from these factors accumulates over time, until the threshold is crossed that incites the disease. “Once you reach the threshold, a self-perpetuating process begins,” he said, to spread the disease through the central nervous system.

The site of onset and pattern of spread help determine prognosis, although it is not yet possible to give more than the broadest predictions in any individual person. Those with bulbar onset which affects swallowing muscles, progress fastest, while those with the “flail leg” form, affecting the muscles of the lower extremities, typically progress slowest.

But for virtually all people with ALS, the disease progresses in broadly similar fashion, which Dr. Al-Chalabi characterized into 5 stages:

Stage 1. Involvement of the first anatomic region (e.g., limb or bulbar region)
Stage 2. Involvement of the second anatomic region (e.g., second limb, etc.)
Stage 3. Involvement of the third anatomic region
Stage 4. Need for interventions. Stage 4A: gastrostomy tube; Stage 4B: non-invasive ventilation
Stage 5. Death

Diagnosis typically occurs in Stage 2, he noted, meaning that clinical trial enrollment is usually delayed until later in Stage 3. Those enrolled in trials typically must continue to have a minimum level of function as defined by the ALSFRS, meaning those who progress rapidly tend
to drop out, leaving those who progress more slowly in the trial. “Differing progression rates are a problem for clinical trials,” he noted.

Staging allows more conscious and rational planning of care. In Stage 1, the person with ALS is still typically looking for a diagnosis. In Stage 2, shortly after diagnosis, speech therapy and other forms of support may be considered. Stage 3 is usually the time for discussion and planning for the interventions that are needed in Stage 4, and once Stage 4 is reached, end-of-life planning is usually considered. “Staging can help the health care professional know what to prioritize through the course of the disease,” Dr. Al-Chalabi said. The timing of stages is variable, but with the exception of Stage 1, which typically lasts about 18 months, the duration of the others is approximately 5 to 6 months.

The paper describing the system was published in 2012 and is available in full for free at http://brain.oxfordjournals.org/content/early/2012/01/17/brain.awr351.full.

“The ideal thing would be to combine biomarkers, or biological markers of disease progression, with staging.” Multiple groups are working on developing such biomarkers.

“This is clearly going to be an evolving field,” said ALS Association Chief Scientist Lucie Bruijn, Ph.D. “It is very exciting to see this development,” with the potential for better design of clinical trials and patient care.

To view the entire presentation, visit https://alsa.webex.com/alsa/ldr.php?AT=pb&SP=MC&rID=67860102&rKey=cb7850eca78f88d8