Understanding ALS Treatment Trials – Part 2

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Introduction
In Part 1 of this series, published in the Summer 2009 newsletter, we explored the concepts of drugs approved by the Food and Drug Administration (FDA) for particular disorders vs. those approved for one disorder and being used for another (off-label use) vs. experimental compounds, and we discussed the design of phases I, II, and III of treatment trials. In this second and final part of our series, my goal is to describe more specifically the clinical trial experience, clarify the need for placebos and controlled trials, and provide some guidelines to help individuals with ALS determine whether enrollment in a treatment trial is appropriate for them.

The Clinical Trial Experience
Patients enrolled in clinical trials have a much different experience than those for whom medication is prescribed by their physician for an FDA-approved indication or those for whom their physician prescribes a drug off-label. All clinical trials are reviewed and approved by the Institutional Review Board (IRB) of the medical center at which the study is being conducted, in order to ensure that the potential benefits justify the known risks. The IRB consists of a group of medical professionals and non-medical personnel whose responsibility it is to review the study being proposed and to recommend any changes needed to ensure the safety of participants. Once the study begins, all participants must provide formal consent via an informed consent document which explains the study, its risks, and its benefits in detail. The patient and the investigators (usually a physician and researchers) are bound by a formal protocol which provides strict rules that must be followed with regard to dose of the drug being tested, tests which will be done to monitor efficacy and side effects, frequency of visits, and all other conditions of the study. Safety of participants is further assured by a data safety monitoring board, a group of independent physicians or scientists who review results of the study periodically to determine whether it should be allowed to continue. Patients are permitted to withdraw at any time, of course.

The Concept of Placebos and Controlled Trials
A placebo is an inactive compound. The use of placebos in medicine has been the subject of much scientific and ethical discussion. It was found in a 1955 study that 35% of subjects given placebo exhibited a response, with the response rate in individual trials ranging from 15% to 58%. This formed the basis for subsequent trial designs which have assigned some patients to receive placebo and others to receive active drug. Subjects in these trials are randomly assigned to one or the other, and neither they nor their physician

are aware which of the two they are receiving. These studies are termed randomized, blinded, controlled trials. ALS trials are not entirely based on placebo, because patients are permitted to continue taking riluzole. Thus, ALS controlled trials usually involve the comparison of patients who are taking riluzole plus placebo to those taking riluzole plus the compound being tested.

Patients with ALS frequently express frustration with placebo-controlled trials that are used to assess the efficacy of proposed new treatments. If the disease is uniformly fatal, why not treat all patients with active medication? In a similar manner, physicians may at times become frustrated by the necessity of randomizing some patients to placebo in clinical trials, because they want to be able to offer treatments that are beneficial. In light of this, are placebo controls necessary? Most scientists and physicians believe they are, at least for the current generation of proposed ALS treatments. If treatments being investigated for ALS were expected to result in benefits large enough to be unambiguous, such as improving strength or completely halting any worsening, and if risks were low, then placebo controls would be unnecessary, because the effects would be obvious when compared to the natural history of the disease, and side effects would be minimal. In contrast, treatments under investigation in humans at this time are aimed at slowing ALS progression. Because the disease has an extremely variable presentation and course, the efficacy of such treatments cannot be determined without a control group. Patients in the control group are assigned to placebo, or riluzole plus placebo. The most frequently discussed alternatives to placebo controls are historical controls. Historical controls may consist of data about the natural course of the disease in large numbers of patients gathered over time, or may be determined by designing a trial with a pretreatment phase followed by a treatment phase, permitting patients to act as their own controls. There are arguments both for and against the use of such natural history controls, but the concept is still controversial, and for phase III and many phase II trials, patients should expect randomization to drug or placebo.

Is a Treatment Trial Right for Me?

Treatment trials are not for everyone. The entry criteria for trials are usually quite rigid, and may exclude patients whose breathing is too weak, or whose EMG or clinical findings do not fit into a specific pattern, or whose course is so slowly progressive as to make it impossible to determine whether the drug is working, or who have other diseases or conditions which would prevent them from safely receiving the drug under study. If patients meet entry criteria, then the decision as to whether they should choose to enroll in a clinical treatment trial involves balancing many factors. Individuals must be comfortable with the uncertain efficacy of the drug being tested (it could have no effect, make them better, or make them worse), the possibility of unexpected side effects, the need to travel for visits on a rigidly scheduled basis, the lack of flexibility with regard to dosage adjustment, and the possibility that they will be given placebo rather than active drug. Individuals wishing new treatments must weigh all these factors and make a decision they are comfortable with, because these trials often last for many months.