Understanding ALS Treatment Trials – Part 1

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Introduction

One of the most frequent questions I'm asked is whether there are any new treatments available for ALS. Of course, this is precisely what our patients should be asking, because the ultimate purpose of all the research being done in ALS is to develop effective treatments through a better understanding of the disease. To better judge treatment options, including trials of new compounds, knowledge of some basic terminology and concepts is useful. This will help to avoid disappointments by patients and misunderstandings between patients and their physicians. In this first part of our 2-part series, we explore the concepts approved vs. non-approved drugs, and explain the basic design of clinical trials.

Approved vs. Non-Approved Drugs

Medications given for conditions such as ALS may be of 3 principal types: 1) compounds approved by the Food And Drug Administration (FDA) which are prescribed for an approved use; 2) compounds approved by the FDA which are prescribed for a use different from that for which they have been approved ("off-label" use); 3) compounds considered investigational by the FDA.

The first category of medication above is the one with which people are most familiar. Prescribing an antibiotic for bronchitis or an analgesic for pain are both examples of this. The only medication for ALS which falls into this category is riluzole (brand name Rilutek), which has been demonstrated to prolong lifespan by an average of 2-3 months in individuals with ALS. A physician can simply write a prescription and give it to the patient if both the physician and patient agree that it would be a useful treatment. Insurance usually will cover their portion of the cost.

Category 2 includes medications which have been shown to be effective in animal models of ALS, or have shown possible efficacy in small clinical trials, but which have not yet been proven to be effective in larger ALS trials. Lithium and ceftriaxone fall into this category with regard to their use for ALS. In the past, minocycline and topiramate, when prescribed for ALS, were in this category. Physicians can prescribe these medications to patients with ALS if they wish, because it is legal for physicians to prescribe medications for uses other than those for which the medication is FDA-approved. However, the physician and patient must both realize that the use of such

medications in ALS is unproven, and that ultimately the medications may be shown not to change the course of ALS, or that they may even worsen ALS (as was the case with minocycline). Also, the physician and patient must both feel comfortable that the potential side effects of the medication do not outweigh the potential benefits. Thus, most ALS neurologists are reluctant to prescribe large intravenous doses of the antibiotic ceftriaxone for ALS, but often will prescribe lithium because of the lower potential for side effects. Medications in category 2 often are available through clinical treatment trials as well (see below).

Medications in category 3 are available only through experimental treatment trials. It is not known whether they are effective for ALS or any other disorder. The Knopp trial of KNS-760704 and the Arimoclomol trial both involved compounds of this type.

Clinical Trials

Clinical treatment trials are the mechanism whereby medications are formally assessed for safety and efficacy. They may involve medications in category 2 or 3 above. There are several phases to clinical treatment trials.

Phase I trials are usually conducted in small numbers of healthy volunteers, but they may also be conducted in patients. These are the first types of studies of a promising new treatment conducted in humans, and it is important for participants in such studies to understand that the purpose is to assess safety and tolerability, but not to determine whether the drug is effective. The drug may have a positive effect, but this phase of a study will have too small a number of participants to determine efficacy in a definitive manner. Patients are trailblazers, and there may be no personal benefit from participation in the trial, although knowledge will be gained and others ultimately may benefit. The maximally tolerated dose is identified, and unless unacceptable toxicity is found, the drug continues to phase II trials.

Phase II trials include larger numbers of participants and are conducted on patients rather than healthy volunteers. The purpose of these trials is to obtain additional safety data as well as preliminary data on efficacy. However, these studies do not enroll large enough numbers of individuals to provide definitive evidence of efficacy. Usually, this phase is controlled, meaning that some patients receive the drug (usually in varying doses) and some receive placebo (an inactive compound), in order to compare the course of the disease in individuals in the two groups. Our recent trials of Arimoclomol and of Knopp KNS-760704 have been phase II trials. If the phase II trials indicate that the drug may be effective, and if the level of toxicity is acceptable, the drug advances to phase III trials.

Phase III trials involve large numbers of patients with the disease. They are designed to definitively assess effectiveness, usually by comparing patients receiving the drug to those receiving placebo. Our current trial of Ceftriaxone is a phase III study.

What Next?

In Part 2 of this series, we will describe the experience of patients enrolled in clinical trials, with specific attention to how this differs from taking a medication prescribed by a physician and distributed by a commercial pharmacy. We will also explore the concepts of placebos, controlled trials, and randomization in an attempt to help individuals with ALS understand how to determine whether involvement in a clinical treatment trial is right for them.