

Muscular Dystrophy Association Motor Neuron Disease Clinic

At
The University of Utah
Department of Neurology

DRUG TREATMENT FOR ALS

Patients are most concerned about what drugs are available that can change the progression of weakness in ALS. Unfortunately, at this time, there is no drug that will make a patient stronger or stop the progression of ALS. There is one drug that has been shown to affect the course of ALS and is discussed later in this handout.

There are major research efforts to find such drugs. This handout discusses the different types of drug trials that are conducted for ALS and the challenges of conducting trials for a disorder such as ALS. This will help you to understand more about the one drug that has been found to be effective for ALS and what to expect when taking it.

There are many symptoms that can occur with ALS. We do have effective drugs to manage many of these symptoms. We have prepared separate handouts on a number of symptoms and their management.

Challenges in Conducting Drug Trials in ALS

ALS is a progressive disorder, but it is difficult to determine what is the best method to measure and follow progression. There are several choices. (1) Muscle strength is an obvious choice. However, early in the course only some muscles are weak, while others are strong. Usually multiple muscles are tested, and a combined measure of strength is used. (2) Breathing muscle strength can also be tested. This is called forced vital capacity (FVC). However, FVC values tend to fall late in the course of ALS, and therefore are not a helpful measure to follow early in the course. (3) Questions about daily function can be asked and a score generated. This is called the ALS Functional Rating Scale (ALSFRS). (4) Finally, since ALS progresses to shorten one's life, survival can be used. Survival is a common measure in cancer drug trials.

No matter what measure is selected, there is marked variability in rates of progression among ALS patients. Some people have rapid progression, some very slow progression, and most have a rate of progression somewhere in between. It is not known why rates of progression vary and we are unable to predict how fast a patient will progress.

In testing drugs for ALS, it is important to understand that a successful drug cannot restore strength that has been lost, because once a nerve cell dies it cannot be replaced. It is hoped in the future that strength can be regained, but for now, a successful drug would slow the rate of progression of weakness. With such variable rates of progression, it is very challenging to detect a modest effect of a drug

Importance of Statistics in Drug Trials

The purpose of statistics is to help determine if something happens by chance alone or due to the drug. Because of the different rates of natural progression in ALS, drug trials involve large numbers of patients. This is to average out the effect of very rapid and very slow rates of progression. Drug trials compare one group of patients to another,

for example, one group taking a placebo or inactive drug compared to another group taking the study drug.

Statistics help determine if a slowing in the rate of progression between two groups is likely due to the drug or just that one group happened to naturally progress more slowly (chance alone). A “statistically significant” result is one where the result is unlikely to be due to chance alone, and therefore is more likely to be due to the drug. Drug trials are only considered to be positive if they are statistically significant.

To be more certain that a drug is truly effective, the Food and Drug Administration (FDA) usually requires that two trials for the same drug are statistically significant. The FDA is the federal regulatory agency that helps ensure that a drug is safe and effective (that it does what the drug company says it does and without harmful side effects).

Different Types of Drugs Tested in ALS

There are two basic classes of drugs tested for ALS. (1) New drugs, also called experimental drugs, are compounds tested by drug companies. They can only be obtained in drug trials because they have not been approved for use by the FDA. (2) Drugs already approved by the FDA for other conditions can also be tested for ALS. Because these drugs have been approved, they may be prescribed by any physician. Food and nutritional supplements are not considered drugs and are not regulated by the FDA, and can be purchased by anyone. Some supplements have been or are being tested in ALS.

Although previously approved drugs and food supplements can be prescribed or obtained by anyone, without a formal trial they remain untested in ALS. That means there is no demonstration that they actually slow the rate of progression. There may also be side effects that can be troublesome or even serious in ALS patients.

Different Types of Clinical Trials

Drugs for ALS can be tested in a number of different ways.

(1) Formal clinical trials, also called randomized controlled trials, involve large numbers of patients. Usually, several hundred patients are divided into groups. In order to recruit the several hundred ALS patients, these trials are conducted at multiple medical centers, and are called multicenter trials. It is these large trials that are able to show definitely whether a drug is effective or not.

(2) Pilot trials are conducted with a small number of patients to get a feeling for whether a drug may have an effect. These trials are not definitive. If there is a suggestion of an effect, a larger formal trial is conducted.

(3) Exploratory trials may be conducted with only a few patients. These trials are inconclusive because of the small number of patients tested and the variability of rates of progression among ALS patients.

Clinical Trials of Riluzole (Rilutek®)

At this time, only one drug has been approved by the FDA for ALS. The generic name is riluzole and the brand name is Rilutek®. Riluzole was originally tested in two trials, and both trials were statistically significant and the drug was approved. The measure of progression was survival, and riluzole was found to prolong survival compared to taking no drug (placebo). The figure shows how patients taking riluzole compare to patients

taking placebo in the trial; after the first 3 months, patients taking Rilutek showed better survival than patients taking placebo.

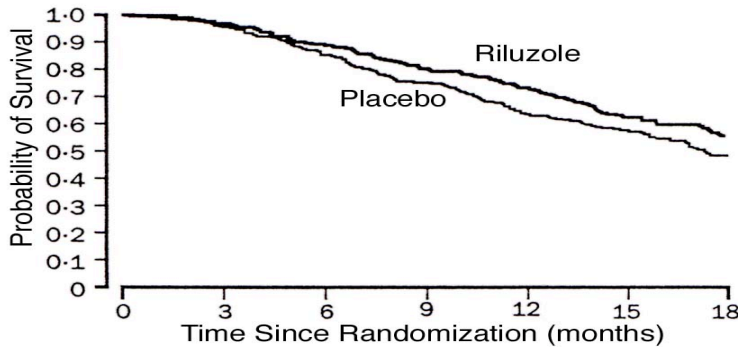


Figure showing the probability of survival in ALS patients taking placebo or riluzole (Rilutek). Note, higher probability of survival with riluzole.

A natural question that arises is how much extra time does Rilutek give? This question was not specifically addressed in the study, but extrapolation of the survival lines indicates that survival is enhanced by an average of three to five months. Patients frequently comment that this may not seem to be a long time or a significant advantage. When placed in the context of other diseases, such as cancer, a drug that prolongs survival by three to five months is impressive.

There have been other studies assessing the effect of riluzole and all show a positive effect on survival compared to those not taking riluzole.

Rilutek is a 50 mg tablet taken twice a day. To maximize absorption, it should be taken either one hour before or two hours after meals. Rilutek has few side effects. Rare patients will have an elevation in liver enzymes. Enzymes should be checked every two months for the first six months, and then yearly. Occasionally patients will feel some mild nausea, and this usually goes away after a few weeks taking the medication. Overall, Rilutek is a very well tolerated medication. It does not interfere with other medications.

It is very important to understand that a patient will not feel that Rilutek is working. They will feel no different. There will still be a loss of strength. However, it is hoped that the patient and family will have confidence from the two studies that the drug is having an effect. In other words, confidence that the patient is progressing more slowly than he would if were not taking Rilutek.

Other Drugs and Supplements Tested in ALS

A large number of other drugs and supplements have been formally tested in ALS. Unfortunately, none have shown any effect and riluzole is the only drug that has shown a positive effect. The table shows drugs that have been recently tested or are currently being tested.

DRUG	RESULT
Gabapentin (Neurontin®)	No effect (two trials)
Topiramate (Topamax®)	No effect
Celecoxib (Celebrex®)	No effect

Creatine	No effect (three trials)
Minocycline	Results in early 2007
IGF-1	Results in early 2008
Co-enzyme Q10	Results in early 2008

There are major efforts using high-powered techniques to identify promising drugs and compounds. As a result, there are about 10 new drugs that are in early stages of testing for ALS. It will be some time before we know the results, but these techniques are accelerating the process.

There are a large number of supplements that are taken by ALS patients. Some have been around for a long time and others are offered on the internet with very enticing sales pitches. Many of these compounds and supplements have few side effects, and the choice of whether to take them is an individual choice. Others may have potential side effects or other interactions that could cause discomfort or harm. We in the Motor Neuron Disease Clinic focus on drugs that either have been demonstrated effective for ALS or are undergoing formal drug trials. What is most important is that you, the patient with ALS, are comfortable. We will be happy to answer questions about drugs and supplements. We have a clinical pharmacist with a doctoral degree in pharmacy to answer your questions.

10 November 2005