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SESSION 9B CLINICAL TRIALS & TRIAL DESIGN

C76 RESULTS OF A RANDOMIZED, CONTROLLED PHASE II TRIAL OF COENZYME Q10 (COQ10) FOR ALS

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Keywords: Coenzyme Q10, Clinical Trial

Background: CoQ10 is a mitochondrial co-factor and antioxidant. Mitochondrial dysfunction and oxidative stress are considered key pathogenic mechanisms in ALS.

Objective: To report the detailed results of the clinical trial of High Dose Coenzyme Q10 (CoQ10) in ALS (QALS study), an NIH-funded, two-stage, phase II, randomized, placebo-controlled, double-blind, multicenter clinical trial.

Methods: The QALS study had two aims: 1) to select between two doses of CoQ10 and 2) to conduct an early efficacy test of CoQ10 compared to placebo. The primary outcome measure was the decline in amyotrophic lateral sclerosis Functional Rating Scale-revised (ALSFRS-R) score from baseline to nine months. The first stage (dose selection) identified a preferred dose of CoQ10 (1800 mg or 2700 mg) using a selection procedure rather than a formal hypothesis test. The second stage (early efficacy test) compared this preferred dose against placebo using a non-superiority or futility design. A bias correction adjusted the early efficacy test result to take account of the inclusion of stage 1 data in the stage 2 analysis.

Results: A preferred dose (2700mg) was selected in December 2006 at the end of stage 1, using data from 70 patients (35 at each dose). Thirty five patients were concurrently randomized to the placebo in stage 1. In stage 2, an additional 80 patients were randomized 1:1 to CoQ10 2700mg and placebo. The stage 2 early efficacy analysis included 150 patients (75 on CoQ10 2700mg and 75 on placebo). The final stage 2 patients completed the trial in March 2008.

Discussion and Conclusions: A two-stage multicenter phase II randomized controlled trial of high-dose CoQ10 for ALS has been completed. The early efficacy test result for the primary outcome measure and limited safety data only was reported at the American Academy of Neurology Meeting in Chicago. For the International Symposium on ALS/MND, we will present the detailed efficacy and safety results and discuss our interpretation as to whether or not a definitive phase III trial comparing CoQ10 2700mg to placebo is justified.

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C77 SUBCUTANEOUS INSULIN-LIKE GROWTH FACTOR TYPE 1 (IGF-1) IS NOT BENEFICIAL FOR PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS IN A TWO YEAR TRIAL

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Keywords: Clinical trial; IGF-1; neurotrophic factors

Background: Previous human clinical trials of insulin-like growth factor, type I (IGF-1) in amyotrophic lateral sclerosis (ALS) have been inconsistent. One large study in North America suggested a beneficial effect as measured by the Appel ALS rating scale and one large European study failed to demonstrate benefit. We completed a multicentered, NIH funded study to assess the efficacy of subcutaneous IGF-1 in slowing the progression of ALS.

Objective: To determine if subcutaneously IGF-1 is effective at slowing the rate of progressive weakness in subjects with ALS. Secondary objectives: to determine if subcutaneous IGF prolongs survival or slows functional deterioration as measured by the ALSFRS-r.

Methods: This study was a randomized, double-blind, placebo-controlled study. 330 patients from 20 medical centers were randomized to receive 0.05 mg/kg body weight of human recombinant IGF-1 given subcutaneously twice daily or placebo for 2 years. The primary outcome measure was the rate of change in their manual muscle testing (MMT) score. Secondary outcome measures included tracheostomy-free survival and rate of change in the ALSFRS-r. Intention to treat analysis was used.

Results: There was no difference between treatment groups in the primary or secondary outcome measures after the 2 year

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treatment period. The IGF-1 treatment group MMT scores changed at a mean rate of 0.44 units per month and the placebo group changed at a rate of 0.39 units per month ($p = 0.716$). Survival analysis demonstrated a median survival of approximately 2 years with no difference between the treatment or placebo groups ($p = 0.415$). For the ALSFRS-r, the IGF-I treatment group changed at a rate of 2.5 units per month and the placebo group changed at a rate of 2.2 units per month ($p = 0.312$).

Conclusions: We found no evidence that subcutaneous IGF-1 benefits patients with ALS.

C78 TWO-YEAR PLACEBO-CONTROLLED RANDOMIZED TRIAL OF GENE THERAPY IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS.

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Keywords: gene therapy, VEGF, angigenin

Background: Polymorphisms in VEGF gene are associated with decreased expression of VEGF and increased risk of amyotrophic lateral sclerosis (ALS) (1). Mutations in angiogenin gene are detected in patients with ALS (2). Gene therapy with lentivirus vectors, expressing VEGF, in mouse G93A model increased survival time (3).

Objectives: We investigated safety, tolerability and effectiveness of gene therapy with recombinant adenovirus vectors, expressing VEGF and angiogenin, in ALS patients.

Methods: We conducted a two-year placebo-controlled randomized trial. 10 ALS patients with cervical onset of the disease were included in the study. They were randomized in two groups. Groups were comparable by age, sex and disease duration. We made intramuscular injections of medication in three muscles (m.trapezius, m.deltoideus, m.quadriceps) bilaterally every four weeks for two years. Every 4 weeks we conducted clinical and neurological examinations and laboratory tests. We also measured VEGF levels in serum and levels of adenovirus -neutralizing antibodies.

Results: All patients were deteriorating. There was no difference in the dynamics of forced vital capacity (FVC) and ALSFRS scores. In the group of patients receiving therapy, we registered increased survival under hypoxic conditions. We detected high level of virus neutralizing antibodies in one patient, receiving medication, who died during the first year of therapy. No serious adverse events were registered.

Discussion and Conclusions: We demonstrated safety and good tolerance of this therapy. We showed, that virus neutralizing antibodies may decrease effectiveness of therapy with recombinant adenovirus vectors. Gene therapy may increase resistance to hypoxia.

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C79 PYRIMETHAMINE AS A THERAPY FOR SOD1 ASSOCIATED FALS: EARLY FINDINGS

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Keywords: Pyrimethamine, familial ALS

Background: Three percent of ALS patients have a familial form of the disease (FALS) caused by a mutation in the gene coding for the free radical scavenging enzyme copper/zinc superoxide dismutase (SOD1). Inhibiting expression of the SOD1 gene prevents transgenic ALS animals from developing the disease. Increasing or decreasing the number of mutated genes proportionately speeds or slows the progression of the disease. Therefore, reducing SOD1 levels in patients with SOD1 associated FALS may be an objective for future therapies. Through an extensive in vitro screening program for medications having the ability to reduce SOD1 levels, several molecules that reduce SOD1 protein levels are known. One of the most potent molecules is pyrimethamine, an FDA approved medication used for the treatment of malaria and toxoplasmosis. Pyrimethamine reduces SOD1 levels in the spinal cord and blood lymphocytes in the G93A SOD1 transgenic mouse.

Objectives: To describe changes in SOD1 levels and muscle strength in FALS patients receiving pyrimethamine over an 18 week time period.

Methods: After obtaining FDA and IRB approval, 7 patients with El Escorial definite ALS associated with an SOD1 mutation were enrolled in an 18 week open label trial. The protocol defined pyrimethamine dose to be increased from 25mg to 100mg in the first 6 weeks, remaining at 100mg through to week 18. Lymphocyte SOD1 levels were measured at each visit. Disease severity was measured by Appel score (AALS), ALSFRS, and MQOL at weeks 6, 12 and 18. Leucovorin, 10 mg per day was given throughout the 18-week study.

Results: Four different SOD1 mutations were identified in seven patients: D90A (2: 1 man; 1 woman), A4V (2: 1 man; 1 woman), L144F (2 men), N65S (1 woman). Adverse effects of variable severity were encountered in all patients. Two patients (N65S and D90A) were unable to complete the study because of adverse effects. In non-A4V patients, SOD1 levels showed medication dependent reduction in SOD1 levels between 30–60 percent. Pyrimethamine administration had no effect on SOD1 levels in the 2 patients with the A4V mutation. In the 18 week period, AALS, ALSFRS, and MQOL scores showed no significant change in non-A4V patients. There was, however, significant deterioration in patients with A4V mutations during the study period.

Discussion and Conclusions: Pyrimethamine is capable of reducing levels of SOD1 in mouse lymphocytes, mouse spinal cord and persistently in human lymphocytes to up to 60% of normal. However, patients with the A4V mutation seem resistant the effects of pyrimethamine. While the safety and tolerability of PYR in FALS patients remains unsettled, we believe determination of an optimal dose will decrease adverse events. Larger trials to determine clinical efficacy and possible mutation specific effects are needed.

C80 A BAYESIAN MODEL TO DESIGN TWO STAGE CLINICAL TRIALS IN ALS

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Keywords: Trial design, historical controls, screening

Background: Clinical trials in ALS are generally designed one-at-a-time, testing a single drug. In reality, however, many drugs are waiting in a pipeline for testing and patients are eager to enter trials, especially if they can avoid being placed in a placebo group. We explore whether it is possible to design a series of trials, which can efficiently test several drugs using a consortium of clinical trial treatment centers.

Objective: To investigate, using a Bayesian model simulation, whether a two-stage sequential strategy can result in greater efficiency in finding useful drugs for treating ALS.

Methods: We simulated a process where there is a pool of drugs waiting to be tested for efficacy in ALS. We assumed that the effect of drugs on ALSFRS-R rate of decline (slope) comes from a normal distribution, with a specified mean. The standard deviation of the pool is used to specify the percentage of drugs that are truly effective, i.e. above a specified threshold. Testing occurs sequentially in two stages. First a drug is selected from the pool and in the initial "screening" stage patients taking the selected drug are compared to a pool of historical placebo control results. If the drug passes the screening test, a sample size is calculated, based on the estimated effect size from the first stage, for a second stage, randomized placebo controlled trial. If the drug does not pass the screen, another drug is selected for testing.

We investigated the effect of the theoretical distribution of drug efficacies on the optimal sample size for the first stage of the trial, based on total number of patients required to find effective drugs in the two-stage design.

Results: We modelled a scenario with 20% of drugs having a 20% or greater reduction in ALSFRS slope. The results are summarized in the text below where N is the number of patients selected for the screening stage:

The proportion of True Positive (a 20% or greater ALSFRS slope reduction) detected in a single-sample screening test when N was 30, 52%; 40, 61%; 50, 68% and 100, 88% respectively. The proportion of single-sample screening tests resulting in a False Positives when N was: 30, 31%; 40, 33%; 50, 32% and 100, 28% respectively. The average number of patients to test 10 drugs, screening plus a placebo-controlled phase III for 30 patients was 681, for 40 patients was 771, for 50 patients was 874 and for 100 patients was 983.

Conclusions: Small screening trials prior to large phase III trials can result in savings in numbers of patients required to find an effective drug.

C81 *TIME TO FAILURE* CLINICAL TRIAL FOR PROMISING THERAPEUTICS IN ALS: A NOVEL DESIGN FOR THE BEST OF BOTH WORLDS

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Keywords: clinical trial, study design, statistical methods

Background: The inclusion of a placebo or untreated control group in a randomized clinical trial testing novel therapeutics is necessary to control the placebo for the placebo effect in this heterogeneous disease and is required to detect a mild to moderate treatment effect. Successful recruitment requires a committed and selfless population of research subjects who may only have the opportunity of participating in one clinical trial. In addition, many subjects will never receive the active compound and will have a long exposure period to placebo or observation when mortality, or the rates of functional decline are the outcome measures.

To optimize recruitment, clinical trials designed for subjects with Cancer and HIV frequently employ a *time to failure* or *time to progression* design to minimize the duration of time research subjects receive the control treatment.

Objective: We evaluated a novel *time to failure* design for patients with ALS with time from randomization to a six unit drop in ALSFRS-R, death or permanent assisted breathing as the primary measure of treatment efficacy. Patients in the placebo group who decline by six units in the ALSFRS-R will be designated as treatment failures and switched to active treatment as soon as they reach this endpoint.

Methods: North Eastern ALS consortium's trials of creatine, topiramate, and celebrex were used to simulate how such a design would work in practice.

Conclusions: A total of 250 patients randomized 1:1 is required in a dual arm trial design to detect a 40% reduction in the rate of decline in the ALSFRS-R, with 90% power. A conventional trial design that used a random effect model to compare the rate of decline over 12 months would require 180 patients. However, the novel *time to failure* design would only expose patients to an average of seven months on placebo and patients with a rapid progression in the placebo group would receive active compound earlier in the course of their disease.

This novel trial design testing promising therapeutics in ALS provides a compromise between determination of efficacy and limiting the period of time patients are on placebo. This study design will be applied to an upcoming clinical trial of Lithium in the United States and Canada and details of study design along with advantages and disadvantages will be discussed.