My Experience in an ALS Trial

Topiramate didn't turn out to be a miracle drug, but I'd do it all again.

BY CATHERINE WOLF, PH.D.

It was the fall of 1999, two years after my initial diagnosis of amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease). I had just been rejected from a clinical trial at the Columbia University Medical Center Eleanor and Lou Gehrig MDA/ALS Research Center in New York, NY, and I was desperate to get into a clinical trial. I knew time was short because my forced vital capacity (FVC)—a measure of breathing—was plummeting. Many ALS trials require a minimum FVC.

So on a beautiful fall day my husband and I drove from our home one hour north of New York City to Massachusetts General Hospital in Boston. I was apprehensive as I rolled off the elevator in my wheelchair onto the eighth floor for my screening appointment. What if I didn't meet the breathing criterion?


Massachusetts General Hospital

COURTESY MASSACHUSETTS GENERAL HOSPITAL

INTRODUCTIONS

I was greeted by Merit Cudkowicz, M.D., M.Sc., the principal investigator. She explained that the experimental drug was topiramate, commonly prescribed for epilepsy. The investigators hypothesized that topiramate could slow ALS by blocking a receptor on nerve cells (neurons) called the AMPA glutamate receptor. Glutamate functions as a neurotransmitter, helping to transmit signals between nerve cells. However, excess glutamate had been implicated as a factor in ALS in some studies.

The goal of the 20-site trial was to determine if topiramate was safe and slowed disease progression in people with ALS. The study was a double-blind, placebo-controlled study, meaning neither the participants nor the researchers knew who received topiramate and who received the placebo. A placebo is an inert substance, such as a sugar pill, made to look like the experimental drug. Placebos are necessary to make sure that the results aren't due to the powerful effect of participating in a trial. Often, people who receive the placebo report the same effects as people receiving the experimental drug.

By comparing the two groups on the outcome measures, and also comparing the percentage of people in each group who report a particular side effect, researchers can determine the *true* effect of the experimental drug. Of the approximately 300 participants in this trial, two-thirds received topiramate and one-third received the placebo.

First, they took my medical history and obtained my informed consent, which is a process of communication between a patient and physician that results in the patient's agreement to undergo a specific medical intervention.

Then it was time for the breathing test. Forced vital capacity is calculated as a percentage of a healthy person's capacity of the same sex, age, and height. I was given three tries, and the best of three counted. I took a deep breath and blew out as hard as I could while an assistant cheered me on by saying, "Blow, blow, blow!" My FVC was in the mid-60s, well above the criterion of 50 percent.

THE BASELINE VISIT

About two weeks later, I was back at Mass General for my baseline visit. At this visit, participants were assigned to either the experimental drug (in this case, topiramate) or the placebo group. The primary outcome measure of the trial—that is, the most important measurement—was arm strength. I was assisted into a contraption that measured strength in four muscles in each arm. The secondary outcome measures were also assessed: FVC; grip strength; and the ALS Functional Rating Scale, a clinical measure of fine and gross motor strength as well as breathing.

Topiramate (or the placebo) was in-

creased gradually from 50 mg to a maximum of 800 mg over a 16-week period. The typical dose for epilepsy is 400 mg, but 800 mg was well within the prescribed range. Dr. Cudkowicz explained that the dose was limited to 800 mg in order to minimize known adverse effects, such as poor appetite, weight loss, nausea, diarrhea, and abnormal thinking.

> "I helped advance the search for treatment. Even negative results further research."

At any point, though, a participant could decide not to increase the dose or even reduce it. I decided not to increase the dose once during the 16-week period due to nausea but reached the 800 mg maximum. I believed I was in the placebo group because of my lack of adverse cognitive effects, which sometimes occur with topiramate. The only cognitive effect I experienced was trouble spelling long words like "phenomenon" during the maintenance phase of the trial.

FOLLOWING UP

After the baseline visit, study participants visited at one, three, six, nine, and 12 months. The primary and secondary outcome measures were assessed, as well as vital signs and any adverse effects. At one, six, and 12 months, blood samples were taken to measure the level of topiramate in the blood. These samples were analyzed only *after* the trial to ensure that the investigators did not know who was in which group.

My veins had become small due to the disease, because there is less need for blood as muscle atrophies. My veins were a particular challenge for the expert nurses of Mass General. Sometimes it took two attempts to coax blood out of my veins, and sometimes my veins refused to yield a drop.

After the 12-month visit, I had the option of taking topiramate. This is called the open-label stage of the trial, in which all participants have the opportunity to take the experimental drug. During the open-label stage, I learned that I had been in the topiramate group. I was happy: finally something that might slow the relentless progression of ALS.

But my happiness was short lived. Dr. Cudkowicz called to tell me to stop taking the drug because of an increased risk of pulmonary embolism (a clot in the lungs) or deep venous thrombosis (a clot in a deep vein, often in the calf). When the researchers analyzed the results, they found 6.1 percent of the participants in the topiramate group experienced such an event, vs. 1 percent in the placebo group. I was disappointed.

Fifty-five percent of the participants in each group completed the trial. In the topiramate group, 43.7 percent discontinued the study medication, vs. 29.9 percent in the placebo group. The most common reasons for early discontinuation in the topiramate group were adverse events—mainly weakness, abnormal thinking, and diarrhea. In the placebo group, the most common reason was participant choice. In addition, only 33 percent in the topiramate group achieved the maximum dose of 800 mg/day, compared with 54 percent in the placebo group. Weight loss declined two and a half times more rapidly in the topiramate group than the placebo group. In other words, the 800 mg dose of topiramate was not well tolerated.

THE RESULTS

The results of this clinical trial revealed that the primary outcome measure—arm strength—declined more rapidly in patients who received topiramate. The same was true for grip strength. Forced vital capacity, ALS Functional Rating Score, and survival did not differ in the rate of decline between the two groups.

Even after weight loss was taken into account, there was still a difference in the rate of decline of arm strength, suggesting that weight loss was not directly or solely responsible for the decline. The researchers concluded that the reason topiramate accelerated decline in strength was unknown. They theorized that the adverse effects associated with topiramate were responsible for the greater rate of decline, rather than the possibility that topiramate was toxic to motor neurons in some way.

Dr. Cudkowicz says the most surprising finding from this trial was "the weight loss—and [its] impact on disease course. We know now how critical this is in ALS. This was not known in 1999."

Recently, Dr. Cudkowicz performed additional analyses on the effect of weight loss on survival in the topiramate trial. She found that for the participants who did not lose weight, topiramate actually increased the rate of survival. "This argues that perhaps another drug that works on the same target but that does not have the weight loss effect may still be helpful for ALS," she concluded.

Most drugs tested in clinical trials fail to have a beneficial effect. Although topiramate didn't turn out to be the miracle drug that slowed ALS progression, there were benefits to participating in the trial. First, I helped advance the search for an effective treatment. Even negative results often suggest further research. Second, the frequent study visits, and in particular the measurement of FVC, helped me be proactive concerning my care: During the trial, I went on a BiPaP, a noninvasive device that aids breathing, and I had a feeding tube inserted. Even knowing the adverse effects of topiramate, I would do it all again. NN