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Open label study of riluzole for the treatment of amyotrophic lateral sclerosis.

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RESUMEN: La esclerosis lateral amiotrófica (ELA), tiene una mortalidad de 80% a 5 años de iniciada. Se han utilizado múltiples tratamientos para tratar de detener su progresión. El objetivo del presente estudio es evaluar los efectos del riluzole en la progresión de la ELA mediante el uso de la escala de Jablecki. Se seleccionaron 50 casos de ELA definitiva en base a los criterios de El Escorial, realizando valoraciones con la escala al inicio y al final del estudio, que se llevó a cabo durante un año con dosis de 100 mg/día. De los pacientes iniciales, 31 (62%) completaron el estudio. La progresión inicial fue de 0.6895 puntos/mes y la final de 0.5682 ($p<0.05$). En 14 casos de ELA de inicio bulbar, la velocidad inicial fue de 0.7133 y la final de 0.5551 puntos/mes ($p<0.05$) y en 17 pacientes con inicio espinal, se tuvo una velocidad inicial de 0.6702 y una final de 0.5789 puntos/mes ($p<0.05$). No se presentaron efectos adversos relevantes durante el tratamiento. El uso del medicamento disminuyo la progresión de la enfermedad, sin producir regresión de la misma, por lo que es importante a pacientes y familiares las características no curativas del fármaco, debiendo valorarse en cada caso la relación costo-beneficio.

ABSTRACT: Amyotrophic lateral sclerosis (ALS) has a 5-years mortality of 80%. Several treatment modalities have been used to delay disease progression. The aim of the currrent study was to evaluate of riluzole on clinical progression as assessed by jablecki's scale in Mexican patients with ALS. Fifty patients with a definitive diagnosis of ALS according to El Escorial criteria were selected. To measure the usefulness of riluzole therapy, disease progression was measured before and after treatment with jablecki's scale. Patients received a daily oral dose of 100 mg of riluzole throughout the one-year study period. For the 50 patients initially enrolled, 31 (62%) completed the study. After the one-year, monthly progression decreased to 0.5682 points per month ($p<0.05$). In the 14 bulbar-onset patients with spinal-onset, initial progression was 0.6702 points per month, which decreased to 0.5551 ($p<0.05$). In 17 patients with spinal-onset, initial progression was 0.6702 points per month, which decreased to 0.5789 ($p<0.05$). There were no severe side effects related to therapy. Riluzole can delay disease progression and its use should be considered in ALS patients, after making it clear to them and their families that they will not be cured, and after taking into account cost-benefit issues.

The term motor neuron disease is used to designate a variety of neurologic conditions characterized by a variable dysfunction of superior and inferior motor neurons. One of these disease is amyotrophic latera sclerosis (ALS). The sporadic form of ALS is the most common one, accounting for more than 90% of the cases worldwide. It is more prevalent in men, with a peak incidense in the fifth and sixth decades of life. It has a 5-year mortality of 80%, and survival is inversely related to age at diagnosis. Multiple mechanisms have been implicated in its pathogenesis, but is has not been possible to define the precise events leading to disease. The main hypothesis include glutamate excitotoxicity, formation of antibodies against calcium channels and decreased neural growth factors.

Several treatment modalities have been used to stop or delay disease progression, including steroids, thyroid hormones and neural growth factors. The only one that as demonstrated beneficial affects is riluzole (2-amino-6-trifluorometoxibenzotiazol), which interferes with glutamic acid effects on

the CNS (excitatory amino acid). Double-blind, placebo-controlled trials have showed and increase in tracheostomy-free time in patients treated with riluzole. The are few side effects related to riluzole administration, these include elevated liver enzymes and leukopenia, which usually have been reported in the first 3 month of treatment. For this reason therapy should be monitored with serum chemistries and blood counts frequently. The aim of the current study was to evaluate the effect of riluzole on clinical progression as assessed by Jablecki's scale in Mexican patients with ALS. This scale had not been used in previous studies.

PATIENTS AND METHODS

Fifty patients with a definitive diagnosis of ALS according to El Escorial criteria were selected to participate in the current study (January 1996 to January 1998). Diagnosis was established by at least two staff neurologist National Institute of Neurology and Neurosurgery, Mexico City. Every patients underwent complete clinical and laboratory evaluation, including thyroid hormones, liver chemistry, electrophysiologic testing (electromyography, motor and sensitive conduction velocities), MRI, and pulmonary function test. Inclusion criteria were: definitive diagnosis of ALS, sporadic case, age less than 65 years old, vital capacity greater than 60% normal liver chemistries and signed informed consent. Exclusion criteria were, vital capacity less than 60% elevated enzymes of participation in other experimental treatment studies for ALS. In every patient blood was drawn for lives functional test, blood chemistry and complete blood counts at entry and at 1,2,3,6,9, and 12 month after starting treatment. Patients were followed with clinical and laboratory evaluations for one year by at least two of the study investigators.

We decided to use the Jablecki scale for clinical evaluation, which enabled us to obtain objective clinical criteria to gauge the progression of ALS. Previous studies have demonstrated the usefulness of this scale to predict disease progression, and also its easy of application.

Jablecki's scale is based on the score of 6 clinical parameters: language (4 points), swallowing (2 points), muscle strength and muscular status in each of the 4 limbs (16 points for muscle strength and 8 points for muscle status), which comprise the most affected in ALS. The maximum score possible is 40 points, which would reflect the degree of disease progression in a single patient. After clinical evaluation, Jablecki's score was divided by the time since disease onset in month, so as to assess the degree of ALS progression was measured before and after treatment as previously described.

The study was designed with a one-year follow-up so as to determine safety of riluzole treatment and short-term effects on ALS progression. The patients and families were informed of the risks of riluzole therapy and were asked to give written informed consent before entry to the study. It was also made clear to them that treatment was intended to modify disease progression and not to cure ALS. Patients received a daily oral dose of 100 mg of riluzole throughout the one-year study period.

RESULTS

One-year treatment ended January 1998 for the 50 patients initially enrolled, of which 31 (62%) completed the study. Of those did not complete treatment protocol, 14 (28%) were because of non-compliance with study visits our voluntary drop-out, mainly in the first two month of treatment with riluzole; 4 patients (8%) died of respiratory failure (none of them presented treatment related side-effects), within a mean of 5 month after riluzole was started; one patient (2%) has to continue drug therapy because of skin rash which disappeared after stopping riluzole.

Thirty-one patients (11 women, 35% and 20 men, 65%), with a men age of 47.67 (SD 10.35) years (49.16 years for women and 44.63 years for men) completed the one-year treatment. Mean clinical evolution of ALS was 25.83 (SD 13.43) months (29.66 months in women and 23.73 months in men). None of the patients had a greater then two-fold increase in aminotransferase . Mean values for alanine aminotransferase and aspartate aminotransferase were 27.78 U/L at study entry, and 27.58 U/L and 26.76 U/L at the end of one-year therapy, respectively. Complete blood counts were not significantly different before and after treatment.

Degree of disease progression as assessed by Jablecki´s scale was 0.6895 points per month, with a mean of 17.8 points at the beginning of the study. After the one-year treatment with riluzole, monthly progression decreased to 0.5682 points with a final progression of 6.81 points at the end of the treatment period. Figure 1 compares disease progression before and after treatment with riluzole in the 31 patients who completed study protocol. Rate of progression was significantly decreased with riluzole therapy ($p<0.001$ using Student's test). Patients response to therapy was analyzed according

to initial clinical presentation of ALS. There were 14 patients with bulbar-onset and 17 with spinal-onset ALS. In the bulbar-onset patients, initial disease progression was 0.713 points per month, which decreased to 0.5551 points per month at the end of study, difference that statisfically significant ($p=0.0223$). Figure 2 depicts disease progression in the 14 subjects with bulbar-onset ALS before and after riluzole therapy. In those patients who presented with spinal-onset ALS, disease progression before treatment was 0.6702 points per month, which decreased to 0.5789 per month at the study period, attaining statistical significance ($p<0.05$). This difference is represented graphically in figure 3. None of the study patients required gastrostomy or tracheostomy. None of the patients complained of ashtenia or sedation, in spite of prior studies reporting this type of side-effects with riluzole.

Figuras 1 y 2

DISCUSSION

ALS has classically been considered a rapidly progressive and fatal disease, without curative options. Treatment modalities are for the main part palliative, with early physical therapy, gastrostomy and tracheostomy playing an import roll in increasing survival and improving quality of life.

Recent advances in the phatogenesis of ALS, specially the recording of the importance that glutamate and neural growth factors have in this disease, have triggered investigation on novel therapeutic approaches. Previous studies have compared riluzole versus placebo, but outcomes have been based on mortality, muscular status or the need for tracheostomy. The use of a simple clinical scale such as the one proposed by Jablecki, offers the advantage of objectively comparing disease in a same patient in a short period of time, and can thus be usefuld to identify therapeutic effect of a certain drug. It also facilitates clinical management and follow-up patient.

In concordance with previous studies, our group of patients had a greater benefit in muscular status and strength, with improvement on language and swallowing problems. These result support the proposed protective effect of riluzole in bulbar areas, as previously described in the literature. There were few riluzole-related side effects, and most of the patients who did not finish the study did so because they could comply with follow-up visits. There were no severe side effects related to riluzole administration, one patient had to discontinue treatment because of skin rash. In none of the patients were important increases of live enzymes or abnormal blood counts detected during riluzole therapy. Management of patients with ALS can not be solely based on standard medical treatment, it should also include family and social support, prevention of depression and malnutrition, and the use of novel disease-specific therapies such as insulin-like growth factor and brain-derived neurotrophic factor, with the intent to delay disease progression and improve quality of life. Rulizole can delay disease progression and its use should be considered in ALS patients, after marking it clear to them and there families that they will not be cured, and after taking into account cost-benefit-issues.

Figura 3.

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