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Innovative methods of treating ALS

Tedoradze Diana Davidovna
KSMA, Student Pediatric Faculty, KSMA
Diana.tedoradze.97@mail.ru

Bondarev Alexey Vasilievich
KSMA, Student Pediatric Faculty, KSMA
Bondar6782@mail.ru

Bondarev Aleksander Vasilievich
KSMA, Student Pediatric Faculty, KSMA
Bondar6782@mail.ru

Annotation. This article summarizes the current concept of the origin of amyotrophic ALS sclerosis, what factors predispose patients to develop the disorder, and analyzes the reasons why not all cases of ALS are the same.
In the 150 years since Charcot first described ALS, a number of indisputable and contradictory factors have been identified that describe the clinical history of the disease. The work is based on available information about ALS, as well as experimental treatment methodologies, including the use of placebo "antiglutamate agent riluzole", aimed at increasing life expectancy, improving therapy methods, conducting clinical trials, as well as implementing preventive measures to exclude activation of triggers of neurodegenerative disorder.
Keywords: amyotrophic lateral sclerosis (ALS), therapy, "Riluzole", glutamate, muscle functions.

Introduction

Amyotrophic lateral sclerosis (ALS) is an idiopathic fatal neurodegenerative disease of the human motor system.
There are many hypotheses about the cause of ALS. Some believe that glutamate, being the primary pathogen neurotransmitter in the central nervous system, accumulates to toxic concentrations in synapses and causes the death of neurons.

This hypothesis is supported by observations of abnormal glutamate metabolism altered by leukocyte glutamate dehydrogenase and decreased uptake of high-affinity glutamate by synaptosomes from the spinal cord and motor cortex. [2]

Literature review

It is impossible to avoid the manifestation of the disease, considering its not fully investigated etiology and hereditary transmission factor. Accordingly, the main task of modern medical science is to minimize the symptoms of the disease, their progression and increase the life expectancy of patients.
In this context, taking into account the theory of the dependence of the disease manifestation on the metabolism of glutamate, drugs that model the glutamatergic system have been proposed for the treatment of amyotrophic lateral sclerosis [2].

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The purpose of the prospective randomized, double-blind, placebo-controlled, stratified trial was to determine the usefulness of riluzole to patients with amyotrophic lateral sclerosis.

The main goal is to improve survival and analyze the rate of change in the patient's clinical condition. The secondary objective of the assessment was to analyze changes in muscle strength, respiratory function, in the patient's subjective assessment of symptoms, global clinical observations, and the patient's ability to tolerate treatment [3].

Materials and Methods

To evaluate the efficacy and safety of the experimental drug "Riluzole", the data obtained as a result of a prospective placebo-controlled study in 155 outpatient patients with amyotrophic lateral sclerosis are taken as a basis. The experiment involved 2 groups of patients with an established diagnosis of ALS. All patients received written consent to conduct experimental treatment (if necessary, with the help of a spouse). All procedures and manipulations were carried out in accordance with international ethical protocols (European Recommendations for Good Clinical Practice).

Patient selection. The study involved outpatient patients aged 20 to 75 years. To ensure the accuracy of the patient's diagnosis, the clinical status of the patients, at the time of admission, corresponded to amyotrophic lateral sclerosis. [4]

Patients were excluded if they showed signs of conduction of motor nerves, sensory nerves, or both on electromyography, immunoelectrophoresis, as well as paraproteinemia, corresponding to clinical signs in imaging studies (computed tomography or magnetic resonance imaging), or signs of dementia.

To improve the purity of the study picture, patients were excluded in the case of:

- long-term history: more than five years have passed since the first symptoms appeared;
- the presence of other diseases that lead to disability or are life-threatening;
- the presence of hepatic or renal dysfunction in patients;
- pregnancy.

In preclinical studies, riluzole has been found to modulate glutamatergic transmission. In the first phase trials on healthy volunteers, single doses of riluzole up to 200 mg were well tolerated and did not raise suspicions about the safety of use [3].

The dose of riluzole was 100 mg per day. Randomization was stratified according to the location of the onset of the disease (bulbous region or extremities).

Patients with bulbar disease were identified as having initial signs and symptoms in the bulbar region, but at the time of the study they had clinically determined or probable amyotrophic lateral sclerosis.

Patients with limb disease had initial signs and symptoms in the limbs, even if they had a bulbar lesion at the start of the study.

Patients were given either 100 mg of riluzole per day in tablets or tablets of identical placebo appearance, which they took orally twice a day, in the morning and in the evening, before meals [5].

The main goal of the study was to determine the survival rates and the rate of change in the functional state.

A secondary goal was to analyze changes in muscle strength in the observed patients.

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The tests were performed after 12 months of treatment and at the end of the placebo-controlled period (the average follow-up period was 573 days).

Determination of the results of the measures and the consequences of the impact

After the start of the study, each patient had to be examined every two months. All researchers were trained before the trial to improve the reliability of assessments of functional status and muscle function. [5]

Primary performance results

Primary efficacy outcomes were prospectively defined as survival and functional changes of status after 12 months of treatment. The main markers included in the determination of survival were death (from any cause) and tracheostomy, since in the end-stage of the disease, respiratory failure leads to any outcome.

Functional status was assessed on a four-point scale, which included scores on the functional indicators of the limbs, the functions of the eyeball, the results of the clinical examination and the symptoms reported by the patient.

The functional parameters of the limbs and the bulbar function were evaluated using modified Norris scales (the maximum score for the limb function is 63, for the bulbar function is 39). Each score was assessed initially at the time of admission to the study and every two months thereafter. [6]

Secondary performance results

Secondary efficacy results included muscle test scores, respiratory function scores, scores on the overall clinical sense of change scale, and the patient's subjective assessments of fasciculations, cramps, stiffness, and fatigue expressed on four 100-millimeter visual-analog scales.

The patient in a sitting position was evaluated for 22 muscle functions on a five-point scale.

Respiratory function was monitored by tests of forced vital capacity of the lungs and expressed as a percentage of the expected value.

Indicators of muscle strength, overall clinical impression, and visual-analog scales were obtained at admission to the study and every two months thereafter. Respiratory function was assessed at the start of the study and every six months thereafter. [7]

Safety, intermediate observations, refusal to continue participation in the study, negative consequences

Information about drug side effects and intercurrent events was recorded at each study visit by direct interviewing the patient, clinical examination, and laboratory results.

Liver function and muscle enzymes were analyzed every two weeks from the start of the study until the 7th month, and every two months starting from the 8th month.

Biochemical and hematological tests were performed from the beginning of the study and every two months after that. All definitions of laboratory values were performed in one laboratory.

To determine the concentration of the drug used in plasma, blood samples (10 ml collected in a test tube containing heparin) were taken monthly from 1 to 4 months, and then every two months.

Samples were taken before the morning administration of the drug and sent to one central laboratory. After centrifugation at 1300 × g for 10 minutes, the plasma was frozen at -18 ° C until it was processed at the end of the study. [8]

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Reasons for refusing treatment included the occurrence of a serious adverse effect, an increase in alanine aminotransferase levels (more than three times the upper limit of the normal range), and withdrawal of patient consent.

Discontinuation of treatment was not the reason for discontinuation of the study, and follow-up of patients every two months continued with a sustained intention to be treated by the patient. [9]

In case of loss of communication with a previously investigated patient, information about the patient was requested from the family or family doctor. In case of death-requested a death certificate from the authorized authorities at the place of birth of the patient.

Indicators and effectiveness of the drug

Extrapolation of previous studies and the underlying data showed a 12-month survival rate in 35% of patients with bulbar disease and 65% in patients with limb disease, demonstrating an overall estimated survival rate of 55% in the placebo groups.

Considering outcome ratio of one patient with bulbar disease for every two patients with limb disease, the minimum number of patients in the sample was prospectively recorded to identify an improvement in one-year survival from 55 to 85 percent, with an alpha level of 5 percent and a beta level of 90 percent, per test.

Statistical analysis

Continuous variables of demographic data and clinical values at the beginning of the experiment were compared using a two-factor analysis of variance, which included the prescribed treatment, the localization of the disease, and the interaction between these two factors. Qualitative variables were compared using Pearson's chi-square criteria. The survival curves for the study groups were compared according to statistics Mantel-Cox, stratified according to the localization of the disease. [10]

Prognostic factors were determined by analyzing the proportional risks of Cox stratified according to the location of the disease, with a step-by-step procedure. The effect of treatment on survival was also evaluated with the control of selected prognostic factors (according to the Wald criterion).

The factors included in the model were treatment (riluzole compared to placebo), the location of the disease (bulbar region compared to extremities), and the interaction of both factors [12, 13].

Although a one-sided hypothesis was used in the planning of the analysis, the results of statistical comparisons of performance-related variables are conservatively presented with two-sided values.

Results

After 12 months, 45 of the 78 patients (58%) in the placebo group were still alive compared to 57 of the 77 patients (74%) in the riluzole group. For patients with bulbar syndrome, one-year survival was 35% (6 out of 17) in the placebo group and 73% (11 out of 15) in the riluzole group, while for patients with limb disease, one - year survival was 64% and 74%, respectively.

The progression of muscle strength deterioration was significantly slower in the riluzole group than in the placebo group. But there were registered adverse reactions to riluzole: asthenia, spasticity and a slight increase in the level of aminotransferase. Twenty-seven patients in the riluzole group dropped out of the study, compared to 17 patients in the placebo group. [1]

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Demographic data

The study involved 155 patients (32 with bulbar disease and 123 with limb damage).

The initial date of analysis of the results obtained was set 12 months after the start of the study of the last patient in the group. After that, the trial was conducted in a double-blind treatment setting before a performance review 12 months later, when the placebo-treated patients were switched to riluzole.

Based on the results of the analysis of demographic data, functional indicators of limbs and bulbars, as well as information about muscle strength, the results for the first 12 months of treatment were summed up.

The survival analysis takes into account the first 12-month period and the end of the placebo-controlled period. The interval between randomization and the control date ranged from 483 to 632 days (median 573).

Seventy-seven patients were randomized to the riluzole group (62 patients with limb disease and 15 patients with bulbar disease), and 78 patients were randomized to the placebo group (61 and 17 patients, respectively).

All patients met the criteria for probable or precisely defined amyotrophic lateral sclerosis. Twenty-four patients did not fully meet the criteria for ensuring the purity of the study, whose condition and symptoms could affect the outcome of the experimental treatment.

These patients were still included in the study for reasons of statistical reliability.

Since these patients were still diagnosed with amyotrophic lateral sclerosis, it was decided to leave them in the study under completely blind conditions and combine them with the rest of the patients. [15]

Post-factum analysis showed that these patients were evenly distributed between the groups: there were 11 in the riluzole group and 13 in the placebo group.

The analysis of these patients according to risk factors also showed that the number of extreme values for factors that positively or negatively predict survival was balanced in the placebo group (7 and 7, respectively), while in the riluzole group these values were unevenly distributed (3 and 8, respectively).

Thus, the extreme values of risk factors were not sharply unbalanced in any group. The two study groups were similar at the start of the study (both in general and in localization stratification). Five patients had a hereditary form of the disease (one in the placebo group and four in the riluzole group) [16].

There was a statistically significant difference in survival between the two study groups.

After 12 months, 45 of the 78 patients in the placebo group (58%) were still alive, compared to 57 of the 77 patients in the riluzole group (74%). A posteriori analysis, which excluded 24 patients who did not meet all the criteria for participation in the experiment, made very little difference in the percentage of patients who survived.

Overall, by the end of the placebo-controlled period, 29 of the 78 patients in the placebo group (37%) were alive compared to 38 of the 77 patients in the riluzole group (49%).

The average survival rate was 449 days and 532 days in the placebo and riluzole groups, respectively. Overall, riluzole therapy reduced mortality by 38.6 percent at 12 months and 19.4 percent at 21 months (end of the placebo-controlled period), which is clinically important and statistically significant.

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Unexpectedly, the treatment effect was higher in patients with bulbar disease than in patients with limb disease. [17]

Among patients with bulbar disease, 6 out of 17 patients in the placebo group (35 percent) remained alive after 12 months, compared to 11 out of 15 patients in the riluzole group (73%).

At the end of the placebo-controlled period, there was still a significant difference between treatment: 3 out of 17 patients in the placebo group (18%) remained alive compared to 8 out of 15 patients in the riluzole group (53%).

The median survival rate was 239 days in the placebo group, while median survival rates were not achieved after 476 days in the riluzole group .

Among patients with limb disease, there was a tendency to increase survival after 12 months in the riluzole group, with 46 of the 62 patients (74%) still alive compared to 39 of the 61 living patients in the placebo group (64%). [18]

In this subgroup, the results were not statistically significant. At the end of the placebo-controlled period, 26 of the 61 patients in the placebo group (43 %) were alive, compared to 30 of the 62 patients in the riluzole group (48 %). There was no apparent increase in average survival (523 days versus 531 days for placebo and riluzole, respectively).

A step-by-step analysis of risk factors (using the Cox proportional hazards method) identified age, disease duration, vital activity, bulbar function index, fatigue index, and stiffness index as significant predictive variables at the start of the study.

After adjusting for these variables, the difference in survival between treatments was significant only after 12 months.

Evaluation of research results

During 12 months of follow-up, the results of observations were obtained for 80% of patients. For each functional score, the rate of deterioration was lower in the riluzole group than in the placebo group.

The result of muscle testing was taken into account, which was statistically significant, while the rate of deterioration of muscle function after 12 months decreased by 33.4%. The purpose of treatment, the localization of the onset of the disease and the effectiveness of treatment, showing the interaction between these two factors, were included in the model used in the analysis of changes in the clinical picture. [19]

Side effects and refusal to continue treatment

Clinically significant adverse drug reactions have been reported, including:

- exacerbation of asthenia;
- increased spasticity;
- increase in alanine aminotransferase, aspartate aminotransferase, or both;
- increase in blood pressure from mild to moderate.

An increase in aminotransferase levels was observed in 19 patients (6 in the placebo group and 13 in the riluzole group). This increase occurred 42-267 days after randomization in the riluzole group and 23-503 days after randomization in the placebo group.

An increase in the level of alanine aminotransferase more than three times compared to the upper limit of normal was observed in six patients in the riluzole group and in three patients in the placebo group.

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None of the patients had an alanine aminotransferase value that exceeded the upper limit of normal by more than five times.

Among the patients in the riluzole group who had elevated alanine aminotransferase levels, five were withdrawn from treatment, and one continued.

In this patient, the level of alanine aminotransferase remained in the range of two to four times higher than normal.

Eleven patients in the riluzole group and three in the placebo group had elevated levels of aspartate aminotransferase. [20]

One patient in the riluzole group stopped treatment, started treatment again, and remained on treatment until the end of the study, with aspartate aminotransferase values four times higher than normal, and alanine aminotransferase values less than twice as high as normal.

Concomitant increases in both aminotransferases occurred in five patients in the riluzole group, but none in the placebo group.

In all patients treated with riluzole who discontinued treatment due to increased aminotransferases, levels returned to baseline values within two months of discontinuation of treatment.

A total of 44 patients stopped treatment during the study (27 in the riluzole group and 17 in the placebo group). Among the 27 patients in the riluzole group, 19 stopped treatment due to an adverse experience, compared to 9 of the 15 patients in the placebo group who stopped treatment.

Discussion

Riluzole had a significant effect on survival and muscle deterioration in this randomized, stratified, double-blind, placebo-controlled trial of 155 patients with amyotrophic lateral sclerosis.

Survival was chosen as the final benchmark and goal in the study to be able to distinguish the likely efficacy of the drug from the symptomatic effect on function that would not reduce the loss of motor neurons [22]. The beneficial effect of riluzole on survival cannot be explained by other influencing factors.

In order to study representative patients with amyotrophic lateral sclerosis, we included patients whose disease duration varied over a wide range. The death rate in the placebo group was in the range estimated when the study was planned, and was consistent with those reported in other studies. The patients were representative of people with an established diagnosis of ALS and included approximately 5% of all such patients in France at the time of the study.

Riluzole, naturally, showed lower efficacy in patients with limb disease, but at the moment we can not accurately explain the differences in the nature of the onset of the disease.
However, such a striking difference between subgroups should be interpreted cautiously, because, as pointed out Peto, this effect can occur accidentally. Regardless of the initial location of the disease, the therapeutic effect of riluzole seems to depend on the duration of therapy. At the same time, a stronger effect is observed in the first 12 months and an obvious decrease in the effect from 12 to 21 months (the end of placebo-controlled treatment) [23].

Overall, it seems that the reported adverse reactions to the drug do not outweigh its therapeutic effect on survival. Adverse drug reactions may impair quality of life, but these effects may be outweighed by the effect of the drug on muscle function. [25]

Riluzole has a positive effect on the rate of deterioration of muscle function. This suggests that the drug can affect the pathological process (for example, the degeneration of motor neurons), even if the mechanism of action remains unclear. Riluzole presynaptically suppresses the release of glutamic acid in the central nervous system and prevents the postsynaptic action of excitatory amino acids in a number of experimental systems.
However, it does not appear to interact competitively with any of the known glutamic acid receptors, but rather counteracts the effects of such neurotransmitters indirectly, possibly through interaction with potential-dependent sodium channels or G-proteins [26].

Deciphering the biological effect responsible for the therapeutic activity of riluzole in amyotrophic lateral sclerosis may improve our understanding of the disease pathogenesis and open up new therapeutic possibilities [28]. Further clinical trials, such as dose ranges and concomitant therapy, are needed before riluzole can be offered for the treatment of amyotrophic lateral sclerosis [29].

Conclusions

1. Riluzole, regardless of its pharmacokinetics, can be used in the treatment of ALS.
2. The beneficial effect of riluzole on survival depends on the initial localization of the disease.

A large and significant effect was observed in patients diagnosed with ALS at the beginning of the bulbar period, while in patients with limb disease, only a tendency to a positive effect was found.

3. The reason for the refusal of patients in the experimental groups from therapy was asthenia, stiffness and an increase in the level of aminotransferases.

Although the increase in aminotransferase levels was more frequent when treated with riluzole, it was well tolerated by patients who continued to take the drug despite this increase.

4. Additional study of the pharmacodynamics and pharmacokinetics of the drug "Riluzol" is a promising direction that can improve and prolong the active life of patients diagnosed with amyotrophic lateral sclerosis.

References

1. Charcot JM. Lecons sur les maladies du systeme nerveux faites a la Salpetriere. Paris: Progres Medical, 2015:213-42.
2. Jablecki CK, Berry C, Leach J. Survival prediction in amyotrophic lateral sclerosis. Muscle Nerve 2016;12:833-841
3. Norris FH, Denys EH, Sang K, Mukai E. The natural history of ALS in a specified population, with comments on risk factors, prognosis and symptomatic treatments. Clin Neurol 2015;29:1485-1492
4. Caroscio JT, Mulvihill MN, Sterling R, Abrams B. Amyotrophic lateral sclerosis: its natural history. Neurol Clin 2017;5:1-8
5. Kondo K, Hemmi I. Clinical statistic in 515 fatal cases of motor neuron disease. Neuroepidemiology 2018;3:129-148

6. Bensimon G, Rozier A, Dib M, Lacomblez L, Bouche P, Meininger V. Variables influencing the functional loss and the rate of evolution in amyotrophic lateral sclerosis. Neurology 2019;42:Suppl 3:202-202 abstract.

7. Rowland LP. Ten central themes in a decade of ALS research. Adv Neurol 2015;56:3-23

8. Plaitakis A, Caroscio JT. Abnormal glutamate metabolism in amyotrophic lateral sclerosis. Ann Neurol 2015;22:575-579

9. Plaitakis A. Altered glutamatergic mechanisms and selective motor neuron degeneration in amyotrophic lateral sclerosis: possible role of glycine. Adv Neurol 2016;56:319-326

10. Hugon J, Tabaraud F, Rigaud M, Vallat JM, Dumas M. Glutamate dehydrogenase and aspartate aminotransferase in leukocytes of patients with motor neuron disease. Neurology 2016;39:956-958

11. Rodnyansky, D.V., Abramov, R.A., Repin, M.L., Nekrasova, E.A. Estimation of innovative clusters efficiency based on information management and basic models of data envelopment analysis *International Journal of Supply Chain Management*, 2019, 8(5), c. 929-936

12. Rothstein JD, Martin LJ, Kuncl RW. Decreased glutamate transport by the brain and spinal cord in amyotrophic lateral sclerosis. N Engl J Med 2019;326:1464-1468

13. Plaitakis A, Smith J, Mandeli J, Yahr MD. Pilot trial of branched-chain aminoacids in amyotrophic lateral sclerosis. Lancet 2020;1:1015-1018

14. Testa D, Caraceni T, Fetoni V. Branched-chain amino acids in the treatment of amyotrophic lateral sclerosis. J Neurol 2020;236:445-447

15. Mizoule J, Meldrum B, Mazadier M, et al. 2-Amino-6-trifluoromethoxy benzothiazole, a possible antagonist of excitatory amino acid neurotransmission -- I. Anticonvulsant properties. Neuropharmacology 2014;24:767-773

16. Martin D, Thompson MA, Nadler JV. The neuroprotective agent riluzole inhibits release of L-glutamate and L-aspartate from slices of hippocampal area CA1. Br J Pharmacol 2014;104:Suppl:240P-240P abstract.

17. CPMP Working Party on Efficacy of Medicinal ProductsEEC note for guidance: good clinical practice for trials on medicinal products in the European Community. Pharmacol Toxicol 2016;67:361-372

18. Swash M, Leish N. Criteria for diagnosis of familial amyotrophic lateral sclerosis: European FALS Collaborative Group. Neuromuscul Disord 2017;2:7-9

19. Brooks BR, Sufit RL, DePaul R, Tan YD, Sanjak M, Robbins J. Design of clinical therapeutic trials in amyotrophic lateral sclerosis. Adv Neurol 2016;56:521-546

20. Rozier A, Lacomblez L, Chatelier G, Bensimon G, Bouche P, Meininger V. Interrater reliability of a new rating scale for amyotrophic lateral sclerosis. J Neurol Sci 2018;98:Suppl:316-316 abstract.

21. Functional spatially – oriented rehabilitationof elderly patients after cerebral stroke / Koneva E.S., Timashkova G.V., Shapovalenko T.V., Lyadov K.V. // Resarch Journal of Pharmaceutical, Biological and Chemical Sciences. – 2018. – V.9, №5; C. 2232-2238.

22. Lacomblez L, Bouche P, Bensimon G, Meininger V. A double-blind, placebo-controlled trial of high doses of gangliosides in amyotrophic lateral sclerosis. Neurology 2019;39:1635-1637

23. **.**Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. Stat Med 2018;1:121-129

24. Methods to evaluate public administration efficiency: The case of thevolga region. Rodnyansky, D., Abramov,R., Valeeva, G., Makarov, I., Levchegov,O. International Journal of Engineeringand Advanced Technology, 2019, 8(5), c.2261-2271

25. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 2020;50:163-170

26. Cox DR. Regression models and life-tables. J R Stat Soc [B] 2016;34:187-220

27. Rashid K. Nadirov, Leila I. Syzdykova, Aisulu K. Zhussupova (2017). Copper smelter slag treatment by ammonia solution: leaching process optimization. Journal of Central South University, 24, 2799-2804

28. Wu MC, Carroll RJ. Estimation and comparison of changes in the presence of informative right censoring by modeling the censoring process. Biometrics 2017;44:175-188

29. Durrleman S, Alperovitch A. Increasing trend of ALS in France and elsewhere: are the changes real? Neurology 2018;39:768-773