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RESEARCH ARTICLE

Effectiveness of the Treatment with Botulinum Toxin type A (BTX-A) in the Management of the Spasticity in Patients with Amyotrophic Lateral Sclerosis (ALS)

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is an unknown pathogenesis progressive neurodegenerative disease of the central nervous system that leads to death within 1-5 years. Clinically, it is often possible to find at the level of the lower limbs some clinical manifestations of damage of the I motor neuron with spastic paralysis, iperflexia and clonus, with impairment of the ability of patients' deambulation and their management of the activities of daily living (such as personal hygiene or dressing). So, the first therapeutic approach in these patients are antispasmodic drugs orally and after Botulinum toxin type A injection (BTX-A). Aim of this study is to demonstrate the efficacy of BTX-A in patients with ALS and spasticity of lower limbs no responder to the treatment with oral antispastic drugs with no adverse events. We enrolled 5 patients (3 female and 2 male); they were evaluated at baseline (**T0,** before BTX-A treatment), and over the following three months with three follow-up visits (**T1** 30 days after the infiltration, **T2** 60 days after infiltration and **T3** 90 days after infiltration) with myometric measure of tone, Modified Ashworth Scale, Barthel Index, Adductor Tone Rating Scale and Hygiene Score. We treated the adductor muscles (AM) of patients with incobotulinum toxin type A (Xeomin®, Merz) with ultrasound guide. We obtained an improvement of spasticity with miometric measurement, Modified Ashworth Scale, Barthel Index, Adductor Tone Rating Scale and Hygiene Score for 90 days after injection ($p<0,05$). Our preliminary study shows the possibility to use BTX-A in the treatment of the spasticity in patients with ALS no responders to oral antispastic drugs, with no side effects.

Keywords: Amyotrophic Lateral Sclerosis, spasticity, botulinum toxin type A, activities of daily living, physiotherapy, oral antispastic drugs

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease of the central nervous system with an unknown pathogenesis[1]. This devastating neurodegenerative disease usually leads to death within 1-5 years period of diagnosis [2,3]. Clinically ALS is characterized by a gradually involvement of the motor neurons both upper (I motor neuron), localized at the level of the cerebral cortex (UMN), and lower (II motor neuron), situated in the brainstem and spinal cord (LMN). Diagnostic criteria for ALS rely on clinical assessment of upper and lower motor neuron deficits in multiple body regions together with a history of progres sion of symptoms, and also on para-clinical observation of LMN by electromyography [4]. No para-clinical assessment of UMN involvement has reached enough validity to be included in diagnostic criteria. In the past decade non-conventional magnetic resonance techniques have been shown to be sensitive to detect UMN involvement in the ALS disease process, namely: resting-state connectivity measured with functional MRI, cortical thickness measured by high-resolution imaging, diffusion tensor imaging (DTI) metrics such as fractional anisotropy and radial diffusivity, and more recently magnetic resonance spectroscopy (MRS) measures of gamma-aminobutyric acid concentration[5]. An additional symptom shared by ALS is the occurrence of neuroinflammation and infiltration of T-lymphocytes in some areas of the CNS or spinal cord [6,7,8]; in fact the number of regulatory T-lymphocytes correlates inversely with disease

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progression [9,10]. Clinically, in the majority of cases, it shows with signs of damage of II motor neuron with flabby paralysis (sign of the claw hand), areflexia, muscular atrophy and muscle fasciculations, giving rise to muscular weakness and atrophy; if it concerns the cranial nerves appears dysphagia, dysarthria and dysphonia [11]. This loss of motor neurons leads to fatal paralysis and death and is the most frequent disease of motor neurons [2,12]. It is often possible to find at the level of the lower limbs some clinical manifestations of damage of the I motor neuron with spastic paralysis, iperflexia and clonus. These clinical symptoms can jeopardize both the ability of patients' deambulation and their management of the activities of daily living (ADL) such as personal hygiene or dressing [12,13].

Spasticity sometimes appears as symptom of ALS. Muscles are contracted and they are opposed to stretching by fixing the joints in forced positions, resulting in joint pain. The first therapeutic approach in these cases is the therapy with antispasmodic drugs orally (BACLOFEN) [14,15]. In some cases spasticity can also be resistant to these drugs and be a source of very intense pain or fix the limbs in positions that hinder, for example, the hygiene and care of the person. It may be necessary to use Botulinum toxin type A (BTX-A), injected into the muscles, to determine paralysis reducing spasticity. To treat therefore the symptom spasticity can be useful to improve the quality of life of the patients.

The aim of this study is to demonstrate the efficacy of BTX-A in patients with ALS and spasticity of lower limbs no responder to the treatment with oral antispastic drugs with no adverse events.

MATERIALS AND METHODS

Study Population and Inclusion Criteria

We enrolled 10 patients (6 female and 4 male) with mean age of 49,4±SD 3,8.

Inclusion criteria were: 1- diagnosis of probable or definite ALS based on revised El Escorial Criteria (Brooks 2000); 2- presence of spasticity of lower limbs that determined a progressive disability in the Activities of Daily Living (ADL); 3- previous use of oral antispastic drugs (Lioresal® 75 mg/die); 4- inefficacy of previous therapies or appearance of side effects such as cough, dyspnea and asthenia that had led to the interruption of the treatment; 5- absence of antibiotic therapy during the week preceding the treatment; 6- availability of the patient to undergo a continuing and intensive physiotherapy, every day for the first 30 days and then tri-weekly for the following two months, after the treatment; 7- absence of fibrotic degeneration of the spastic muscles, evaluated by ultrasounds.

All patients signed written informed consent.

Study was conducted between January and May 2016.

Methods

Patients were evaluated at baseline (**T0,** before BTX-A treatment), and over the following three months with three follow-up visits (**T1** 30 days after the infiltration, **T2** 60 days after infiltration and **T3** 90 days after infiltration).

At baseline were performed:

1- neurological visit by a neurologist, expert in motor neuron diseases. The evaluation included a standard neurological exam and the functional assessment through the Amyotrophic Lateral Sclerosis- Functional Rating Scale revised (ALSFRS-r) (Cedarbaum 1999);

2- the ultrasonography study of the muscles of interest to exclude the presence of fibrotic degeneration.

At baseline and during the follow-up visits patients underwent a physiatric examination with the use of myometric measure to evaluate muscle tone, elasticity and stiffness and the following scales: Modified Ashworth Scale, Barthel Index, Adductor Tone Rating Scale, and Hygiene Score [16,17].

After the treatment patients started an intensive rehabilitation program consisted in muscular stretching, functional rehabilitation, active and passive mobilization, training of the step, exercises for the perception of herself, advising not to exceed the hard work threshold[18]. This program was carried out every day for the first 30 days and then tri-weekly for the following two months.

At the physiatric examination patients showed: independent erected standing possible only with bilateral support and for few minutes, deambulation possible with double support for a short time, by little steps and of precautionary type. It was present spastic paraparesis. Our patients complained both a difficulty in washing and dressing themself because of an excessive tone at the level of the adductor magnus (AM) bilaterally that determined a crossing of the lower limbs and a difficulty in the deambulation.

We treated the adductor muscles (AM) of patients with incobotulinum toxin type A (Xeomin®, Merz); mean dose was 78,33±9,18; we injected BTX-A with ultrasound guide.

Statistical Analysis

Data were expressed as mean (standard deviation). The TWO – WAY ANOVA method was used to compare statistical differences of myometric measures and scales' value between baseline and follow-up.

RESULTS

We obtained the following results:

1- The mean values of muscle tone measured by myoton at the beginning of the study (t0 AM dx=18,45±1,23, t0 AM sn=17,99±1,11) decreased in a statistically significant at t1 (AM dx=15,30±1,16, AM sn=15,32±1,12) and t2 (AM dx=15,45±1,21, AM sn=15,99±1,22), with $p<0,05$. At t3, instead, data was not statistically significant if compared to the initial value (AM dx=17,67±1,21, AM sn=17,11±1,02), with $p<0,05$. (Fig. 1)

2- Values of MAS (to AM dx=3±1,1, AM sn=3±1,1) also followed this trend, with statistic significance at t1 (AM dx=1,4±0,8, AM sn=1,3±1,0) and t2 (AM dx=1,4±0,8, AM sn=1,3±0,8) and no significance at t3 (AM dx=2,6±1,1, AM sn=2,7±0,6), with $p<0,05$. (Fig. 2).

3- The baseline mean value of Barthel Index (to=31±9,1) increased in a statistically significant way at t1 (49±4,1)

and t2 (46±4,8), with p<0,05. At t3, instead, value (34±5,4) was not statistically significant if compared to the initial value, with p<0,05. (Fig. 3)

4- The baseline mean value of Adductor tone rating scale (to=3±1,1) decreased in a statistically significant way at t1 (1,3±0,8) and t2 (1,4±0,8), with p<0,05. At t3, instead, value (3±1,1)was not statistically significant if compared to the initial value, with p<0,05. (Fig.4)

5- The baseline mean value of with Hygienic score (to=3,2±1,3) decreased in a statistically significant way at t1 (1,3±0,4) and t2 (1,4±0,6), with p<0,05. At t3, instead, value (3,2±0,5) was not statistically significant if compared to the initial value, with p<0,05. (Fig.5)

DISCUSSION

Spasticity often is a typical symptom of ALS. The first therapeutic approach is the therapy with antispasmodic drugs orally; spasticity can often be resistant to these drugs with very intense pain or fixing the limbs in positions that hinder, for example, the hygiene and care of the person. It may be necessary to use BTX-A, injected into the muscles, to determine paralysis reducing spasticity. This study shows that BTX-A, normally used treating sialorrhea[19], associated with moderate physiotherapy[20], can be helpful in improving spasticity of patients with ALS for three months at least. The treatment is safe, because we had no side effects such as general weakness and/or dysphagia. Our study shows that combined therapy BTX-A/FKT in patients with ALS can improve the rheological parameters of the spastic muscle tissue (see Fig.1 and 2); in this way it makes easier exercise with the slowing of the decay of motor skills, acting both cardio-respiratory efficiency both on complications from reduced joint mobility. Clinical benefits obtained from this activity relate to the physical efficiency, mood and quality of sleep (all 5 patients reported an increase in the number of hours of sleep). The activity of stretches and exercises of joint range prevent muscle contractures and retractions of connective tissues favored by immobility, as well as help to contain the resulting pain syndromes. The joint mobilization should be practiced by the patient or caregiver daily. The study also proves that the specific action on the AM muscles supports their passive motion (see Fig. 3). Patients have a better personal hygiene and a better personal autonomy (see

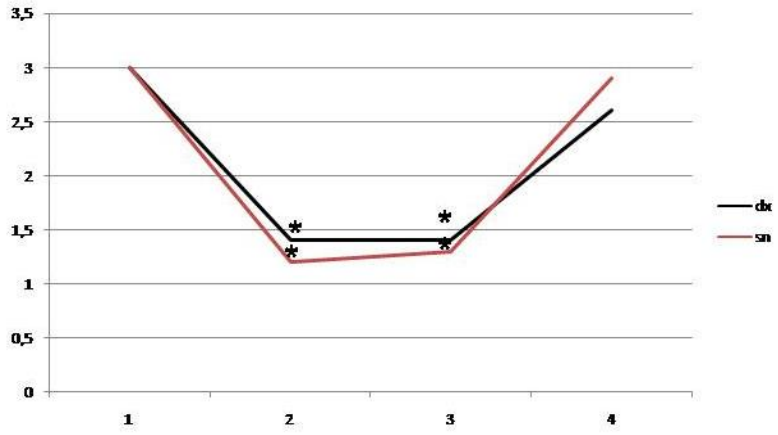

Fig. (1). Miometric tone modification of Adductor Magnus right and left; we demonstrated a statistical difference reduction of tone until 90 days after injection (p<0,05).

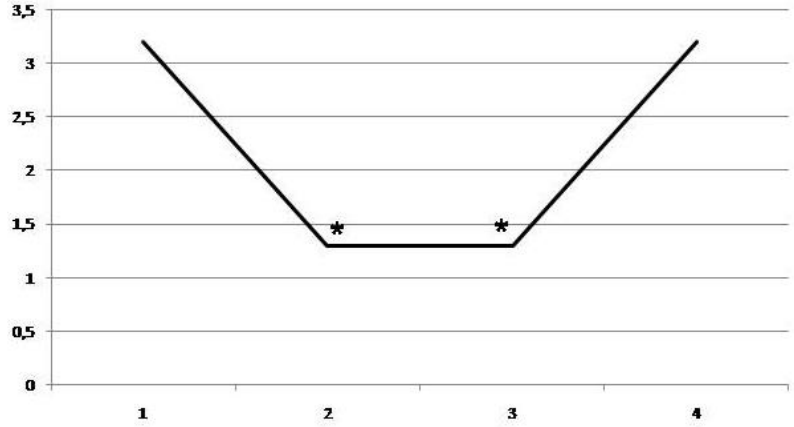

Fig. (2). MAS modification of Adductor Magnus right and left; we demonstrated a statistical difference reduction until 90 days after injection (p<0,05).

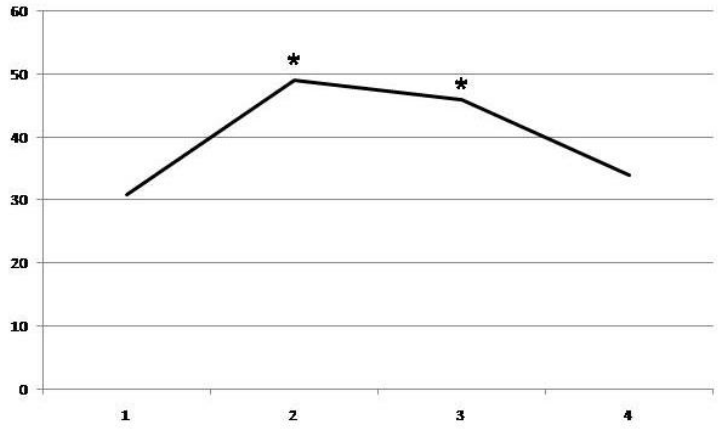

Fig. (3). Barthel Index modification of patients; in the Fig. (we observed a statistical improvement of value until 90 days after injection ($p<0,05$).

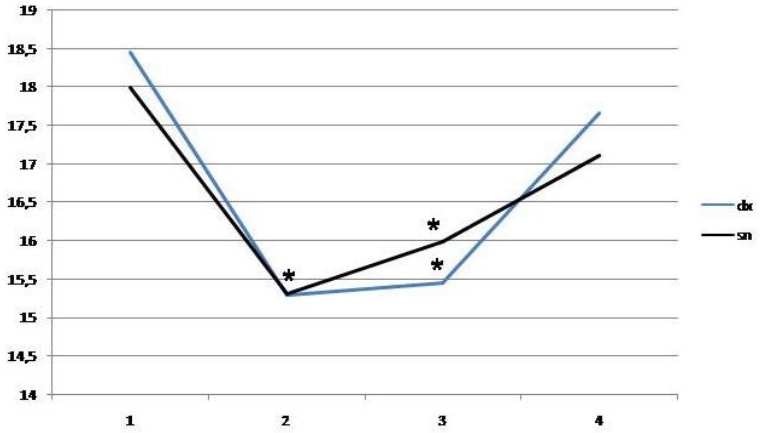

Fig. (4). Adductor tone rating scale modification of right and left muscles; we observed a statistical reduction of value until 90 days after injection ($p<0,05$).

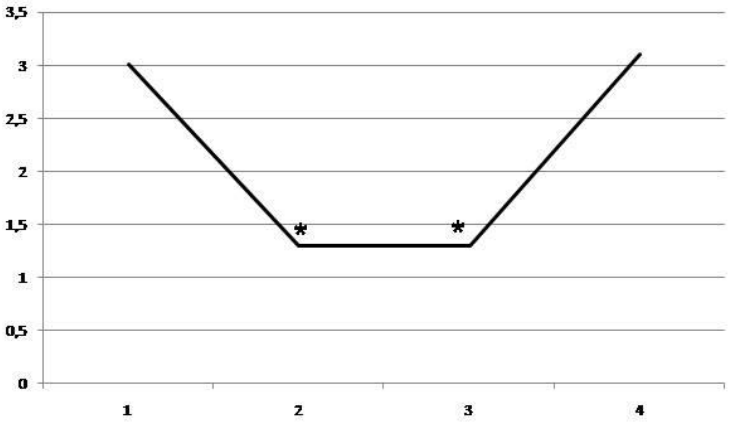

Fig. (5). Hygienic score modification; we demonstrated a statistical reduction until 90 days after injection ($p<0,05$).

fig. 4 and 5), for which they can be made easier some maneuvers, such as the catheterization or the hygiene of the perineal areas, which reduce the risk of infection of urinary tract, often leading cause of death in these patients. Combination therapy BTX-A/ physiotherapy has also shown efficacy in the onset of fatigue. Fatigue recognizes multifactorial etiology[21], being able to achieve the progressive deficit of strength and muscle tone (which favors a mechanical strain on joints and bone segments) and / or the onset of contractures \ muscle spasms from spastic hypertonia that determine the appearance of degenerative lesions of the joints and connective tissue retraction from prolonged immobility and alterations in the microcirculation. So the reduction of muscle tone and easier mobilization of skeletal segments of a limb, by mechanisms still poorly understood, may be help in reducing the onset of fatigue.

BTX-A and rehabilitation allowed a reduction of muscular tone (analyzed both in subjective ways with the Modified Ashworth Scale or with the objective appraisal of miometric measure) and an improvement of the muscular elasticity and stiffness for up to three months, when it was necessary a second infiltration. In this way, there was also an improvement of the values of the Barthel Index Scale, Adductor Tone Rating Scale and Hygiene Score. Good values of muscular properties have an important repercussion on the rehabilitative treatment[22], enabling a better mobilization of the lower limbs and preventing the establishment of muscular contractures and articular deformities, treating with surgical technique[23]; all this with an important impact on the quality of the life of the patient.

CONCLUSIONS

Our preliminary study shows the possibility to use BTX-A in the treatment of the spasticity in patients with ALS no responders to oral antispastic drugs. In the near future it is planned the monitoring of patients clinically and with miometric measure after the following infiltrations. We also planned to increase number of patients to obtain more informations about the efficacy of BTX-A in spasticity of these patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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