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Therapeutic Benefit of Botulinum Toxin a (Incobotulinum Toxin) for the Treatment of Spasticity of the Triceps Surae in Multiple Sclerosis: An Observational Study

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Abstract

Objectives: To assess the benefit of the incobotulinum toxin in the treatment of spasticity of the triceps surae in patients suffering from MS with gait and posture disorders.

Design: Observational study.

Setting: Rehabilitation centre.

Participants: patients with MS (N=28) presenting with spasticity of the triceps surae was suggested were enrolled in this study. This study received a favourable opinion from the local Ethics Committee.

Interventions: An injection of an intramuscular injection of 200 U of xeomin in 6 ml of physiological serum was performed in the 2 gastrocnemius muscles and the soleus muscle

Main Outcome: Initial evaluations, then at 6 weeks and at 3 months comprising an evaluation of spasticity, walking and balance, with GAS score, time up and go test, 6 minutes walk test and Multiple Sclerosis Walking Scale.

Results: 28 patients, 9 men and 19 women with an average age of 48.2 +/- 12 years were enrolled. The average EDSS score was 4.2 +/- 1.5. At 6 weeks a significant improvement was observed in the Ashworth score, the GAS score, the TUG score and the MSWT. At 3 months the benefit was less clear with a significant increase persisting in the Ashworth score and the GAS score. On the other hand a significant increase was noted in the 6MWT.

Conclusion: This observational study confirms the benefit of treating spasticity in multiple sclerosis with the incobotulinum toxin, with a functional objective. Additional studies are required to specify more precisely the place of botulinum toxin in the treatment of spasticity in patients suffering from multiple sclerosis.

Keywords: Multiple sclerosis; Spasticity; Botulinum toxin A; Gait

Abbreviations

MS: Multiple Sclerosis; EDSS: Expended Disability Status Scale; GAS: Goal Assessment Scale; TUG: Time up and go; MSWS: Multiple Sclerosis Walking Scale; 6MWT: 6 Minutes Walk Test

Introduction

Pyramidal disorders are common in multiple sclerosis leading particularly to spasticity with a variable impact on functions but which always results in deterioration in the quality of life [1-6]. Thus 85% of patients in the Milinis study were inconvenienced on a daily basis, regardless of the development stage of the disease and the intensity of the spasticity [7]. Apart from the clinical impact, the financial consequence is also a major problem. Stevenson underlined the importance of setting up suitable early treatment to limit the spasticity [8]. Treatment management is facing a challenge: to improve the patient's quality of life and function while retaining the useful spasticity which can in particular enable the patient to stand up and move around under good conditions, particularly for those with an EDSS score higher than 6.

The treatment of spasticity therefore undergoes a precise analysis of the clinical situation: functional complaint, examination of the disabilities and self-sufficiency to enable the choice of well-defined therapeutic targets. The following will be discussed: general oral treatments, such as baclofen or tizanidine..., use of botulinum toxin, intrathecal treatment or surgery, not forgetting, of course, physiotherapy treatment [9-11].

In France, botulinum toxin has become the first intention treatment for focal spasticity after stroke [12-14]. Its use is widespread in several conditions. Concerning multiple sclerosis, the place of botulinum toxin is often discussed in the literature but, paradoxically,

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little data on this use in practice is available [15-22]. In the Arroyo study, 27% of patients suffering from MS benefited from botulinum toxin. For our part we observed similar results in our practice: 24% [23]. Nevertheless, in the Berthoux study, the use of botulinum toxin is only 1.8% of the treatment proposals in American patients [6].

An evaluation of our practices enabled us to extract our main indications and the corresponding injection patterns. The main indication was spasticity of the triceps surae responsible for walk disorders. We therefore set up an observational study aimed at defining the therapeutic effects of an injection of 200U of incobotulinum toxin A (Xeomin) in patients suffering from MS for whom an indication of an injection of toxin in the sural triceps was suggested without another location elsewhere. We will present the results of this study and compare them with those in the literature.

Methods

This prospective study is an observational pilot study aimed at evaluating the impact of a current care treatment with no change in the patient's normal treatment regime.

Inclusion criteria

A patient over 18 years of age and suffering from MS with walking problems due to spasticity of the triceps surae, walking 10m in less than one minute, with or without a technical aid, with an EDSS lower than or equal to 6.5 [24] and spasticity of the triceps surae rated between 1 and 3 inclusive on the modified Ashworth scale.

Exclusion criteria

Difficulties with comprehension which did not allow the patient to give his free informed consent to the study. Intolerance to the botulinum toxin, injection of botulinum toxin in the last three months.

Evaluation criteria

The evaluation criteria are:

- the Timed up and Go test (TUG)

- the 6-Minute Walk Test (6MWT).

- the Multiple Sclerosis Walking Scale (MSWS-12) self-completed questionnaire score on the quality of walking (0 - 100).

- the Goal Assessment Scale (GAS): main objective is defined with the patient and assessed at each evaluation with a specific score : -2: worse than before, -1: no change, 0: objective achieved, 1: result better than expected, 2: unhoped-for result [25].

- the tolerance of the injection.

After receiving clear information and giving his consent the patient is enrolled in the study. The evaluation is performed before then at six weeks and at three months from the toxin injection to monitor the tolerance and the therapeutic benefit.

The botulinum toxin injection consists of an intramuscular injection of 200 U of xeomin in 6ml of physiological serum injected into 5 points respectively in the 2 gastrocnemius muscles and the soleus muscle after the first evaluation in accordance with the protocol normally used in our current practice.

Table 1: Clinical assessment during the study.

	Initial N= 28 M +/-sd (med/ interquartile)	6 weeks N= 27 M +/-sd (med/ interquartile)	3 months N = 27 M +/-sd (med/ interquartile)
Ashworth Scale	2.4 +/- 0.7 (3/1)	1.8 +/- 1 (2/2) 0.0006	1.9 +/- 1 (2/2) NS 0.07
TUG (seconds)	13.9 +/- 13 (9.4/6.5)	12.9 +/- 11 (8/6.6) 0.0033	11.8 +/- 8 (9/7) N=26 NS
6 MWT (metre)	358.5 +/-127 (370/157) N= 23	376.6 +/- 133 (360/147) N=21 NS	382.5 +/- 145 (340/250) N=22 0.004
MSWS-12	40.6 +/-10 (42/13)	37.9 +/- 10 (40/17) 0.015	40.3 +/- 8 (42/14.7) NS
GAS	-1+/-0 (-1/0)	0+/-0.85 (0/1.75) 0.003	0+/-1.2 (0/2) 0.0006

Statistical analysis

The descriptive quantitative data includes the mean and the standard deviation as well as the median and the quartiles.

The changes in the various scores were compared using the non-parametric Wilcoxon test with a significance threshold of 0.05, taking into account the absence of the normal distribution of results.

This study of current care received a favourable opinion from the Ethics Committee of the Rennes University Hospital Centre, France.

Results

Population

28 patients with an average age of 48.2 +/- 12 years suffering from MS were enrolled in this study, 19 women and 9 men. The disease had been developing for 15.2 +/- 12 years relapsing for 14, secondarily progressive for 5 and primary progressive for 9, with an average EDSS of 4.2 +/- 1.5. The spasticity of the triceps surae on the modified Ashworth scale is 2.4 +/- 0.7.

With regard to the GAS, the initial objective is to improve the quality of walking for 18 patients and the range of walking for 5. 2 patients want a reduction in spasticity, 1 in pain, finally 1 patient hopes to run again and 1 to be able to cook standing up.

Five patients, all with an EDSS greater than or equal to 5.5, were not able to complete the initial 6 minute test.

At 6 weeks one patient could not be evaluated but was evaluated at 3 months.

At 3 months one patient did not want to complete the final evaluation in its entirety and one patient did not want to complete the functional tests.

Walking data

The results of the initial, intermediate and final assessments are shown in Table 1.

At 6 weeks there was a significant improvement in the GAS, in spasticity assessed on the modified Ashworth scale, the TUG and the MSWS-12 but no impact on the 6 minute test.

At 3 months there was a reduction in the benefit for spasticity assessment with, nevertheless, a continued significant increase in the GAS, associated with a significant improvement in the 6 minute test with an average increase of 30.7 +/- 66 metres compared with the initial assessment.

No adverse event was recorded.

Discussion

Spasticity is responsible for a major deterioration in the quality of life in MS [7]. Initially it mainly concerns the lower limbs affecting walking and balance. The therapeutic approach will be different depending on whether spasticity is focal or diffuse. If botulinum toxin is currently considered to be the first intention treatment of focal spasticity in stroke, little data are available for multiple sclerosis [14,22].

It appears to be important to define the indications, the expected benefits and the injection procedures which will allow the therapist to use this therapeutic option in the best conditions. The level and type of handicap presented are clearly involved in the discussion and must be taken into account. With low EDSS scores, spasticity is most often focalised and the place of botulinum toxin, by analogy with the recommendations for stroke, therefore seems obvious. For high EDSS scores above 6, spasticity is usually diffuse, and sometimes is useful for standing up and moving around but it remains a barrier for positioning or personal hygiene tasks. High doses of toxin may aggravate the fatigue that is already present in multiple sclerosis and therefore do not appear to be recommended as a first intention [16]. On the other hand, targeted use on certain muscle groups, such as adductors, may be an interesting alternative by improving comfort and preserving useful spasticity [15,16,22].

In our practice, walking disorders is the main indication for the use of botulinum toxin [22]. Few studies in the literature have been devoted to the therapeutic benefit of botulinum toxin in this indication [17,20].

For this pilot study, we therefore targeted a population presenting with a moderate handicap, and a main complaint of deterioration in walking and balance. The proposed treatment corresponds to our normal therapeutic practices in terms of injection technique, target muscles and toxin dose. Whereas reference is frequently made to the use of botulinum toxin as a treatment for spasticity in MS, few studies in the literature are available, particularly for the indication of spasticity in the triceps surae. The Giovannelli study [20] aimed to define the contribution of physiotherapy during a treatment with botulinum toxin A and involved 38 patients with secondary progressive MS with an average EDSS score of 6. The therapeutic regime was variable depending on the patients and involved the upper and lower limbs, average doses were 100 U of botox for the upper limbs, divided between the flexor carpi ulnaris and radialis as well as the superficial digitorum superficialis and between 100 and 300 U of botox in the lower limbs involving the triceps surae and the posterior tibialis. The therapeutic benefit was evaluated with the modified Ashworth scale and a self-evaluation of satisfaction on a scale of 0 - 10. An improvement in the Ashworth score was observed with a satisfaction score of 6.56 for the toxin group and 7.86 for the group with toxin and physiotherapy.

These results are consistent with ours, even if the precise functional objective is not well defined by the authors in terms of evaluation by the visual analogue scale. More recently, Paoloni also showed that botulinum toxin injected into the lower limb (rectus femoris, triceps surae) at doses varying in total between 100 and 300 U of botox reduced spasticity of the triceps surae in patients with an average EDSS of 5 [17]. A good tolerance was observed with even an improvement in the fatigue sensation.

Our results show a major improvement at 6 weeks both in the patients' subjective evaluation recorded by the GAS and the MSWS-12 and in objective criteria such as the TUG test [26].

The improvement observed on function seems linked to a reduction in spasticity and tends to confirm the local therapeutic efficacy of botulinum toxin.

We had programmed our first evaluation at 6 weeks because this period corresponds to the maximum peak efficacy of the toxin. At 3 months, the effect on spasticity of the triceps surae is less, with an effect particularly on the TUG which is no longer significant, as with the MSW-12 score. However, satisfaction according to the GAS persists, with a significant improvement in the 6MWT. An indirect effect of the botulinum toxin on the walking centre perhaps explains this paradoxical result that will have to be confirmed by studying the spatio-temporal parameters of walking.

This study therefore confirms the benefit of an injection of 200U of Xeomin into the triceps surae for walking problems in MS suffering from focal spasticity. We deliberately did not change the rehabilitation treatment of our patients so as not to bias the results of this observational study.

Additional studies are necessary to answer outstanding questions: the dose required: does it have to be calculated depending on the intensity of the spasticity, body mass, age, the associated muscle deficiency?

Our results will serve as a basis for reflection on later research protocols in order to define better the place of botulinum toxin in the treatment of spasticity in patients suffering from multiple sclerosis.

Acknowledgement

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Conflict of Interest

Dr P Gallien has worked as expert for Merz, pharmaceutical company.

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