Interest of Botulinum Toxin for Treatment of Spasticity in Multiple Sclerosis

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Abstract

Background: Pyramidal tract lesions are common in multiple sclerosis (MS) patients and cause symptoms of spasticity, weakness and paralysis. OnabotulinumtoxinA treatment for spasticity is well-recognised, but remains to be defined in MS.

Objective: Analysis of practices in the treatment of spasticity in MS in a rehabilitation centre: Treatment of spasticity in MS with onabotulinumtoxinA according to level of disability.

Methods: Retrospective patient data review was conducted on MS patients treated with onabotulinumtoxinA from 2007 to 2010 in our neurologic rehabilitation center, with the aim to assess the modalities of use and effectiveness of onabotulinumtoxinA injections in everyday clinical practice.

Results: 126 patients (mean age: 49.4 ± 11 years), with a mean Expanded Disability Status Scale (EDSS) score of 5.8 ± 1.7 (range: 2.5-9.5) received onabotulinumtoxinA treatment. Key treatment goals were improved walking in the less disabled patients (mean EDSS: 5 ± 1), and improved comfort and nursing care for the most disabled patients (mean EDSS: 7.7 ± 1).

Therapeutic benefit was assessed using a Visual Analogue Scale and results were 6 ± 2.5 and 6.3 ± 3, respectively, with repeat injections for 65% of patients.

Conclusion: OnabotulinumtoxinA used in daily practice seems to be an effective, well-tolerated treatment in MS, with goals that vary according to the level of disability: i.e., improved walking and patient comfort. Further studies are needed to define the place and the effectiveness of onabotulinumtoxinA treatment in MS.

Keywords: Botulinum toxin; Drug utilization evaluation; Multiple sclerosis; Muscle spasticity; OnabotulinumtoxinA

Introduction

Spasticity is a common symptom in MS that causes significant functional impairment [1-5]. The therapeutic management of spasticity is problematic for therapists since the aim of treatment is to remove or reduce the disability induced by spasticity, whilst also retaining its benefits. Spasticity can be beneficial for some patients, particularly for those who are more severely disabled, i.e., with an Expanded Disability Status Scale (EDSS) >6, for example by assisting with walking or standing. Therefore, it is essential when managing spasticity to assess the individual clinical situation to establish clear targets for therapy, for example by considering level of functional impairment, degree of autonomy and choice of therapeutic agents. There is a range of available standard treatments, i.e., oral treatments (such as baclofen), botulinum toxin, intrathecal therapy, or surgery, together with adjuvant physiotherapy [4,6,7]. Botulinum toxin type A is a neurotoxin derived from the bacterium Clostridium botulinum. It prevents the release of acetylcholine at neuromuscular junctions, thereby inhibiting muscle contraction. It has become the first-line treatment for focal spasticity in France, including multiple sclerosis and post-stroke spasticity, and is now widely used [8,9]. However, there are few published studies investigating its use in MS [10-16]. The aim of this study was to provide a description of the use of onabotulinumtoxinA in the treatment of spasticity in MS based on a retrospective observational approach in our center by reviewing indications, treatment goals, injection patterns and therapeutic benefits.

Patients and Methods

Our rehabilitation center receives MS patients but also other patients with neurological diseases. We have used onabotulinumtoxinA treatment for MS on a regular basis since 2005 and we have closely monitored its effectiveness in this indication since it was introduced.

This study comprised a retrospective review of the records of MS patients who received onabotulinumtoxinA treatment between 1 January 2007 and 31 December 2010. We analysed treatment goals, target injection sites, and toxin doses. Benefits of treatment are currently assessed using a Visual Analogue Scale (VAS) that measured patient satisfaction on a scale of 0 to 10 [15]. A score of 0 correspond to the absence of improvement or an increase of the impairment, a score of 10 is synonymous of a total disappearance of symptoms. We consider the therapeutic results as good for a score upper than 5.

Treatment objectives and indications were analysed according to the degree of disability rated with EDSS score [17]. Statview 5 (SAS institute Inc.) was used for all statistical analysis. Means and standard deviations were calculated, statistical interference between groups were examined with ANOVA.

Results

During the study period, a total of 524 patients with MS were...
treated in our neurologic rehabilitation center, either as an inpatient or as a day hospital case. Of these 524 patients, 126 were treated for spasticity by onabotulinumtoxinA, 10 underwent implantation of a pump for intrathecal baclofen therapy. The remaining 388 patients benefited from physiotherapy in association when necessary with oral antispastic agents (baclofen or dantrolene). The characteristics of the 126 patients are presented in Table 1.

The two main goals of treatment were walking improvement, nursing improvement Table 2. Patients wanting to improve their gait were significantly less disabled than those whose objective was the improvement of nursing (p < 0.0001) or pain (p < 0.0001). The same results were observed for patients with dysuria (nursing p < 0.0001, pain = 0.0009) [Table 2].

Target areas for treatment comprised the lower limbs in 107 patients, upper limbs in 5 patients, and both upper and lower limbs in 6 patients. The striated sphincter muscle was the target muscle for 9 patients. The standard injection protocol for treatment of the lower limbs with the aim of improving walking consisted of injections into the triceps surae (i.e., gastrocnemius and soleus). Sometimes injections of either flexor digitorum longus, tibialis posterior or anterior tibialis were associated.

For patients whose treatment objective was to improve nursing care, onabotulinumtoxinA injections were given into the following lower limb muscles: adductor magnus, semitendinosus, semimembranosus, as well as the following upper limb muscles: pectoralis major, biceps brachii and brachialis. These patients were older (p = 0.045) and more severely impaired (p = 0.001)

For the two patients with a treatment objective of improved use of the upper limbs, the flexor pollicis longus, flexor digitorum profundus and the flexor digitorum superficialis were targeted.

In the particular case of pain reduction as aim of treatment, no specific clinical pattern emerged. However, the patient profile in this group was quite similar to that of the MS patients whose treatment objective was improved nursing care.

In those patients with detrusor-sphincter dyssynergia where the treatment objective was dysuria, defined as difficulty for voiding as a result of involuntary contractions of the external urethral sphincter during detrusor contraction and micturition. OnabotulinumtoxinA injections were administered into the sphincter muscle according to the technique described previously [18]. Table 3 provides details of the average onabotulinumtoxinA dose per unit injected into each target muscle. The maximum dose injected per session never exceeded 200 U

| Lower Limb: | Number of injection sessions | Length between injection |
|-------------|-----------------------------|-------------------------|
| Triceps surae | 2.5 +/- 0.8 | 100 U |
| Tibialis anterior | 3.5 +/- 3 | 10 U |
| Tibialis posterior | 4.9 +/- 2 | 7 U |
| Flexor digitorum longus | 5.2 +/- 4 | 100 U |
| Adductor magnus | 6.5 +/- 2 | 70 U |
| Hamstring | 7.7 +/- 1 | 67 U |

| Upper Limb: | Number of injection sessions | Length between injection |
|-------------|-----------------------------|-------------------------|
| Pectoralis major | 6.5 +/- 2 | 100 U |
| Biceps brachii and brachialis | 7.7 +/- 1 | 47 +/- 9 |
| Flexor pollicis longus | 8.3 +/- 2.9 | 45 U |
| Flexor digitorum profundus | 8.4 +/- 2.9 | 44 U |
| Flexor digitorum superficialis | 8.5 +/- 2 | 43 U |

Table 3: Average Onabotulinumtoxin A dose for the most commonly injected muscles.

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| Goal | Satisfaction score | Number of injection sessions | Length between injection |
|------|-------------------|-----------------------------|-------------------------|
| Gait improvement | 6.1 +/- 2.6 | 4.4 +/- 4.5 | 3.3 +/- 0.8 |
| Nursing improvement | 6.3 +/- 2.9 | 3.5 +/- 3 | 3.32 +/- 1 |
| Dysuria | 6.3 +/- 2.9 | 2.84 +/- 3 | 4.9 +/- 2 |
| Pain | 6.5 +/- 2 | 5.2 +/- 4 | 4 +/- 2.8 |

Table 4: Results.

| Goal | Number of injection sessions | Length between injection |
|------|-----------------------------|-------------------------|
| Gait improvement | 77 | 48.5 +/- 11 | 4.98 +/- 1.1 |
| Nursing improvement | 30 | 52.4 +/- 11 | 7.7 +/- 1 |
| Dysuria | 9 | 48.4 +/- 12.5 | 5 +/- 1.3 |
| Pain | 8 | 47 +/- 9 | 7 +/- 1.9 |
| Use of upper limb | 2 | 41 +/- 12.5 | 5.7 +/- 0.7 |

Table 2: Goals of treatment.

Therapeutic Benefits

Treatment benefits were assessed using standard clinical evaluation, together with analysis of any emergent adverse effects. Patient self-assessments were performed using the VAS and appear in Table 4. The mean VAS scores were 6.2 ± 2.6. No adverse effects were reported by patients. A total of 65% of patients received repeat injections. Decision for repeating injection was taken with the patient according to the tolerance and the benefit of treatment. In case of treatment failure an increase of dose or a change of muscle targets were discussed. The decision to stop this treatment was generally due to a result which was assessed as insufficient by the patient. Mean length of time between injections was 3.56 months [Table 4].

Discussion

This retrospective study carried out at our center focused on two main treatment objectives in our patients: improved walking and improved nursing care. These two objectives comprised two different MS patient populations. In those patients where improved walking was the goal, these were ambulatory patients with a mean EDSS score of 5, which corresponds to patients with a walking distance of 200 metres without use of a walking aid.

The group seeking improved nursing care involved severely disabled and dependent patients who were usually not capable of walking and wheelchair bound. In fact more disabled MS patients are predominantly the focus of published literature. Snow et al. published a study of 9 patients with an EDSS score >6 [14]. This was a crossover study assessing botulinum toxin versus placebo to evaluate the effectiveness of the toxin injected into hip adductor with the aim of improving nursing care. The
dose of toxin was 400 mouse Units and injections were administered into the adductor muscles unilaterally. No adverse effects related to the toxin were observed. A positive treatment effect was noted regarding muscle tone that also resulted in improved toilet hygiene and urine control. Hyman recently reported the results of a study of 74 patients with an EDSS score >7 [11]. The injection regimen concerned the hip adductors treated bilaterally and the study investigated 4 different doses: placebo, 500, 1000, and 1500 U abobotulinumtoxinA. The results were rather disappointing, although improved hip abduction was noted, characterised by an increased distance between the knees when in passive motion. No other obvious benefits were noted. Since the highest dose of 1500 U was also associated with an increase in adverse effects, such as excessive muscle weakness without obvious therapeutic gain, the authors concluded that they would recommend the slightly lower dose of 1000 U abobotulinumtoxinA in this indication.

The importance of combining botulinum toxin treatment with adjuvant physiotherapy was investigated by Giovannelli [15]. In this study, 38 patients with secondary progressive MS with a mean EDSS score of 6 received a variable treatment regimen into the upper and lower limbs. Average onabotulinumtoxinA doses were 100 U into the upper limbs, divided between the ulnar and radial carpal flexor and superficial finger flexors, and 100 to 300 U onabotulinumtoxinA into the lower limb triceps surae and posterior-tibial muscles. Therapeutic benefit was assessed using the Modified Ashworth Scale (MAS) and patient self-assessment of treatment satisfaction using a VAS scale of 0 to 10. Improvements in the MAS scores were observed with a post-treatment score of 6.56 for onabotulinumtoxinA alone and 7.86 for the toxin associated with physiotherapy treatment patient group. These results emphasise the importance of combining treatments to achieve the best possible patient outcomes. Although improved function was not assessed by the investigators as part of this study, it is interesting to note that the VAS patient satisfaction scores observed 12 weeks post-treatment were similar to those found in our observational study. Paoloni recently showed that onabotulinumtoxinA injected into the lower limb (i.e., rectus femoris, triceps surae) at total doses ranging from 100 to 300 U decreased spasticity of the triceps surae in patients with a mean EDSS score of 5 as evidenced by the MAS [12]. A positive effect was also noted on fatigue, but no benefits were found regarding the activities of daily living according to the Barthel Index. However, it should be noted that a significant study limitation was that the doses of toxin used were not accurately determined.

These studies raise the issue of the lack of consistency regarding the primary outcome adopted for the different studies. The MAS is the standard assessment tool, but it is not always well-correlated with functional benefit, while the Global Assessment Scale (GAS) for assessing overall functioning is generally the preferred scale, but its use is not always clear [20,21]. In our current practice, we have chosen to use a VAS for a specific goal identified in collaboration with the patient at the beginning of treatment. This tool constitutes simple common practice, but is probably not sufficiently robust to be used in a randomised clinical trial setting. Whichever assessment tool is adopted, it is necessary to focus on patient functional assessment. The use of onabotulinumtoxinA for intra-sphincter treatment remains questionable in MS. In a previous study, we demonstrated the lack of therapeutic benefits of an intra-sphincter injection of 100 U on postvoiding residual urine volume, however, we continued with this therapeutic approach in specific limited cases, such as in patients who found self-catheterisation difficult, or in case of dysuria associated with painful bladder and limited retention [18]. For some patient we noticed some real benefits. By contrast, in the field of neurourology, botulinum toxin is now widely used for treatment of bladder over activity with intra detrusor injections [22].

In conclusion, analysis of our clinical practice has enabled us to evaluate the use of onabotulinumtoxinA in MS. Two major goals treatment emerged in our practice on two different patient populations: improved walking in the less disabled population and improved nursing care in the more severely disabled patients. OnabotulinumtoxinA treatment was well-tolerated with good therapeutic efficacy, leading to repeat injections administered to 65% of patients. This study is just an evaluation of clinical practice, but it provides evidence in terms of indications and dosage which is important for the establishment of best practice guidelines for the treatment of spasticity with onabotulinumtoxinA in MS.

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