Does reduction of number injection sites of abobotulinum toxin A impact efficacy in Neurogenic Detrusor Overactivity (NDO) in the spinal cord-injured (SCI) rat model?

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Peyelpharm, Montpellier-Lez-Cesnnes, France, 1,4 Biorep, Aix-en-Provence, France, 3,4 Biopharm Ltd, Winchester, UK. Antibiotics (except gentamycin) and anesthetics were purchased from Centralvet (Dinan, France) and Roche Pharma (Neuilly-sur-Seine, France).

OBJECTIVES

Spinal cord injury (SCI) induces plasticity within neural pathways innervating the lower urinary tract (LUT), with the recruitment of nociceptive “silent” C-fibers leading to the development of an abnormal autonomic micturition reflex and emergence of neurogenic detrusor overactivity (NDO), thereby greatly compromising bladder filling during the micturition cycle.

In SCI patients, botulinum toxin A has been evaluated for the treatment of refractory NDO and have been reported to decrease urinary incontinence frequency and maximum intravesical pressure while increasing bladder capacity and compliance Onabotulinum (Ona) toxin A intradetrusor injections is registered as a second-line treatment to treat NDO in humans. Injection protocol remains variable among clinical studies. However approved Ona label recommends 30 injection points in the bladder wall.

The main objective of this study was to determine the effect of reducing the number of injection sites by comparing the effect of 4 versus 8 injection sites with abobotulinum toxin A (aboBoNTA) in the SCI rat, a relevant model of NDO

METHODS

Experimental design

Nineteen days old rats received intradetrusor injections in 4 or 8 sites of saline or aboBoNTA 22.5U. Two days after injections, effect of aboBoNTA on urodynamic clinically relevant parameters was determined by analysis of variance test versus aggregated saline groups (ASG). Four experimental groups were considered: saline (NS, n=9); 4 sites (12.5µl total volume, n=12; 5.25µl sites), saline 8 sites (25µl total volume, n=11; 5-Bisites), aboBoNTA 4 sites (12.5µl total volume, 5.6µl per site, n=20; aboBoNTA-4sites) and aboBoNTA 8 sites (25µl total volume, 2.8µl per site, n=20; aboBoNTA-Bisites).

RESULTS

I- Effect of intradetrusor injections of aboBoNTA-A 22.5U in 4 or 8 sites in rats 19 days after SCI-induced NDO

A- Effect on saline groups

To perform statistical analysis versus aboBoNTA treated groups, 4-Sites and 8-Sites groups were aggregated as they were not significantly different for all urodynamic parameters (ns, P>0.05; Table 1)

Table 1: Rats reduced in, in 4 or 8 sites of saline

<table>
<thead>
<tr>
<th>Corresponding clinically relevant parameters</th>
<th>Treatment</th>
<th>Saline (4 vs 8 sites)</th>
<th>Neuronic sites</th>
<th>Aggregated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal pressure at contraction (IP Max)</td>
<td>30.3±1.6</td>
<td>30.6±1.9</td>
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<td></td>
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<tr>
<td>Post-void residual volume in bladder</td>
<td>87.2±4.9</td>
<td>87.3±5.9</td>
<td></td>
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<tr>
<td>Maximal storage capacity</td>
<td>80.1±4.58</td>
<td>80.9±6.69</td>
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<tr>
<td>Compliance index, % or Cmax/Rmax</td>
<td>8.1±0.82</td>
<td>8.1±0.82</td>
<td></td>
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<tr>
<td>Pressure at first involuntary contraction</td>
<td>5.0±0.8</td>
<td>5.0±0.8</td>
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</tbody>
</table>

B- Effect on physiological parameters

- Before intradetrusor injections, body weight of SCI rats was similar between all experimental groups of rats.
- Four days post-intradetrusor injections, body weight was significantly lower for aboBoNTA-4sites compared to 8-Sites (237±3.8 versus 279±4.1g respectively, P<0.001) and aboBoNTA-Bisites compared to 5-Sites (253±3.55 versus 279.96±0.6g respectively, P<0.01).

However, there was no difference in the AUC of body weight loss between aboBoNTA-Bisites and aboBoNTA-Bisites groups

II-Doses reduction of number injection sites of abobotulinum toxin A impact efficacy in NDO in the SCI rat model?

Fig 1: Effect on Maximal pressure

Fig 2: Effect on Bladder capacity

Fig 3: Effect on Compliance

Fig 4: Effect on non-voiding contraction

Fig 1: aboBoNTA 22.5U administered either in 4 or 8 sites significantly and similarly decreased maximal pressure of voiding contraction compared to aggregated saline groups, without affecting voiding efficiency.

Fig 2: aboBoNTA 22.5U increased, significantly (-4 sites) and non significantly (-Bisites), the infused volume, index of bladder capacity.

Fig 3: aboBoNTA 22.5U improved compliance of the bladder albeit at the limit of significance when injected in 8 sites.

Fig 4: Whatever the number of sites, the amplitude of NVIC [Pressure at first involuntary contraction] was significantly decreased.

CONCLUSION

- This study is the first preclinical investigation comparing the effect of aboBoNTA intradetrusor injections when reducing the number of injection sites in the SCI rat model and showing similar efficacy of aboBoNTA in NDO regardless of the number of injections.
- This may provide insights for improvement and flexibility of clinical injection procedures of BoNTa to treat NDO and further in idiopathic overactive bladder (IOAB).
- Larger preclinical studies are warranted to better understand BoNTa effects according to injection procedure variations, thereby setting the grounds for optimized dosing schemes to improve the risk-benefit ratio of BoNTa-based treatment modalities for NDO and IOAB.