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A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY INVESTIGATING EFFICACY OF BOTULINUM TOXIN TYPE A (DYSPORT®) IN MS RELATED OVERACTIVE BLADDER SYNDROME (OAB): PROVISIONAL 36 WEEK RESULTS.

Hypothesis / aims of study
The use of botulinum toxin type A in the treatment of OAB is increasing. However, with few placebo controlled studies performed the majority of current evidence supporting its efficacy depends on non-randomised and anecdotal data. Our aim to undertake a pilot placebo controlled study assessing the efficacy of botulinum toxin type A (Dysport®) in MS related overactive bladder syndrome (OAB).

Study design, materials and methods
20 patients with a formal diagnosis of MS for at least one year, made by a Consultant Neurologist, were included and randomised into the study. Each also had OAB syndrome diagnosed by a Consultant Urologist and had at least one episode of leakage per day. All had urodynamically proven detrusor overactivity and had found anti-cholinergics either ineffective or their side effects intolerable. Patients with symptoms of stress related incontinence were excluded from the study. With the investigators and recruits “double-blinded”, 10 patients were injected with 500units Dysport® diluted in 5ml 0.9% saline, and 10 patients with 5mls placebo. Injections were performed via flexible cystoscopy. Continence diaries assessing daytime frequency, nocturia and episodes of leakage were completed for three consecutive days prior to injections (baseline), at 12 weeks and at 36weeks. 24 hour pad weights were also performed at these points. Urodynamics were performed at baseline, 6 weeks and at 36 weeks. Patients were asked if they had seen an overall improvement in symptoms, those who had not were withdrawn from the study at 12 weeks.

Results
13 patients noticed improvements and stayed in the trial. 7 withdrew at the 12 week stage; none of which had been given active treatment. For analysis the change in mean/ median values from baseline to the 12 week stage (6wks in the case of urodynamics) were compared between the placebo and active arms using the two sample T-test, the Mann-Whitney test or the Fischer exact test. As only 3 subjects receiving placebo were present at the 36 week stage a paired t-test was performed between the active group at the 12 and 36 week points.
A significant reduction was seen in daytime frequency, pad weights and the number of patients requiring anti-cholinergics at the 12 week stage. These improvements persisted at the 36 stage with no significant deterioration seen. However, no significant difference was seen in nocturia and number of leakage episodes at either points, (table 1; mean (s.d.) / median, *p<0.05).
Significant improvements were seen at the 6 week stage in maximum cystometric capacity (Ccmax), Volume of first overactive contraction (VFOC), and Pressure of first overactive contraction (PFOC). However, at the 36 week stage there was a significant reduction in maximum cystometric capacity. Residuals had increased significantly at both stages. No significant effect was seen upon either the first desire to void (FDV), or normal desire to void (NDV), (table 2; mean (s.d.)/ median, *p<0.05).

	Change in mean/ median from baseline to 12 weeks			Change in mean/ median from 12 to 36 weeks[$]	
	Placebo group	Active group	P - value	Active group	P - value
leakage episodes/ day[§]	-1.74 (2.04)	-4.27 (5.99)	0.235	0.93 (2.39)	0.248
Frequency/ day[§]	0.37 (2.10)	-2.18 (2.79)*	0.035	0.57 (1.42)	0.237
Nocturia/ night[§]	-0.07 (0.75)	-0.53 (0.92)	0.229	0.48 (0.86)	0.108
Pad weights/ day[†]	-12	-168*	0.0046	18.3 (39.5)	0.177
Anticholinergic use[‡]	0	-50%*	0.029	-63% (from baseline)	---

Table 1: the effects of botulinum toxin type A (Dysport®) on variables recorded in a 3-day diary.([§] Two sample T-test, [†] Mann-Whitney test, [‡] Fischer exact test (between baseline and 12 weeks). [$] paired t-test between 12 and 36 week data.)

	Change in mean/ median from baseline to 6 weeks			Change in mean/ median from 6 to 36 weeks[$]	
	Placebo group	Active group	P - value	Active group	P - value
Ccmax[§]	53 (111)	185 (110)*	0.016	-90 (125.7)*	0.049
FDV[†]	42.5	126	0.521	-57.5 (118)	0.158
NDV[§]	85 (110)	151 (114)	0.204	-54.7 (138.2)	0.242

VFOC[§]	31.1 (64.5)	149 (145)*	0.036	-57.4 (86.8)	0.066
PFOC[†]	6.5	-7.5*	0.001	6.6 (20.8)	0.389
Residual[§]	-5.4 (43.9)	98 (79.5)*	0.003	-2.4 (91)	0.936

Table 2: the effects of botulinum toxin type A (Dysport®) on urodynamic parameters. ([§] Two sample T-test, [†] Mann-Whitney test, (between baseline and 12 weeks). [$] paired t-test between 12 and 36 week data.)

Interpretation of results

In MS patients suffering from associated OAB wet botulinum toxin type A (Dysport ®) is effective in reducing daytime frequency and the amount of leakage. In addition many patients (50%) feel that they can stop their anticholinergic medication as a result of this treatment. These clinical improvements are reinforced by associated improvements in the urodynamic parameters maximum cystometric capacity, and the volume/ pressure of the first overactive contraction. Clinical improvement persists at 36 weeks although there is a reduction in maximum cystometric capacity at this stage.

Concluding message

Botulinum toxin type A (Dysport®) is an effective treatment in MS related OAB wet persisting for 36weeks and significantly improving the troublesome symptoms of leakage and frequency that many patients with this condition find socially limiting.

FUNDING: **Ipsen, Slough, UK**
DISCLOSURES: **NONE**
CLINICAL TRIAL REGISTRATION: **This clinical trial has not yet been registered in a public clinical trials registry.**
HUMAN SUBJECTS: **This study was approved by the Lothian Ethics Committee, Scotland. and followed the Declaration of Helsinki Informed consent was obtained from the patients.**