Botulinum toxin injections for treating neurogenic lower urinary tract dysfunction

Botulinum toxin A (BoNT/A) is the most potent biological toxin known to man. Nevertheless its therapeutic applications do not stop increasing. BoNT/A is commercially available as protein complexes under the trade names of Botox®, Dysport® and Xeomin® and Prosigne®. Units used to measure BoNT/A potency are not equivalent between brands and comparative studies were never carried out. FDA, recognizing the potential risk of dose miscalculation, introduced non-proprietary names for each brand. Onabotulinum toxin A (onabotA), abobotulinum toxin A (abobotA) and incobotulinum toxin A (incobotA) are the non-proprietary names for the toxins available under the proprietary names Botox®, Dysport® and Xeomin®, respectively.

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Until now only onabotA received approval for application in the lower urinary tract. The first licence was to treat urinary urinary incontinence due to neurogenic detrusor overactivity (NDO), a process that started in 2011 following the positive conclusion of two large regulatory phase 3 trials.[1,2] These two studies, the long-term extension study that followed them and a pooled analysis of phase III data will be reviewed here.

Main studies

The DIGNITY (Double-blind InvestiGation of purified Neurotoxin complex In neurogenic deTrusor overactivitY) program included two pivotal phase 3 studies where efficacy and safety of onabotA in doses of 200 and 300U were compared against placebo in about 700 patients with multiple sclerosis (MS) or spinal cord injury (SCI) and NDO leading to urinary incontinence insufficiently treated by anticholinergic drugs.[1,2] Patients were randomized to receive 200 and 300U of onabotA or saline in 30 bladder injections of 1ml each above the trigone. Primary outcome measure was the change from baseline in the number of episodes of urinary incontinence during week 6 after treatment.

KeyPoints

- OnabotA 200U injected in 30 sites above the bladder trigone (1ml per site) is an approved, effective treatment for NDO in patients with MS and SCI not adequately managed with anti-cholinergic drugs.
- OnabotA 200U also provides significant clinical and urodynamic improvement and increasing quality of life of MS and SCI patients.
- The effect of OnabotA 200U may last 9 months and is consistently re-observed after re-injections.

Secondary outcome measures included the change from baseline in maximum cystometric capacity (MCC), maximum detrusor pressure during first involuntary detrusor contraction (PdetmaxIDC) and quality of life using the I-QOL total score also at week 6 after injection.[1,2] The two doses were more effective than placebo in controlling incontinence, without clinical relevant differences between them. In all secondary endpoints both doses were also more efficacious than saline without relevant differences between them. Duration of the effect was superior in the onabotA arms, again without differences between the two doses.[1,2] However, as adverse events were more common in the 300U arm,[1,2] health authorities in US and Europe approved onabotA 200U reconstituted in 30ml of saline and injected in 30 points above the trigone (1ml in each point) to treat NDO refractory to anticholinergic drugs.

A recent pooled analysis of the two studies gives a clear picture of the benefits of OnabotA 200U on urinary inconti-

nence.[3] Similar reductions in UI episodes were observed regardless of aetiology, MS or SCI, at week 6. Mean decreases of –22.6 and –19.6 episodes of incontinence per week were seen in MS and SCI patients, respectively. Dry rates were 41.5% in MS patients and 30.9% in SCI patients. These numbers are in both aetiologies much above those observed in the placebo arm (10.7% in MS and 7.3% in SCI patients, respectively). The change in the number of voluntary voids per week was examined only in the non-catheterizing MS subpopulation. At week 6, onabotA 200U decreased the number of week voids by 15 times, a number much higher than in the placebo arm, around 2 per week.[3] A large proportion of patients in both etiologies treated with onabotA 200U had no involuntary detrusor contractions (IDC) compared to placebo (68.0% versus 18.5% in MS, and 58.7% versus 18.2% in SCI patients). In patients who had an IDC a substantial decrease in detrusor pressure was found, bringing maximal detrusor pressure to values well below 40cmH_2O. OnabotA 200U, in contrast with placebo, also caused a marked improvement in quality of life of both MS and SCI patients.[3] The median duration of the effect of onabotA 200 U in the MS population was 295 days and in the SCI population was 253 days.[3]

Non-complicated urinary tract infection was the most common reported adverse event after onabotA 200U, the incidence being higher in MS patients than in SCI patients, an observation that reflects the lower percentage of patients doing clean intermittent catheterization (CIC) in the MS group. The rate of de novo CIC due to urinary retention was 31.4% after onabotA 200U (4.5% in the placebo group). About 15% of patients used CIC for ≤36 weeks, while 16.3% used CIC for >36 weeks.[3] It should however be stressed that CIC was not required in about two thirds of the MS patients treated with onabotA 200U. Nevertheless, in order to investigate if it is possible to reduce urinary retention and CIC in MS patients with less severe forms of incontinence, an ongoing double blind placebo controlled trial is with onabotA 100 U was initiated. The results are expected by the beginning of 2015.

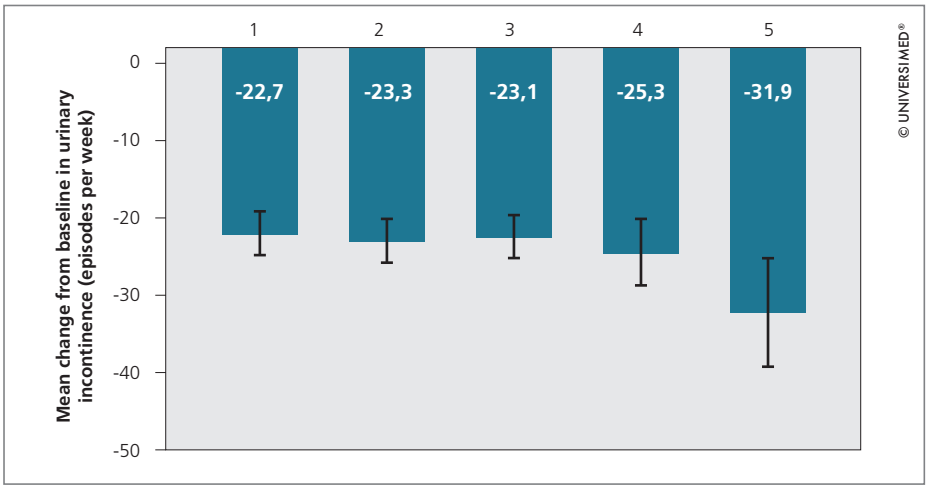

Fig. 1: Reduction of the episodes of urinary incontinence per week after 5 treatment cycles. The mean number of UI episodes/week at baseline was 31.2

OnabotA treatment and concomitant anticholinergic medication

At the time of study entry in the Dignity trials, slightly more than 50% of the patients were not taking any anti-muscarinic drug.[1, 2] These patients could not initiate an anti-muscarinic drug during the entire length of the study. Those taking anti-muscarinics at baseline had to maintain the baseline dose unchanged. This allowed a post-hoc analysis of the effect of onabotA 200U according to the situation of anticholinergic use.

Similar reductions in urinary incontinence episodes were observed after onabotA 200U regardless of anticholinergic use. The percentage of patients fully dry at week 6 was also similar among anticholinergic users and non-users. For patients treated with onabotA 200U, dry rates achieved 36.7 for anticholinergic users and 37.4 for non-users. In what concerns urodynamic outcomes, similar increases in MCC and decreases in detrusor pressure were observed among anticholinergic users and non-users. The duration of the effect of onabotA 200U was also similar in the two groups.[3, 4] In addition, the incidence of urinary tract infections and the incidence of urinary retention were similar among anti-cholinergic users and non-users. Thus, a systematic maintenance of a daily anti-cholinergic medication in NDO patients after onabotA 200U administration may not be justifiable.[3, 4]

Repeat injections of onabotA 200U

Patients who completed the two phase 3 trials could join an extension open label study. An interim analysis of this study was recently reported.[5] The reduction of the episodes of urinary incontinence observed after the first injection of onabotA 200U was consistently maintained up to five re-injection cycles (decreases of –22.7, –23.3, –23.1, –25.3 and –31.9 episodes per week from cycle 1 to 5). Figure 1 depicts these data. The proportion of patients fully dry also remained stable, around 40% over the 5 cycles.[5] ■

Literature:

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