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Platinum Priority

Reply from Authors re: Christopher R. Chapple. Finding the Correct Starting Dose for OnabotulinumtoxinA. *Eur Urol* 2012;61:530–2

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The editorial comment submitted by Chapple [1] is of great value, and we thank him for this. OnabotulinumtoxinA (ObTA) seems destined to become one of the new treatments for non-neurogenic (idiopathic) refractory overactive bladder (OAB). The risks and benefits are clearly demonstrated through the results of our work [2] and through the recent studies described by Chapple that focus on finding the optimal dosage, with a clear trend to reducing the dose in comparison with patients with neurogenic detrusor overactivity (NDO) [3–5]. The issue of defining clinically significant residual urine and urinary tract infection (UTI) has not been solved at this time.

The development of new minimally invasive treatments with specific modes of action allows us to question whether we are able to select the best treatment for the best patient. Over the last 30 yr, because the only available treatments were anticholinergic drugs, OAB has been defined as an association of symptoms and the target for these drugs. In this way, we failed to emphasize the fact that the OAB patient population is clearly heterogeneous (male and female, young and aged, premenopausal and postmenopausal, with or without stress incontinence, with or without previous pelvic

surgery, with and without detrusor overactivity [DO]). Most clinical studies have tried to control these potential biases by selecting patients without urinary retention, with no urodynamic signs of obstruction, and so forth, but this approach does not reflect routine clinical practice and represents a real risk of misuse. New treatments such as ObTA for refractory OAB requires more comprehension of mode of action and pathophysiology as well as better selection of patients for an improved risk–benefit balance—a matter of importance in such a large population of patients.

NDO treatment with ObTA (Botox, Allergan), which is now licensed in most countries, should be a good demonstration that trying to incorporate this population into one group (NDO) fails to reflect the differences in terms of pathophysiology, symptoms, patient expectations, and risk of side effects. The differences observed between multiple sclerosis and spinal cord injury patients in terms of efficacy, placebo effect, and side effects perfectly illustrate this risk [6]. Moreover, the lack of evidence in stroke, dementia, or Parkinson's disease, despite frequently observed NDO in these populations, requires caution with the use of ObTA in those patients when indicated.

Based on the results from our study [2] and on the other double-blind placebo-controlled studies [6–9], we help determine a minimally efficient dose of 100 U ObTA as a second-line treatment for refractory OAB. Urinary retention, clean intermittent catheterization, and UTI risk seems to be dose dependent. These issues point to the need for a reduction of the dose used compared to that for neurogenic patients, but there are still unresolved questions. A recent article from the London group reported that in cases of detrusor oversensibility, 100 U of Botox failed to improve symptoms [9]. Confoundingly, in a recent phase 2 study, it seems that patients with or without DO may have the same benefit in term of symptom improvement [7]. Because of the relatively small numbers of patients in each group in all

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published clinical studies, there is still no information about risk factors for urinary retention. We are still awaiting a large study in which risk factors of urinary retention are clearly described. Refractory OAB in clinical practice is a mix of patients that may behave very differently. Dose titration seems like the pragmatic approach to individually control side effects with efficacy that fits with patient expectations. This will help in clinical practice to inform patients, to organize follow-up, and to select the best dose or population of patients for a careful titration strategy.

Conflicts of interest: Pierre Denys is an investigator and speaker for Allergan, Ipsen, and Medtronic. Emmanuel Chartier-Kasler is an investigator for Allergan, Astellas, AstraZeneca, Coloplast, Ipsen and Medtronic. He is a consultant for Allergan, Astellas, Coloplast and Zambon. He is a speaker for AMS, Astellas, AstraTech, Coloplast and GSK.

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