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Patient-reported outcomes in men with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) treated with intraprostatic OnabotulinumtoxinA: 3-month results of a prospective single-armed cohort study

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Study Type – Therapy (prospective cohort)
Level of Evidence 3a

OBJECTIVE

- To evaluate patient-reported and objective outcomes after intraprostatic injection of OnabotulinumtoxinA (BTX-A) in men with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).

PATIENTS AND METHODS

- A prospective single-armed cohort study was designed.
- Patients diagnosed with LUTS due to BPH and unsatisfactory response to medical therapy, were recruited between November 2010 and July 2011.
- Patients received transperineal injection of 200 U BTX-A in the transition zone, under transrectal ultrasonographic guidance.
- The outcome assessment was performed at 3 months and included a patient-reported outcomes (PROs) questionnaire with questions on patient global impression of improvement (PGI-I, 0–6 point scale), of satisfaction (PGI-S, 0–5 point scale), and of efficacy (PGI-E, 0–5 point scale).

RESULTS

- Of 75 screened patients, 64 with a mean (SD) age of 63 (9.3) years were available for the outcome assessment.
- Patients reported a mean reduction of 49% in International Prostate Symptom Score (IPSS), which decreased from 19.7 (7.7) to 10 (7.1) ($P < 0.001$), and a mean reduction of 44% in IPSS-health-related quality of life item score, from 4.17 (1.2) to 2.3 (1.6) ($P < 0.001$).
- There was a 33% increase in maximum urinary flow rate ($P < 0.001$) and an 80% reduction in postvoid residual urine volume ($P < 0.001$).
- In all, 36 (56%) patients had a subjective improvement in LUTS (PGI-I ≥ 4), 43 (67%) reported satisfaction with the treatment (PGI-S ≥ 3), and 44 (68%) judged the treatment as effective (PGI-E ≥ 3). In all, 50 (79%) patients would repeat the same treatment under the same circumstances, while 54 (84%) would recommend the treatment to another person with the same diagnosis.
- There was a statistically significant positive correlation between patients' satisfaction and both baseline IPSS (ρ 0.441, $P < 0.001$) and reduction rate of the IPSS (ρ 0.850, $P < 0.001$).

CONCLUSIONS

- Intraprostatic injection of BTX-A in men with LUTS due to BPH provides clinically significant short-term subjective and objective benefit.
- Increasing severity of baseline LUTS appears moderately associated with the patient-perceived benefit from the treatment.
- Although the non-randomised design and short-term assessment limit the level of evidence of our study, intraprostatic BTX-A seems a promising, safe and minimally invasive option for patients with BPH with unsatisfactory response to standard drug therapy.

What's known on the subject? and What does the study add?
Several short-term studies have shown that intraprostatic injection of botulinum toxin (BTX) improves lower urinary tract symptoms and flow parameters in patients with BPH, but information on patient-reported outcomes is lacking.

The present study provides useful data on patient-perceived level of improvement and effectiveness of intraprostatic injection of BTX, as well as on patient's satisfaction with this therapy. Short-term results are promising and comparable with those reported with standard pharmacological therapy.

KEYWORDS

botulinum toxin, lower urinary tract symptoms, benign prostatic hyperplasia, patient-reported outcome, patient's satisfaction

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INTRODUCTION

BOO secondary to BPH with benign prostatic enlargement represents the most common cause of LUTS in older men [1]. Major treatment goals are fast and sustained long-term relief of LUTS, improvement of health-related quality of life (HRQL), prevention of disease progression and complications, and as important, patient's satisfaction with treatment. Currently, BPH is commonly treated with pharmacological therapy including α-blockers, which reduce urethral resistance, and 5α-reductase inhibitors (5-ARIs), which reduce prostate volume. However, these drugs must be taken continuously, cannot always control the long-term urinary symptoms and progression, and are associated to several side-effects [2–4]. For patients with severe LUTS, prostate reduction can be obtained surgically by TURP or by minimally invasive surgical techniques. Each surgical option has specific adverse consequences and >20% of patients undergoing TURP do not have satisfactory long-term outcomes [5].

Botulinum toxin (BTX) is an emerging, non-invasive and potentially targeted therapy for BPH. BTX blocks the release of neurotransmitters, e.g. acetylcholine and norepinephrine, from pre-synaptic nerves [6,7]. The therapeutic benefit of intraprostatic BTX injection is based on its organ-specific, chemical denervation leading to inhibition of smooth muscle contraction and tissue atrophy [6,7]. Animal experiments have suggested that the mechanism of action in the prostate gland is induction of atrophy, diffuse apoptosis, reduced cell proliferation and decreased expression of α-adrenergic receptors [8–10]. As a result, BTX may have effects on both the dynamic and the mechanic component of BPH.

Several cohort and small randomised studies evaluating the effects of intraprostatic injection of BTX have been published and recently summarised in systematic reviews [11,12]. There is substantial agreement on the safety and effectiveness of BTX in improving both LUTS and BOO parameters. However, these studies focused mainly on objective measures and limited the evaluation of subjective health outcomes to the IPSS [13]. The patients' opinions about the treatment were given little consideration for assessing treatment outcome. The value of patient-reported outcomes (PROs), such as patients' perceptions, preferences and satisfaction with therapy, is increasingly accepted as part of the clinical decision-making process, and has been increasingly acknowledged in clinical practice guidelines for the management of BPH [14–17]. Consequently, we considered it of interest to appraise the PROs of this investigational novel treatment for male LUTS, to provide researchers with pre-trial data relevant for the design of future randomised trials.

The purpose of the present study was to evaluate safety and efficacy of intraprostatic injection of OnabotulinumtoxinA (BTX-A) by assessing both objective and subjective health outcomes, including the impact on sexual function and patients perceptions about their treatment.

PATIENTS AND METHODS

A prospective, single-armed cohort study was designed. The study was conducted in one tertiary referral centre (Urological Clinic, 'Agostino Gemelli' Universitary Hospital, Rome, Italy). Ambulatory patients were recruited between November 2010 and July 2011, after signing written research consent. Patients were followed-up for ≥3 months after treatment.

The study was conducted in accordance with good clinical practice guidelines and the last version of the Declaration of Helsinki and our local Institutional Review Board approved the protocol. The study has been reported according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist. The companies marketing BTX-A had no role in the funding, design and data analysis of the present study.

BASELINE EVALUATION AND RECRUITMENT OF PARTICIPANTS

Before treatment, all patients underwent a comprehensive urological evaluation, including self-administration of the IPSS [13] and the International Index of Erectile Function (IIEF) [18], DRE, TRUS of the prostate to measure total prostate volume (TPV) and transitional zone volume (TZV), uroflowmetry with postvoid residual urine volume (PVR) determined ultrasonographically, and serum PSA assay (for measurement of total PSA, tPSA).

Inclusion criteria

Men aged 50–80 years, diagnosed with LUTS due to BPH with unsatisfactory response to combined α-blockers and 5-ARIs therapy for ≥6 months, prostate enlargement (>30 mL), tPSA level of <4 ng/mL or of 4–10 ng/mL but with a biopsy showing no malignancy, and consenting to the study treatment. Patients were considered with unsatisfactory response to medical therapy if they had an IPSS of ≥8, IPSS-HRQL item score of ≥2, and a maximum urinary flow rate (Q_{max}) of ≤15 mL/s with a voided volume of ≥150 mL.

Exclusion criteria

A PVR of >250 mL, previous prostate ablative treatments, therapy with α-blockers for other conditions, neurogenic voiding disorders, prostate or bladder cancer, bladder stones, urethral stricture, chronic bladder catheterisation, prostatitis, myasthenia gravis or other conditions that precluded the administration of BTX.

INTERVENTION

For the treatment, a solution of BTX-A (Botox®, Allergan, Irvine, CA, USA) was used. With the patient lying in lithotomy position, transperineal intraprostatic injection was carried-out using a 22-G spinal needle under TRUS guidance and local anaesthesia. The dosage of BTX-A was 200 U, diluted in 6 mL saline. Three injections of 1 mL for each lobe were performed. The treatment was administered on a day-hospital regimen. Each treatment took ≈20 min. Each patient underwent antibiotic prophylaxis (single tablet of prulifloxacin 600 mg). Patients discontinued drug therapies for BPH 20 days after treatment, when clinical benefits of BTX injection were expected to be achieved according to previous studies [11,12].

OUTCOME ASSESSMENT AND MEASURES

The outcome assessment was performed in our Outpatient Clinic at 3 months after treatment, when maximum effects have been achieved according to most previous studies [11,12].

The primary outcome efficacy measure was the improvement of LUTS as measured by a ≥4-point reduction in the IPSS.

FIG. 1.
Study flow chart.

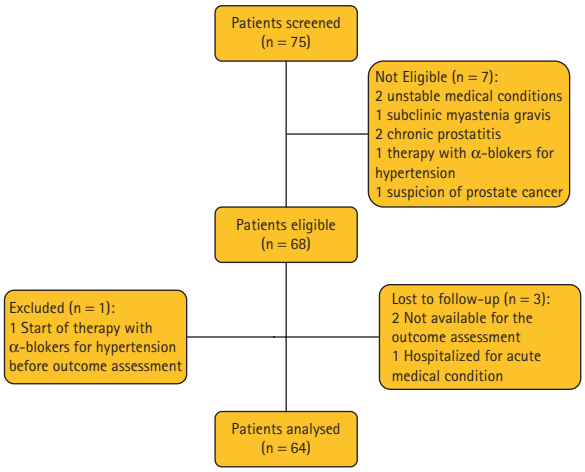


TABLE 1 Baseline characteristics of analysed patients (n = 64)

Characteristics	Baseline values
Mean (SD):	
Age, years	63 (9.3)
TPV, mL	55.1 (22.7)
Adenoma volume, mL	26.9 (19.1)
tPSA, ng/mL	2.26 (2.02)
Q_{max}, mL/s	9.4 (3.9)
PVR, mL	90.2 (29.7)
IPSS (0–35)	20.7 (7.7)
IPSS-HRQL item (0–6)	4.2 (1.2)
IIEF (5–25)	19.5 (9.1)
N (%):	
Therapy with α-blokers:	
Tamsulosin	41 (64)
Alfuzosin	14 (22)
Terazosin	9 (14)
Therapy with 5-ARIs:	
Finasteride	28 (44)
Dutasteride	36 (56)

Secondary outcomes were rate of complications and adverse events, change of HRQL as measured by IPSS-HRQL item score, and change of Q_{max}, PVR, tPSA and IIEF score. Furthermore, patient impression of improvement (Patient Global Impression of Improvement [PGI-I]; 7-point Likert-type response scale), of treatment satisfaction (PGI of Satisfaction [PGI-S]; 6-point Likert-type response scale) and of efficacy (PGI of Efficacy [PGI-E]; 6-point Likert-type response scale) were assessed by three questions of a PROs questionnaire (PROs-q; Appendix S1), higher scores indicating better outcome. The questionnaire also asked patients to report if they would repeat the treatment under the same circumstances and if they would recommend the treatment to another person with the same problem ('yes' or 'no').

SAMPLE SIZE

We calculated that a sample of 65 patients would allow detection of a 4-point difference in the IPSS score with a statistical power of 90% and α set at 0.05 (two-sided). This sample size would allow us to test the hypothesis that at least 70% of treated patients will report a positive perception in at least one question of the PRO-q, setting the null hypothesis value at 50%, with a statistical power of 91% and α set at 0.05 (two-sided). Assuming a rate of loss to follow-up of 10%, the study required 72 patients.

STATISTICAL ANALYSIS

All statistical analyses were performed using MedCalc software for Windows. The results are presented as the mean (SD). Differences between variables were compared using the Wilcoxon test. The degree of association between variables was evaluated using rank correlation and calculating the Spearman's rank correlation coefficient (ρ) with 95% CI. A correlation analysis was performed to study the association between the satisfaction score (dependent variable) and patients baseline characteristics (covariates). A $P < 0.05$ (two-sided) was considered to indicate statistical significance.

RESULTS

Of 75 consecutive screened patients, 68 were eligible and treated with intraprostatic BTX-A injection. Four patients were not available for the outcome assessment, leaving 64 patients for the final analysis. Figure 1 shows the study flow chart and Table 1 shows the patients' baseline characteristics.

PRIMARY OUTCOME

The 3-months analysis showed a mean reduction of 49.2% in the IPSS, which decreased from a mean (SD) of 19.7 (7.7) to 10.0 (7.1) ($P < 0.001$), and a mean reduction of 44.8% in IPSS-HRQL item score, from 4.17 (1.2) to 2.3 (1.6) ($P < 0.001$). The statistically significant mean IPSS reduction of 9.7 (8.9) points supports the rejection of the hypothesis of no difference between the IPSS before and after treatment.

Figure 2 displays the distribution of the IPSS before and after treatment, showing an evident shift toward lower values after treatment.

A more detailed analysis of the IPSS, performed by evaluating separately the voiding and the storage subscores, showed a 48.0% reduction of the IPSS-voiding subscore, from 11.8 (5.4) to 6.1 (5.3) and a 49.1% reduction of the IPSS-storage subscore, from 7.2 (3.1) to 3.9 (3.7) (both $P < 0.001$).

SECONDARY OUTCOMES

During treatment and follow-up, no local complications or systemic adverse events related to treatment were reported. There was postoperative mild haematuria and stranguria in seven (10.9%) and 14 (21.9%) patients, respectively, and both resolved spontaneously within a few days. No patient had urinary retention or acute prostatitis.

OBJECTIVE PARAMETERS

Compared with baseline, there was a 33% mean increase in Q_{max}, from 9.4 (3.9) to 12.6 (4.9) mL/s, with a significant mean reduction of 80% in PVR, from 90.2 (29.7) to 20.1 (15.2) mL (both $P < 0.001$).

The mean serum tPSA level did not change significantly, from 2.26 (2) ng/mL before treatment to 2.20 (2) ng/mL after treatment ($P = 0.54$).

IMPACT ON SEXUAL FUNCTION

There were no statistically significant sexual modifications, as reported by the IIEF, compared with baseline [21.6 (10.3) vs 19.5 (9.2), $P = 0.15$). In particular, no changes of the ejaculatory function were reported.

PROs

The responses to the PROs-q showed that 36 (56.3%) patients reported some degree of subjective improvement of LUTS (PGI-I ≥ 4); among these patients, 19 (29.7%) reported to be 'much' or 'very much improved' (PGI-I ≥ 5; Fig. 3). However, 15 (23.4%) patients reported 'no change', and 13 (20.3%) even reported worsening of LUTS.

In all, 43 (67.2%) patients defined themselves as being satisfied with the treatment (PGI-S ≥ 3); among these patients, 25 (39%) reported to be 'much' or 'very much satisfied' (PGI-S ≥ 4; Fig. 4).

In all, 44 (68.8%) patients reported that the treatment was effective (PGI-E ≥ 3); among these patients, 23 (35.9%) reported that the treatment was 'much' or 'completely effective' (PGI-E ≥ 4; Fig. 5).

In all, 50 (78.1%) patients would repeat the same treatment under the same circumstances, while 54 (84.4%) patients would recommend the treatment to another person with the same diagnosis.

CORRELATION ANALYSES

Table 2 shows the univariate correlation analysis between the PGI-S score and the patients' baseline characteristics. There was a statistically significant positive correlation between PGI-S and both the baseline IPSS and IPSS-HRQL score. As a result, a higher proportion of patients with baseline severe LUTS (IPSS > 28) and low HRQL reported satisfaction with the treatment, compared with patients with moderate (IPSS 20–27) or mild (IPSS < 19) LUTS and better HRQL (Fig. 6).

Baseline IPSS was also positively correlated with PGI-E (ρ 0.402, $P = 0.001$), but not with PGI-I (ρ 0.138, $P = 0.27$). There was also a statistically significant positive correlation between IPSS reduction rate and PGI-I (ρ 0.519, $P < 0.001$), PGI-S (ρ 0.850, $P < 0.001$) and PGI-E (ρ 0.844, $P < 0.001$).

The IPSS reduction rate was also positively correlated to the baseline IPSS (ρ 0.346, $P = 0.006$). For instance, patients with a baseline IPSS of >20 (34 patients) had a mean reduction rate of 53.5% (from 25.6 to 13.7 mean score), and patients with baseline IPSS < 20 (30) had a mean reduction rate of 39.7% (from 13.1 to 7.9 mean score).

FIG. 2. Distribution of patients among different ranges of IPSS, at baseline and at 3-month outcome assessment after treatment with intraprostatic injection of BTX-A. Mean IPSS with standard deviation are also showed (dashed lines). The difference between distributions was statistically significant (P < 0.001).

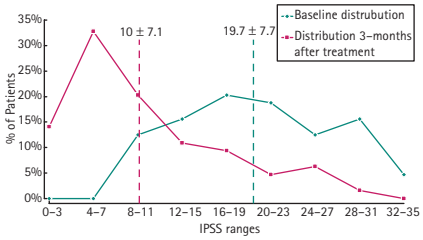


FIG. 3. PGI-I after the therapy with intraprostatic BTX.

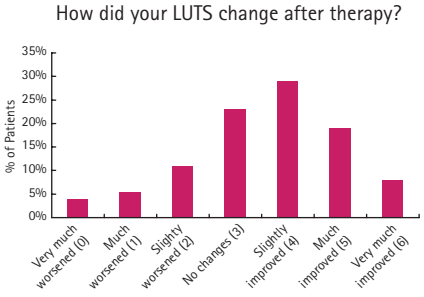


FIG. 4. PGI-S with the therapy with intraprostatic BTX.

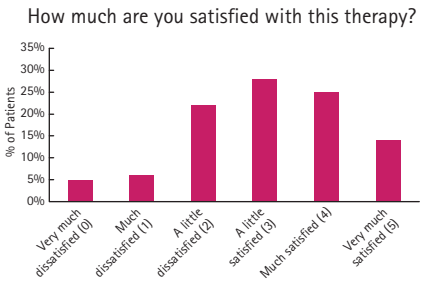


FIG. 5. PGI-E of the therapy with intraprostatic BTX.

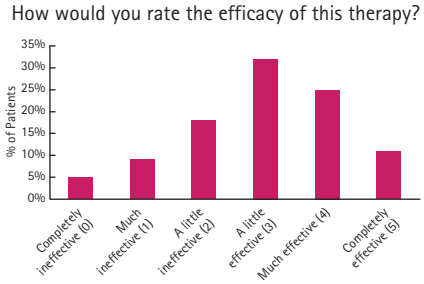


TABLE 2 Correlation analysis

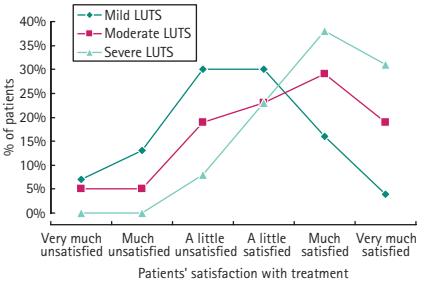
Covariates (continuous)	Correlation coefficient (ρ)	95% CI	*P*
Age	0.137	−0.112 to 0.371	0.276
TPV	0.017	−0.230 to 0.262	0.893
Adenoma volume	0.023	−0.221 to 0.283	0.856
tPSA	−0.012	−0.257 to 0.234	0.922
Q_{max}	−0.105	−0.342 to 0.145	0.405
PVR	0.142	−0.110 to 0.394	0.298
IPSS	0.441	0.218 to 0.619	<0.001
IPSS-HRQL	0.342	0.105 to 0.543	0.007
IPSS reduction	0.850	0.764 to 0.907	<0.001

Dependent variable: PGI-S score.

DISCUSSION

In agreement with most published studies evaluating the efficacy of intraprostatic injection of BTX in patients with BPH [11, 12], in the present study there was a

FIG. 6. Distribution of patients amongst the different responses to the satisfaction with BTX treatment question, based on the baseline severity of LUTS (severe IPSS > 28; moderate IPSS 20–27; mild IPSS < 19).



significant improvement in LUTS and HRQL at 3-months follow-up, without significant complications and side-effects. Compared with baseline, there was a statistically significant reduction in the IPSS and IPSS-HRQL score of 49% and 45%, respectively. Interestingly, both storage and voiding LUTS improved after treatment. This finding is of interest because storage LUTS are the most frequent patient-reported most bothersome symptoms and are often maintained after BPH treatments [19]. The clinical efficacy of the treatment was also supported by an increase in Q_{max} and a reduction in PVR after treatment compared with baseline.

The first pioneering randomised control trial on intraprostatic injection of BTX-A was performed in 2003 by Maria *et al.* [20] on 30 patients who did not respond to conventional medical treatment and declined the surgical option. In 15 patients, both lobes of prostate were injected with 200 U BTX-A, diluted in 4 mL saline; the remaining 15 were injected with saline only. In the treatment group they reported at 2-months follow-up a significant improvement in the AUA Symptom Score of 65%, an increase of 52% in Q_{max} and a reduction of 82% in PVR in 13 of 15 treated patients. Of interest, a significant reduction in TPV (68%) was observed in this work. These results were replicated in an open-label study in the same institution by Brisinda *et al.* [21] that treated 77 patients with 200 U BTX-A. Compared with the present findings, these studies [20,21] reported more impressive results, although the outcome evaluation occurred earlier. There was also a reduction in PSA levels after therapy in these and other studies [22,23], in disagreement with the results of the present and other studies [24,25].

A few studies have evaluated treatment outcomes at 3-months follow-up, reporting results consistent with those of the present study [25–27]. In the work of Kuo [26], 10 patients with BPH were treated with 200 U BTX-A, injected transurethrally into 10 sites in the transitional zone of the prostate. The author reported a statistically significant increase in Q_{max} (31%) and a reduction in PVR (78%) and TPV (30%). Chuang *et al.* [27] used BTX-A in 41 patients with BPH refractory to medical treatment. A dose of 100 U BTX-A was used for prostates of <30 mL and 200 U for prostates of >30 mL, obtaining at 3 months a significant improvement in the IPSS (57%), IPSS-HRQL (49%), Q_{max} (59%), PVR (62.5%) and TPV (14%). Similar results were reported in the study conducted by Park *et al.* [25] in 30 patients, with a greater benefit in the IPSS-storage subscore than the voiding subscore.

None of the published studies assessed PROs, such as patient-perceived level of improvement and success of therapy, as well as the patient satisfaction with intraprostatic BTX-A therapy. BPH might be defined by the LUTS whose severity is not strictly related to objectively measurable parameters and whose impact on patients is heterogeneous and difficult to predict [15]. As a result, evaluations from the patient's perspective, using information gathered directly from the treated patients, are of utmost importance in BPH research and management [14–17]. PROs, e.g. patient's satisfaction with treatment, have been showed to have significant implications in making a full assessment of overall treatment success in patients with BPH. Studying the patient-perceived efficacy of doxazosin, Cam *et al.* [28] reported that, after 1 year, the probability of surgery was significantly higher in patients who considered treatment ineffective than in the those who considered the treatment effective or reported no change ($P < 0.05$), and was also significantly higher in those who felt that their condition remained unchanged than in those who considered treatment effective ($P < 0.05$).

The present study is the first to provide data useful for gaining insight into the way patients perceive the effect that treatment with intraprostatic BTX has on their symptoms and HRQL. The assessment of patients' perception of treatment outcome, for patient-reported improvement, satisfaction and effectiveness, showed promising results, comparable with those reported in the studies on α-blockers and 5-ARIs [28–31]. A subjective improvement of LUTS was reported by more than half of the present patients and nearly two-thirds of them reported some degree of satisfaction and effectiveness.

In the present study, there were also a not negligible proportion of patients reporting no satisfaction or no improvement from the treatment or even a worsening of their LUTS. Considering that patients had to compare their clinical status at 3 months with that before treatment (when they were still on medical therapy), these results could be explained by an efficacy of BTX-A similar (in patients reporting no change) or lower (in patients reporting worse symptoms) than that of medical therapy in these patients. Based on the correlation analysis, these patients tended to have lower baseline IPSS and had lower reductions in the IPSS. However, an appropriate subgroup analysis would need a larger study population and the evaluation of more biological factors. Likewise, other studies on drug therapy of BPH reported comparable rates of no satisfaction [28,30]. Satisfaction with the α-blockers doxazosin (4 mg/day) was evaluated in 178 men in a 3-month open-label trial [28]. Patients were asked 'What is your opinion about the efficacy of the drug you have taken to relieve your urinary symptoms'? Doxazosin was considered effective by 44% of patients, ineffective by 23% and there was no change in 33%. Using the Patient Perception of Study Medication (PPSM), a questionnaire exploring patient-reported satisfaction with treatment and validated for use in men with BPH, Montorsi *et al.* [30] reported 36%, 24% and 24% of no satisfaction with improvement in urinary problems at 3 months after treatment with dutasteride, tamsulosin and combined therapy, respectively.

Some patients (11%) reported satisfaction with the treatment and judged the treatment as effective, although they reported no perception of symptoms improvement. This finding may be explained by the fact that these patients were satisfied

by maintaining the same symptoms severity without taking continuous oral drug therapy.

In the present study, a correlation, although moderate, between the reduction in IPSS after treatment and more severe baseline symptoms is in agreement with the findings of some previous studies on the effect of tamsulosin [32–36] and dutasteride [37], and is worthy of further investigation.

We also tried to investigate what drove patient satisfaction. The present data showed an apparent positive correlation between satisfaction with treatment and both the baseline IPSS (moderate correlation) and IPSS reduction from baseline (strong correlation), indicating higher satisfaction in patients with increasing severity of baseline symptoms and more pronounced symptom reduction. Accordingly, a positive correlation between the IPSS reduction and the patient-perceived improvement and satisfaction score has been previously reported in patients treated with dutasteride, tamsulosin or combined therapy [30,38]. Conversely, in the present study there were no correlations between patient-reported satisfaction and baseline objective parameters, e.g. age, prostate volume, PSA level, Q_{max} and PVR. Overall, these findings suggest a clinical benefit with BTX-A therapy in all age ranges and also in patients with known risk factors for disease progression, e.g. severe LUTS, large prostate volume, low Q_{max}, high PVR and PSA level [39]. Together with the quick relief of both voiding and storage symptoms and the improvement of HRQL reported in most studies [11,12], these findings may indicate, if confirmed in large randomised studies, that BTX therapy has the potential to be a treatment option capable of delivering a 'total' management approach for both low/intermediate and high-risk patients with BPH [40].

According to Silva *et al.* [41], we confirmed in the present study that intraprostatic BTX-A injection in patients with BPH does not impair erectile, orgasmic or ejaculatory functions and does not change libido. This is of utmost importance because sexual dysfunctions commonly occur in parallel with BPH [42] and are often associated with α-blockers and 5-ARIs.

The present study does have some limitations. The open-label/non-comparative design, the lack of a placebo arm, and the assessment of PROs with a non-validated questionnaire reduce the generalizability of the present findings and the level of evidence provided. Recall bias also has to be considered when asking patients to compare their present health status with a previous one. In the present study, it was not possible to study the biological effects of BTX-A on human prostate. This is an interesting issue, as little is known about the mechanism of action, which is hypothesised to be related to the induction of apoptosis [8,43]. The short follow-up of the present study did not allow elucidation of the long-term efficacy of BTX treatment and we plan to report the longer term results. According to international guidelines, the treatment strategy for BPH involves the sustained improvement of LUTS and HRQL, and the reduction of the risk of acute urinary retention and BPH-related surgery [16,17]. It would be very interesting to study the long-term effects of BTX therapy, not only on LUTS and HRQL of patients with BPH, but also on the risk of acute urinary retention and BPH-related surgery, especially because the available data suggest that patients are more worried about long-term risks of BPH and prefer therapies that affect long-term disease progression over those that provide short-term symptoms relief [14,31,44].

In conclusion, the present study confirmed that intraprostatic injection of BTX-A is a promising, safe and minimally invasive therapeutic option able to improve both objective and subjective outcomes in patients with LUTS due to BPH with unsatisfactory response to medical therapy.

The study also provided important outcome information from the patient's perspective by showing that most of the treated patients reported favourable subjective outcomes at 3-months follow-up. Noteworthy, PROs appeared not to be associated in this cohort with age and objective baseline parameters, but there was a moderate correlation between PROs and increasing severity of baseline LUTS. This could be explained by the subjective nature of both PROs and the IPSS.

The use of BTX-A in the setting of patients with BPH remains off-label in all countries and further basic research and randomised trials are necessary in order to: (i) identify predictive parameters clinically useful for a better selection of patients, (ii) achieve an adequate level of scientific evidence supporting the introduction of this treatment in clinical practice, and (iii) define the best treatment technique (dose, injection site, route of administration).

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Chute CG, Panser LA, Girman CJ *et al*.** The prevalence of prostatism: a population based survey of urinary symptoms. *J Urol* 1993; **150**: 85–9
2 **Boyle P, Robertson C, Manski R *et al*.** Meta-analysis of randomized trials of terazosin in the treatment of benign prostatic hyperplasia. *Urology* 2001; **58**: 717–22
3 **Narayan P, Lepor H.** Long-term, open-label, phase III multicenter study of tamsulosin in benign prostatic hyperplasia. *Urology* 2001; **57**: 466–70
4 **Lepor H.** Role of long-acting selective alpha-1 blockers in the treatment of benign prostatic hyperplasia. *Urol Clin North Am* 1990; **17**: 651–9
5 **Kallenberg F, Hossack TA, Woo HH.** Long-term followup after electrocautery transurethral resection of the prostate for benign prostatic hyperplasia. *Adv Urol* 2011; **2011**: doi:10.1155/2011/359478
6 **Dolly JO, Aoki KR.** The structure and mode of action of different botulinum toxins. *Eur J Neurol* 2006; **13** (Suppl. 4): 1–9
7 **Simpson LL.** The neuroparalytic and hemaglutining activity of botulinum toxin. In Plenum Press ed., *Neuropoisons: Their Pathophysiological Actions*, New York, 1971: 303–24
8 **Chuang YC, Tu CH, Huang CC *et al*.** Intraprostatic botulinum toxin type A injection relieves bladder outlet obstruction and induces prostate apoptosis. *BMC Urol* 2006; **6**: 12–7
9 **Pennefather JN, Lau WAK, Mitchelson F, Ventura S.** The autonomic and sensory innervation of the smooth muscle of the prostate gland: a review of pharmacological and histological

studies. *J Auton Pharmacol* 2000; **20**: 93–206
10 **Lepor H.** The pathophysiology of lower urinary tract symptoms in the ageing male population. *Br J Urol* 1998; **81** (Suppl. 1): 29–33
11 **Chartier-Kastler E, Mehnert U, Denys P, Giuliano F.** Botulinum neurotoxin A for male urinary tract symptoms. *Curr Opin Urol* 2011; **21**: 13–21
12 **Marchal C, Perez JE, Herrera B, Machuca FJ, Redondo M.** The use of botulinum toxin in benign prostatic hyperplasia. *Neurourol Urodyn* 2012; **31**: 86–92
13 **Cockett A, Aso Y, Denis L *et al*.** Recommendation of the international consensus committee concerning: 1. Prostate symptom score and quality of life assessment. In Cockett ATK, Khoury S, Aso Y *et al* eds, *Proceedings of the Second International Consultation on Benign Prostatic Hyperplasia (BPH), Paris, June 27–30, 1993*, Jersey: Channel Island, Scientific Communication International, 1994: 553–5
14 **Watson V, Ryan M, Brown CT, Barnett G, Ellis BW, Emberton M.** Eliciting preferences for drug treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. *J Urol* 2004; **172**: 2321–5
15 **Hong SJ, Rayford W, Valiquette L, Emberton M.** The importance of patient perception in the clinical assessment of benign prostatic hyperplasia and its management. *BJU Int* 2005; **95**: 15–9
16 **Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M, de la Rosette JJ.** EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *Eur Urol* 2004; **46**: 547–54
17 **McVary KT, Roehrborn CG, Avins AL *et al*.** AUA guideline on the management of benign prostatic hyperplasia (BPH). 2010. Available at: http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines.cfm?sub=bph. Accessed 6 February 2012
18 **Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A.** The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–30
19 **Andersson K-E.** Mode of action of α1-adrenoreceptor antagonists in the treatment of lower urinary tract symptoms. *BJU Int* 2000; **85**: 12–8
20 **Maria G, Brisinda G, Civello IM, Bentivoglio AR, Sganga G, Albanese A.** Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology* 2003; **62**: 259–65
21 **Brisinda G, Cadeddu F, Vanella S, Mazzeo P, Marniga G, Maria G.** Relief by botulinum toxin of lower urinary tract symptoms owing to benign prostatic hyperplasia: early and long-term results. *Urology* 2009; **73**: 90–4
22 **Guercini F, Giannantoni A, Bard RL *et al*.** Intraprostatic botulin toxin injection in patients with severe benign prostatic hyperplasia: a multicenter feasibility study. *J Urol* 2005; **173** (Suppl): 376–7
23 **Nikoobakht M, Daneshpajooh A, Ahmadi H *et al*.** Intraprostatic botulinum toxin type A injection for treatment of benign prostatic hyperplasia: initial experience with Dysport. *Scand J Urol Nephrol* 2010; **44**: 151–7
24 **Silva J, Pinto R, Carvalho T *et al*.** Intraprostatic botulinum toxin type A injectionin patients with benign prostatic enlargement: duration of the effect of a single treatment. *BMC Urol* 2009; **9**: 1–6
25 **Park DS, Cho TW, Lee YK, Lee JH, Hong YK, Lee YT.** Evaluation of short term clinical effects and presumptive mechanism of Botulinum toxin type A as a treatment modality of benign prostatic hyperplasia. *Yonsei Med J* 2006; **47**: 706–14
26 **Kuo HC.** Prostate botulinum toxin A injection – an alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology* 2005; **65**: 670–419
27 **Chuang YC, Chiang CH, Yoshimura N *et al*.** Sustained beneficial effects of intraprostatic botulinum toxin type A on lower urinary tract symptoms and quality of life in men with benign prostatic hyperplasia. *BJU Int* 2006; **98**: 1033–7
28 **Cam K, Akman Y, Kayikci A *et al*.** Short-term subjective efficacy of doxazosin in predicting probability of prostatectomy in the management of benign prostatic hyperplasia in patients with severe symptoms. *Int J Urol* 2003; **10**: 582–6
29 **Barkin J, Roehrborn CG, Siami P *et al*.** Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe BPH: 2-year data from the CombAT trial. *BJU Int* 2009; **103**: 919–26
30 **Montorsi F, Henkel T, Geboers A *et al*.** Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe benign prostatic hyperplasia: 4-year data from the CombAT study. *Int J Clin Pract* 2010; **64**: 1042–51
31 **Emberton M, Marberger M, de la Rosette J.** Understanding patient and physician perceptions of benign prostatic hyperplasia in Europe: the Prostate Research on Behaviour and Education (PROBE) Survey. *Int J Clin Pract* 2008; **62**: 18–26
32 **Lepor H.** Phase III multicenter placebo-controlled study of tamsu- losin in benign prostatic hyperplasia. *Urology* 1998; **51**: 892–900
33 **Michel MC, Mehlburger L, Bressel HU *et al*.** Comparison of tamsulosin efficacy in subgroups of patients with lower urinary tract symptoms. *Prostate Cancer Prostatic Dis* 1998; **1**: 332–5
34 **Barry MJ, Williford WO, Chang Y *et al*.** Benign prostatic hyperplasia specific healthy status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J Urol* 1995; **154**: 1770–4
35 **Chang HS, Park CH, Kim DK *et al*.** Assessment of patient-reported outcome of patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and treated with tamsulosin HCl in Korea. *Urology* 2010; **75**: 1156–61
36 **Brooks SK.** Effect of tamsulosin on AUA symptom score and BPH Impact Index as a function of symptpm severity in patients with benign prostatic hyperplasia. *J Urol* 1999; **161** (Suppl. 4): 267. [Abstract 1031]

37 **Roehrborn CG, Siami P, Barkin J *et al*.** The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol* 2010; **57**: 123–31
38 **Desgrandchamps F, Droupy S, Irani J *et al*.** Effect of dutasteride on the symptoms of benign prostatic hyperplasia, and patient quality of life and discomfort, in clinical practice. *BJU Int* 2006; **98**: 83–8
39 **Jiménez-Cruz F.** Identifying patients with lower urinarytract symptoms/ benign prostatic hyperplasia (LUTS/BPH) at risk for progression. *Eur Urol Suppl* 2003; **2**: 6–12
40 **O'Leary M.** Achieving the total approach in lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH) management. *Eur Urol Suppl* 2003; **2**: 25–33
41 **Silva J, Pinto R, Carvalho T *et al*.** Intraprostatic botulinum toxin type A administration: evaluation of the effects on sexual function. *BJU Int* 2011; **107**: 1950–4
42 **Rosen R, Altwein J, Boyle P *et al*.** Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol* 2003; **44**: 637–49
43 **Chuang YC, Huang CC, Kang HY *et al*.** Novel action of botulinum toxin on the stromal and epithelial components of the prostate gland. *J Urol* 2006; **175**: 1158–63
44 **Kaplan S, Naslund M.** Public, patient, and professional attitudes towards the diagnosis and treatment of enlarged prostate: a landmark national US survey. *Int J Clin Pract* 2006; **60**: 1157–65

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Abbreviations: **5-ARI**, 5α-reductase inhibitor; **BTX(-A)**, botulinum toxin (OnabotulinumtoxinA); **HRQL**, health-related quality of life; **IIEF**, International Index of Erectile Function; **PVR**, postvoid residual urine volume; PGI(-E)(-I)(-S), Patient Global Impression of (Efficacy) (Improvement) (Satisfaction); **PRO**, patient-reported outcome; $\mathbf{Q}_{max}$, maximum urinary flow rate; **tPSA**, total PSA; **TPV**, total prostate volume; **TZV**, and transitional zone volume.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Appendix Patient-reported outcome questionnaire (PRO-q).

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