bjuiknowledge

Source manuscript for e-learning module

Novel intraprostatic injectable agents in the treatment of BPH

John Bailie[1], Suzanne McDonald[2], Edgar Paez[1]
[1]Freeman Hospital [2]Institute of Health & Society, Newcastle University

Learning objectives

By the end of this module the reader should be able to:

- describe the biomedical concepts underlying intra-prostatic injections for benign prostatic hyperplasia (BPH)
- explain how the different types of intra-prostatic injection are administered
- appraise the existing literature relating to intra-prostatic injections.

Introduction

Lower urinary tract symptoms (LUTS) secondary to bladder outlet obstruction (BOO) from benign prostatic hyperplasia (BPH) can have a significant impact on the quality of life of older men [1]. Epidemiological data have shown that more than 50% of men aged 70 and above report moderate to severe LUTS [2, 3]. The current treatment options for LUTS/BPH broadly consist of a conservative "wait and see" approach, pharmacotherapy and a variety of surgical options [4-6].

LUTS secondary to BPH have a multifactorial pathogenesis, resulting in a spectrum of clinical presentations. Broadly speaking α1-adrenoceptor antagonists, 5α-reductase inhibitors, muscarinic receptor antagonists, β3-adrenoceptor agonists and phosphodiesterase type 5 inhibitors are all recognised pharmacotherapeutic agents for LUTS/BPH. The above medication groups may be used as monotherapy or in combination [1]. Problems with existing medical treatments include lack of compliance and adverse effects such as postural hypotension, dizziness and impaired sexual function. Pharmacotherapy fails to resolve symptoms sufficiently in 30% of men, for whom the only remaining option is surgery [7, 8].

Transurethral resection of the prostate (TURP) is considered to be the gold standard minimally invasive treatment for BPH. However, while safe and effective, it has a perioperative morbidity rate of up to 20% and is associated with longer-term complications such as erectile dysfunction, urinary incontinence and urethral stricture [1]. The challenge in the 21st century is to develop alternative treatments that replicate the effectiveness of TURP without the unwanted side effect profile.

Ethanol ablation

Ethanol ablation involves the use of a flexible injection needle to inject dehydrated ethanol into the prostate for the purposes of chemoablation of tissue. The procedure is often performed under cystoscopic guidance and it may be injected via a transurethral, transperineal, or transrectal approach. Inflammation and coagulative necrosis results in cavity formation and destruction of afferent nerves [9, 10]. The procedure is typically performed under sedation or spinal anaesthesia. Ethanol ablation is the oldest and most extensively studied injectable agent used for treating BPH.

The first clinical study into ethanol ablation was published in 1999 [11]. Statistically significant improvements in IPSS, Qmax and post-void residual were demonstrated at three months follow-up, with a sample size of 10 men. A phase I/II multi-centre randomised trial with 79 participants demonstrated statistically significant improvement after ethanol ablation across a range of clinical outcomes; at six months follow-up mean prostate volume had decreased from 46.1g to 39.8g with a 10.6 point improvement in IPSS [12]. However, the favourable initial results were seldom maintained, and re-treatment with another modality was required in at least 40% of patients [13].

One concern regarding prostatic ethanol ablation is the difficulty in controlling distribution and the potential risk of bladder necrosis due to inadvertent injection [14, 15]. Use of anhydrous ethanol in a gel formulation has been described as a potential solution to this problem. A case series with 65 patients reported statistically significant improvements in IPSS and flow rate [16].

Another study followed up 56 men for 54 months, assessing outcomes including International Prostate System Score (IPSS), prostate volume (measured via TRUS), prostate-specific antigen (PSA), Qmax and post void residual. Seventy-three percent of patients had a satisfactory response, while 23% required another form of treatment. However, there was a relatively high loss to follow-up and a lack of data regarding sexual function and continence in

this study [17].

There have been a number of reported complications with ethanol ablation including haematuria, dysuria, urinary retention, urinary tract infection and urinary incontinence. There have been reports of erectile dysfunction and ejaculatory problems despite taking care to avoid the bladder neck. This is thought to be secondary to dissipation of the injected ethanol. Major complications such as widespread bladder necrosis leading to cystectomy has led to ethanol ablation being abandoned as a viable therapeutic option [6, 10, 14].

PRX302/Topsalysin

PRX302 (also known as Topsalysin) is a novel targeted therapy for BPH that causes a reduction in transition zone volume via cellular involution. PRX302 can be administered under local anaesthesia either via a transperineal or transrectal route and under transrectal ultrasound guidance [18, 19]. PRX302 is a genetically modified form of pro-aerolysin, a highly toxic bacterial pore-forming pro-toxin produced by the aquatic pathogen Aeromonas hydrophila [20]. Cleavage by furin proteases produces an active metabolite, aerolysin, which forms highly stable pores in cell plasma membranes, causing apoptosis. With PRX302, the native furin protease activation site is replaced with a PSA-recognised sequence, which is activated by PSA through a process known as proteolyic processing. The activity of PRX302 is confined exclusively to the prostate, which has an abundance of active PSA [1]. Based on the above model, injection of PRX302 into the transition zone may alleviate LUTS as a direct result of prostatic volume reduction.

A phase II trial, published in 2011, evaluated different volumes of PRX302 at a fixed concentration, adjusted for prostate size in 18 participants [18]. A ≥ 30% reduction in IPSS was maintained at 12 months in 63% of participants. A statistically significant improvement in Qmax was observed in 61% of participants at 12-month follow-up. Administration of PRX302 led to a ≥ 20% reduction in prostatic volume in 63% of study participants at 12-month follow-up. Complications in both trials included dysuria, perineal pain/bruising, haematuria and storage lower urinary tract symptoms. All complications were mild to moderate, resolving within 72 hours [18].

The results of a multicentre, prospective, randomised, double-blinded, placebo-controlled phase IIb clinical trial of PRX302 were published in 2013 [21]. Inclusion criteria for the study included severe IPSS and a prostate volume of 30–100mL. A total of 92 patients were eligible and randomly assigned to receive a fixed concentration of PRX302 – adjusted to be 20% of the prostatic volume – or the placebo control. End points included change in IPSS score, Qmax, post void residual and prostatic volume. While a mean reduction in IPSS of nearly nine points for the treatment arm seemed impressive, the mean decrease corrected for control was only 3.3 points at three months, dropping to a non-statistically significant 2.8 points at 12-month follow-up. Mean change in Qmax in the treatment arm was not statistically significant at 12 months compared to baseline and there were no clinically relevant beneficial effects on post void residual volume or prostatic volume. Adverse events were mild to moderate in severity, resolving within a median duration of less than 48 hours.

The results from a phase III multi-centre, randomised, double-blinded, placebo controlled trial conducted by the manufacturer were published in 2015 [22]. The premise of the study was to assess the safety and efficacy of a single intra-prostatic injection of PRX302 for BPH. The data from 479 participants with 12 months follow-up were analysed. While there was a statistically significant improvement in IPSS in the PRX302 group compared to the control group, there was no statistically significant improvement in Qmax. Adverse effects included dysuria, haematuria, frequency and perineal pain and were similar to the control group. PRX-302-related adverse events included moderate instances of acute non-infectious prostatitis [22].

Interestingly, the role of PRX302 in treating localised low- to intermediate-risk prostate cancer is currently being studied in a stage 2b multi-centre trial conducted by the manufacturer. The study aims to evaluate the safety, tolerability and efficacy of PRX302 intra-prostatic focal injection and to determine an effective and tolerable dose. Efficacy will be assessed by prostatic biopsy and multi-parametric MRI scan at 24 weeks post administration. The estimated date of study completion is December 2018 [23].

NX-1207 (Fexapotide Triflutate)

Fexapotide Triflutate (NX-1207) is a protein that reduces prostate volume by inducing selective apoptosis [24, 25]. A single administration of the drug is injected into the transition zone of the prostate leading to non-regressive prostate shrinkage and symptomatic relief [10]. The detailed mechanism of action has not been published by the manufacturer. Two phase II multicentre studies with 175 and 85 men have demonstrated statistically significant improvements in American Urological Association Symptom Index (AUASI) scores and prostate volume in men with severe LUTS and a prostate volume between 30mL and 70mL. One of these studies was a multicentre, randomised, non-inferiority study with two doses of NX-1207 (0.125mg and 2.5mg) compared to finasteride [24]. The dose of NX-1207 was double-blinded and the primary outcome was an improvement in AUA symptom score at 90 and 180 days compared to finasteride. Inclusion criteria included a Qmax of less 15mL per second and a prostate volume of >30mL and ≤70mL. Mean improvement in AUA symptom score at 90 days was 9.71 points for the 2.5mg NX-1207 cohort, 4.29 for the 0.125mg NX-1207 cohort, and 4.13 for the

finasteride cohort. There was a statistically significant improvement in AUA symptom score in the 2.5mg NX-1207 cohort compared to the 0.125mg and finasteride cohorts.

More than 50% of participants in all NX-1207 phase I and II trials have not required any further surgical intervention for BPH at five years follow up [6, 24, 26]. The side effect profile of NX-1207 in trials to date is minimal with no adverse effects on sexual function or urinary incontinence reported [10]. While mild haematuria, dysuria and urinary tract infections have been reported, there has been no significant difference compared to placebo/equivalent transrectal procedures [6].

The results of two phase III trials (n = 978) were published by the manufacturer in July 2015. Primary endpoint was reached with a statistically significant benefit demonstrated compared to placebo ($p < 0.02$) at a median of 42 months (3.5 years) follow-up. There was no evidence of drug-related short-term or long-term toxicity. There was a median improvement in AUA BPH symptoms score of 5.3 points after a median of 3.5 years follow-up. Patients experienced a statistically significant reduction in BPH surgery within 24 months of treatment compared to placebo; overall incidence of BPH surgery was low at 1.7% over a two-year period [27]. Following this, the manufacturer filed for approval to market fexapotide triflutate in five European countries including the UK, Germany and France in May 2015 [28].

Updated data from two phase III trials were combined and published in January 2018 [29]. The first trial enrolled 995 patients in two identical double-blind placebo-controlled prospective parallel group studies. The second pair of studies enrolled 344 patients in an open-label crossover re-injection of fexapotide at ≥ 1 year. Mean follow-up was 43 months. There was a mean improvement in IPSS of 5.7 points after a single injection of fexapotide, with a statistically significant difference compared to placebo from two years onwards. There were no significant safety differences compared to placebo. There was a statistically significant reduction of AUR episodes (1.08%) and prostate cancer (1.1%) in fexapotide treated patients. Need for additional BPH intervention was reduced in the fexapotide versus oral medication group (8.08% vs. 27.85% at three years, $p < 0.0001$). Incidence of intervention or AUR in placebo cross-over group with fexapotide versus placebo cross-over group with oral medications was reduced (6.07% vs. 33.3% at three years, $p < 0.0001$) [29].

Botulinum toxin

Botulinum toxin is produced by the bacterium Clostridium botulinum. There are seven subtypes of toxin, of which sub-type A is the most widely studied and utilised. The mechanism of action of intra-prostatic botulinum toxin is poorly understood. Theories include localised gland necrosis at injection sites and a more widespread apoptotic reaction [10, 30-33].

It has been reported that intra-prostatic botulinum toxin downregulates the expression of a1-adrenergic receptors, which may result in smooth muscle relaxation [30]. Intra-prostatic botulinum toxin may be administered via a transperineal, transurethral or transrectal approach. While similar results have been reported following injection of 100 and 200 international units (IU) of intra-prostatic botulinum toxin, the optimal dose is yet to be determined. 100IU has been described as preferable due to a similar efficacy to higher doses, with reduced costs and adverse effects [34, 35].

A recent placebo-controlled phase II study randomly assigned 380 men to receive either 100IU, 200IU, 300IU or placebo (0.9% saline). While there were improvements in IPSS, maximum flow (Qmax) and quality of life 72 weeks after administration of intra-prostatic botulinum toxin, there was a significant placebo effect with no significant difference demonstrated between treatment and control arms [36]. A prospective single-armed cohort study evaluated patient-reported and objective outcomes following administration of intra-prostatic botulinum toxin in 64 men with symptomatic BPH, refractory to medical treatment. 200IU were administered into the transition zone via a transperineal approach. The study demonstrated a statistically significant positive correlation between patient satisfaction and both baseline IPSS and reduction rate in IPSS [37].

There have been minimal reported side effects of intra-prostatic botulinum toxin and it is well tolerated. However, retreatment rates are as high as 29% [38]. Reported side effects of the procedure include urinary tract infection and/or urosepsis, acute urinary retention and haematuria [35]. There have been no reported effects on sexual function [10, 39, 40]. Limitations of the existing research into intra-prostatic botulinum toxin include a significant placebo effect, limited follow-up, lack of randomisation and/or systematic evaluation of appropriate dose regimens [41].

Current international guideline recommendations

The AUA and NICE do not currently consider injectable agents as potential treatment options for BPH [5, 42]. NICE actively discourages the use of ethanol ablation. The EAU guidelines state that ethanol ablation and intra-prostatic botulinum toxin are experimental treatment options for BPH and should only be considered within the context of clinical trials [41]. No additional injectable agents have yet been considered by the AUA, EAU or NICE, and no injectable agents are currently licensed for use within the UK, outside of the context of a clinical trial.

Conclusion

The potential advantages of an effective intra-prostatic injection are clear [43]. The ideal injectable agent should be relatively straightforward to administer, with minimal side effects and be effective and durable. Ethanol is the most studied injectable agent, first described 18 years ago. Early data were promising, but treatment durability is poor, with a relatively high re-treatment rate. This combined with the serious complication of bladder necrosis has led to ethanol ablation falling out of favour. Initial experimental data for PRX302 were also promising but the outcomes of subsequent clinical trials have been more disappointing with the phase III trial demonstrating a statistically significant difference in IPSS but not in Qmax [22]. Data for NX-1207 and intra-prostatic botulinum toxin have also been conflicting. At present there is no solid evidence to support the potential role for injectable agents in the BPH treatment armamentarium, which is reflected by the lack of guideline recommendations.

Key learning points

- Intra-prostatic injections have been developed to 'bridge the gap' between existing medical and surgical treatments for BPH.
- Further research is needed to demonstrate clinical efficacy.
- Potential advantages include ease of administration and a relatively low side effect profile.

Disclosures

Authors

The authors have no disclosures to make.

Peer reviewers

Oliver Kayes

Paid speaker/Expert testimony/Travel or conference attendance support - Neotract Inc – paid consultant and trainer

Henry Woo

Boards and committees - ANZUP Board; Australasian Urological Foundation Board
Consultancies - Janssen; Astellas; Mundipharma; AstraZeneca; Abbvie; Boston Scientific
Paid speaker/Expert testimony/Travel or conference attendance support - Astellas; Janssen; Neotract; Boston Scientific
Editorial Interests - Associate Editor, Prostate Cancer and Prostatic Diseases journal

References

1. Magistro G, Stief CG, Gratzke C. New intraprostatic injectables and prostatic urethral lift for male LUTS. *Nat Rev Urol*. 2015;12(8):461-71. Crossref | PubMed
2. Chute C, Panser L, Girman C et al. The prevalence of prostatism: a population-based survey of urinary symptoms. *J Urol*. 1993;150(1):85-9. Crossref | PubMed
3. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. *J Urol*. 2008;179(5 Suppl):S75-80. Crossref | PubMed
4. Gratzke C, Bachmann A, Descazeaud A et al. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol*. 2015;67(6):1099-109. Crossref | PubMed
5. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol*. 2011;185(5):1793-803. Crossref | PubMed
6. Nair SM, Pimentel MA, Gilling PJ. Evolving and investigational therapies for benign prostatic hyperplasia. *Can J Urol*. 2015;22(Suppl 1):82-7. PubMed
7. Roehrborn CG. Male lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). *Med Clin North Am*. 2011;95(1):87-100. Crossref | PubMed
8. Verhamme K, Dieleman J, Bleumink G, Bosch J, Stricker BC, Sturkenboom M. Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia: the Triumph project. *Eur Urol*. 2003;44(5):539-45. Crossref | PubMed
9. Plante M, Gross A, Kliment Jr J, Kida M, Zvara P. Intraprostatic ethanol chemoablation via transurethral and transperineal injection. *BJU Int*. 2003;91(1):94-8. Crossref | PubMed
10. Andersson KE. Treatment of lower urinary tract symptoms: agents for intraprostatic injection. *Scand J Urol*. 2013;47(2):83-90. Crossref | PubMed
11. Goya N, Ishikawa N, Ito F et al. Ethanol injection therapy of the prostate for benign prostatic hyperplasia: preliminary report on application of a new technique. *J Urol*. 1999;162(2):383-6. Crossref | PubMed
12. Plante M, Marks L, Anderson R et al. Phase I/II examination of transurethral ethanol ablation of the prostate for the treatment of symptomatic benign prostatic hyperplasia. *J Urol*. 2007;177(3):1030-5. Crossref | PubMed
13. Goya N, Ishikawa N, Ito F, Kobayashi C, Tomizawa Y, Toma H. Transurethral ethanol injection therapy for prostatic hyperplasia: 3-year results. J Urol. 2004;172(3):1017-20. Crossref | PubMed
14. Soler R, Neto JFN, Füllhase C, Simonetti R. Future pharmacotherapies for male lower urinary tract symptoms. *Curr Bladder Dysfunct Rep*. 2014;9(2):134-41. Crossref
15. Chung A, Woo HH. What's truly minimally invasive in benign prostatic hyperplasia surgery? *Curr Opin Urol*. 2014;24(1):36-41. Crossref | PubMed
16. Larson BT, Netto N, Huidobro C et al. Intraprostatic injection of alcohol gel for the treatment of benign prostatic hyperplasia: preliminary clinical results. *ScientificWorldJournal*. 2006;6:2474-80. Crossref | PubMed
17. El-Husseiny T, Buchholz N. Transurethral ethanol ablation of the prostate for symptomatic benign prostatic hyperplasia: long-term follow-up. *J Endourol*. 2011;25(3):477-80. Crossref | PubMed
18. Denmeade SR, Egerdie B, Steinhoff G, Merchant R, Abi-Habib R, Pommerville P. Phase 1 and 2 studies demonstrate the safety and efficacy of intraprostatic injection of PRX302 for the targeted treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol*. 2011;59(5):747-54. Crossref | PubMed
19. Sophitis Bio Corp. A randomized dose-escalation, multicenter safety and efficacy study of a single transrectal intraprostatic treatment of PRX302 for lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). 2013. Available at: https://clinicaltrials.gov/ct2/show/NCT01454349. Accessed August 2018
20. Williams SA, Merchant RF, Garrett-Mayer E, Isaacs JT, Buckley JT, Denmeade SR. A prostate-specific antigen–activated channel-forming toxin as therapy for prostatic disease. J Natl Cancer Inst. 2007;99(5):376-85. Crossref | PubMed
21. Elhilali MM, Pommerville P, Yocum RC, Merchant R, Roehrborn CG, Denmeade SR. Prospective, randomized, double-blind, vehicle controlled, multicenter phase IIb clinical trial of the pore forming protein PRX302 for targeted treatment of symptomatic benign prostatic hyperplasia. *J Urol*. 2013;189(4):1421-6. Crossref | PubMed
22. Sophiris Bio Inc. Sophiris Bio phase 3 BPH study successfully meets primary endpoint. 2015. Available at: http://investor.sophirisbio.com/releasedetail.cfm?ReleaseID=941842. Accessed August 2018
23. Sophiris Bio Corp. SB. Intraprostatic PRX302 injection to treat localised prostate cancer. 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT03081481. Accessed Auguest 2018
24. Shore N. NX-1207: a novel investigational drug for the treatment of benign prostatic hyperplasia. *Expert Opin Investig Drugs*.

2010;19(2):305-10. Crossref | PubMed
25. Albisinni S, Biaou I, Marcelis Q, Aoun F, De Nunzio C, Roumeguère T. New medical treatments for lower urinary tract symptoms due to benign prostatic hyperplasia and future perspectives. *BMC Urol*. 2016;16(1):58. Crossref | PubMed
26. Shore N, Cowan B. The potential for NX-1207 in benign prostatic hyperplasia: an update for clinicians. *Ther Adv Chronic Dis*. 2011;2(6):377-83. Crossref | PubMed
27. Nymox Corporation. Nymox Pivotal Phase 3 NX-1207 BPH Extension Trial Successfully Meets Primary Endpoint. Company Plans to File For Regulatory Approvals For Fexapotide Triflutate (NX-1207). 2015. Available at: https://nymox.com/category/news/. Accessed August 2018
28. Nymox Corporation. NYMOX Files For Marketing Approval For Fexapotide Triflutate in Europe. 2017. Available at: https://nymox.com/category/news/. Accessed August 2018
29. Shore N, Tutrone R, Efros M et al. Fexapotide triflutate: results of long-term safety and efficacy trials of a novel injectable therapy for symptomatic prostate enlargement. *World J Urol*. 2018;36(5):801-9. Crossref | PubMed
30. 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(3 Pt 1):1158-63. Crossref | PubMed
31. Chuang YC, Tu CH, Huang CC et al. Intraprostatic injection of botulinum toxin type-A relieves bladder outlet obstruction in human and induces prostate apoptosis in dogs. *BMC Urol*. 2006;6(1):12. Crossref | PubMed
32. Doggweiler R, Zermann DH, Ishigooka M, Schmidt RA. Botox-induced prostatic involution. *Prostate*. 1998;37(1):44-50. Crossref | PubMed
33. Kuo HC. Prostate botulinum A toxin injection—an alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology*. 2005;65(4):670-4. Crossref | PubMed
34. Saemi AM, Plante MK. Injectables in the prostate. *Curr Opin Urol*. 2008;18(1):28-33. Crossref | PubMed
35. Crawford ED, Hirst K, Kusek JW et al. Effects of 100 and 300 units of onabotulinum toxin A on lower urinary tract symptoms of benign prostatic hyperplasia: a phase II randomized clinical trial. *J Urol*. 2011;186(3):965-70. Crossref | PubMed
36. Marberger M, Chartier-Kastler E, Egerdie et al. A randomized double-blind placebo-controlled phase 2 dose-ranging study of onabotulinumtoxinA in men with benign prostatic hyperplasia. *Eur Urol*. 2013;63(3):496-503. Crossref | PubMed
37. Sacco E, Bientinesi R, Marangi F et al. 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. *BJU Int*. 2012;110(11 Pt C):E837-44. Crossref | PubMed
38. 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(1):90-4. Crossref | PubMed
39. 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(12):1950-4. Crossref | PubMed
40. Marchal C, Perez JE, Herrera B, Machuca FJ, Redondo M. The use of botulinum toxin in benign prostatic hyperplasia. *Neurourol Urodyn*. 2012;31(1):86-92. Crossref | PubMed
41. Gravas S, Bach T, Bachmann A, Drake M, Gacci M, Gratzke C, et al. Guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS), incl. benign prostatic obstruction (BPO). 2015. Available at: https://uroweb.org/wp-content/uploads/Non-Neurogenic-Male-LUTS_2705.pdf
42. Jones C, Hill J, Chapple C; Guideline Development Group. Management of lower urinary tract symptoms in men: summary of NICE guidance. *BMJ*. 2010;340:c2354. Crossref | PubMed
43. Chapple C. Intraprostatic injection therapy for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Eur Urol*. 2011;59(5):755-6. Crossref | PubMed