Medical management of benign prostatic hypertrophy

Jeffrey W. Nix, MD, Culley C. Carson, MD

Division of Urology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA

NIX JW, CARSON CC. Medical management of benign prostatic hypertrophy. The Canadian Journal of Urology. 2007;14(Supplement 1):53-57.

Benign prostatic hyperplasia (BPH) is a common condition of the aging male. The bladder outlet obstruction caused by this condition occurs despite variations in prostate size. Symptoms of BPH include the irritative and obstructive voiding symptoms termed lower urinary tract symptoms (LUTS). While transurethral surgery has long been the gold standard for treatment of LUTS, medical treatment has emerged as the first line of treatment for those men who fail expectant or watchful waiting treatment. Medical options include: alpha blockers, 5α-reductase inhibitors and newly identified PDE 5 inhibitors, drugs for erectile dysfunction that have a relieving effect on the symptoms of LUTS. Newer prostate selective alpha blockers have replaced older nonselective agents as first choice in treatment of most men, especially those with smaller prostates and in whom preservation of sexual function is important. While tamsulosin has the effect of an ejaculation, alfuzosin preserves ejaculatory function. 5α-reductase inhibitors may decrease ejaculate volume, libido and sexual function. While this effect is frequently a self limited, it can be a compliance issue for many men. PDE 5 inhibitors, while effective in relieving LUTS symptoms, have not shown effectiveness in reducing post void residual volumes or increasing urinary flow rates.

Key Words: benign prostatic hyperplasia, aging male, medical management

Introduction

The management of benign prostatic hypertrophy (BPH) is one of the most common issues facing the practicing urologist today, and it will only become more important as our population continues to age. BPH has a histological prevalence of only about 8% of men in the fourth decade of life, but its prevalence increases to about 100% of men in their ninth decade.[1]

Address correspondence to Dr. Culley C. Carson, UNC Division of Urology, 2140 Bioinformatics Bldg CB 7235, Chapel Hill NC 27599-7235 USA

More importantly than the presence of disease is the resultant morbidity it causes, as it is a disease process that is mostly characterized by its impact on quality of life and progression to disease related complications. BPH is the most common cause of lower urinary tract symptoms (LUTS) in the aging male.[2] Studies from North America, Europe, and Asia have shown that the prevalence of men with moderate to severe symptoms, or those necessitating treatment, increases with age.[3] These symptoms include frequency, urgency, nocturia, and hesitancy, among other things; these can be a significant detriment to the quality of life. As a result, men with moderate to

severe LUTS will report significantly decreased quality of life compared with men that have only mild symptoms.[4] Therefore as the population continues to age, the number of patients requiring treatment for BPH will continue to grow.

As this condition has become more prevalent, the trend in management has changed as well. First line medical management of this condition has become standard of care in most patients.[2]

From the years 1998-2001 the number of transurethral resection of the prostate (TURP) procedures done declined by close to 20%, while during the same period of time the number of prescriptions written for the treatment of BPH more than doubled.[5] The confounding variable to the difficulty in determining how to appropriately treat these patients medically is the cost effectiveness of these modalities. There is still no conclusive long-term data on cost effectiveness of medical therapies in the treatment of BPH versus surgical interventions using actual patients; however these trials are now ongoing. Using a computer model, the Canadian Coordinating Office of Health Technology Assessment looked at the cost effectiveness of different treatment modalities of BPH over 15 years. Their final recommendation was watchful waiting for mild symptoms regardless of life expectancy. However, for patients with moderate to severe symptoms the group noted that the more severe the symptoms, and the longer the life expectancy, the more likely that TURP would be the more cost effective strategy in the long run.[6]

Treatment

The successful treatment of BPH should be based on the attainment of certain goals. First, as a form of secondary prevention, the treatment should work to prevent the complications of BPH, (i.e., acute urinary retention, bladder stones, acute renal failure, hematuria, bladder remodeling). Second, the treatment should aim to improve the patient's quality of life by reducing their LUTS symptoms. Third, the urologist should consider the health related costs of the proposed treatment for the patient as well as society. Patients can therefore be categorized into four groups based on selected treatment: 1) watchful waiting, 2) medical management, 3) minimally invasive therapies, or 4) surgical management.[7] It is beyond the scope of this article to discuss each of these treatment arms, thus this article will focus on the medical management of BPH.

It is important to note that many patients will elect out of treatment or will be deemed appropriate for watchful waiting. The EAU guidelines from 2004 recommend watchful waiting for those patients with minimal symptoms or moderate to severe symptoms and no significant impact on the quality of their life.[7] A study of the impact of watchful waiting evaluated 556 men who were stratified to either watchful waiting or surgical intervention. The watchful waiting group had twice as many treatment failures as did the surgical group. However, when stratified by pre-operative symptom score patients with low to moderate symptoms were less likely to undergo TURP.[8] This study illustrates the natural history of disease progression with BPH. The basis of treatment for watchful waiting is continued monitoring for progression of the disease as well as lifestyle modifications to decrease the symptoms that are already present.[7]

Alpha blockers

Alpha-blocker therapy has been a part of the management of LUTS associated with BPH since the 1990's and is the first line treatment used by 80% of physicians.[9] This treatment is based on the theory that increased muscular tone in the prostatic stroma and prostatic urethra, as well as the bladder neck causes obstruction. This is mediated via α-1-adrenergic stimulation of smooth muscle cells and therefore selective α-1-blockers will cause relaxation of these smooth muscle cells.[10] This should result in relief of obstruction and improvement in symptoms.

Alfuzosin, tamsulosin, terazosin, and doxazosin are the four alpha blockers that are approved by the FDA for the treatment of LUTS associated with BPH. A meta-analysis has shown that each of these medications results in a statistically significant improvement in patient symptom scores compared to placebo. The clinical impact is usually within 48 hours of initiation of treatment. Patients typically show improvement of their symptom scores by 4-6 points, which is perceived by most patients as a meaningful difference.[11] Tamsulosin is unique compared to the others in its class in that it is an α1A-receptor blocker. The efficacy of these drugs, as proven by multiple RCTs, has been shown to be virtually equivalent.[12] In both the new AUA as well as EAU guidelines the alpha blockers are recommended equally, thus leaving the final decision to the discretion of the individual clinician.

Side effects with the alpha blockers typically include headache, dizziness, postural hypotension, rhinitis, and sexual dysfunction. This occurs in about 5%-9% of the patients taking these medications.[11]

5-α-reductase inhibitors

Whereas alpha blocking agents treat the symptoms of BPH by decreasing smooth muscle tone, 5-α-reductase inhibitors are postulated to be effective because of reduction in prostate volume. These agents are more effective in patients with prostate enlargement, glands larger than 30 ml-40 ml.[13] The largest trial to date investigated the use of finasteride for the treatment of BPH. In this multicenter, double-blinded, placebo-controlled trial of around 3000 men, there was a 55% risk reduction for the necessity of surgery for BPH as well as a 57% risk reduction of the development of acute urinary retention versus placebo. There was also a mean decrease in symptom score of 3 points in the finasteride group, an increase in urinary flow rates, as well as a significant reduction in prostate volume (20%-30%) compared with placebo.[14] Dutasteride is a second generation 5α-reductase inhibitor. It inhibits both type 1 and type 2 isoforms of the 5α-reductase enzyme. This added effect had been postulated to increase the efficacy of this drug in the treatment of BPH versus finasteride. However, studies have shown dutasteride to be similar in efficacy to finasteride.

It is important to remember that when therapy is initiated with these agents, it may take several months before activity is noted. It is also important to note that finasteride and dutasteride will decrease the PSA level in a patient by about 50%; however they do not decrease the early detection of prostate cancer.

Side effects with finasteride and dutasteride are mostly related to sexual dysfunction and include decreased libido, erectile dysfunction, and decreased ejaculation in 6%, 8%, and 4% of patients respectively.[7] However, it is important to note that these medications can be combined with the PDE-5 inhibitors safely for the treatment of these sexually related side effects.

5α-reductase inhibitors are important agents in the treatment of BPH. They have been shown to impact the complications that develop as a result of the natural history of BPH, such as acute urinary retention and the need for surgical intervention. This class of drug is a good option for patients with moderate to severe LUTS symptoms who also have benign prostatic enlargement (BPE). There is some trend now to the offering of this class of medications to those patients that simply have BPE as prevention to the progression of the disease. This has been shown to be efficacious, but the benefits of this treatment have to be weighed against the risks of sexual side effects as well as cost of long-term treatment.[7]

PDE-5 inhibitors

There has been much research recently focusing on the integrative nature of BPH, LUTS, and erectile dysfunction (ED) with evidence demonstrating a significant link between these disease processes. In a study of 5000 German men aged 30-80 years of age, approximately 70% of the men with LUTS had ED. The men in this study with LUTS had double the risk of developing ED.[15] In the Multinational Survey of the aging male looking at a group of men aged 50-90 years of age, 90% of these men were found to have LUTS. When comparing LUTS and ED a significant correlation was again present, with the severity of LUTS being the best predictor of ED.[16] In both of these studies LUTS was an independent risk factor for ED.[17]

The first major study of its kind looking at PDE-5 inhibitors and LUTS treatment was done in an andrology clinic. One hundred eleven patients were assessed with baseline IIEF and IPSS scores. They were then given oral sildenafil on demand and were reviewed with IIEF and IPSS scores at 1 and 3 months after initiation of treatment. After the initiation of treatment with oral sildenafil, the baseline IPSS scores as well as bother scores improved. Additionaly, men with lower LUTS severity had improvement in their IIEF scores as well. The proposed mechanism for this appears to be the presence of nitric oxide in the human prostate and sildenafil mediated smooth muscle relaxation through the nitric oxide pathway.[16]

The above study illustrates the possibility for PDE-5 inhibitors in the treatment of BPH. There are currently placebo controlled trials looking at sildenifil and tadalafil in the treatment of LUTS. There have also been studies demonstrating the ability to safely combine alpha blockers and PDE-5 inhibitors for the treatment of LUTS and ED. However, more studies are needed with primary end points directed towards the treatment of LUTS before determination can be made as to the efficacy and safety of these medications combined for this indication.

Combination therapy

The initial studies on combination therapy with alpha blockers and 5α-reductase inhibitors did not appear to show a benefit.[18-20] However, the results in the MTOPS trial show an added benefit for the combination therapy. Patients were followed for 4.5 years and treated with either placebo, finasteride alone, doxazosin alone, or combination therapy. The primary end point for the study was clinical progression of disease which was defined as an

increase in AUA symptom score of 4 points, acute urinary retention, renal failure secondary to BPH, urinary tract infections, and urinary incontinence. The study showed a decrease in clinical progression with finasteride of 32% and 39% in doxazosin. These results were significant compared to placebo but there was no statistical significance between the two, showing them to be equally efficacious. However, in the combination therapy group there was a 66% reduction in clinical progression compared to placebo.[21] The same research group also released a study showing that for men with smaller volume prostates (less than 25 ml) there is no added benefit of combination therapy versus monotherapy with doxazosin alone, but that in those with larger volume prostates that combination therapy is again better than either monotherapy with doxazosin or finasteride.[23] Currently the CombAT trial combining Avodart (dutasteride) and tamsulosin is underway to look at the effect of combination therapy with the second generation 5α-reductase inhibitor to evaluate if there is an added benefit compared to the first generation 5α-reductase inhibitor.

It is now becoming clear that in men with an increased risk of clinical progression that combination therapy is the best treatment to prevent progression of disease and improve patient symptom scores. Those patients with increased age, increased severity of symptoms, higher PSA values, higher total prostate volume, lower Qmax, and increased PVRs have been shown to be at increased risk of progression and should be considered candidates for combination therapy.[22]

Future directions

The BPH patient registry and patient survey is currently in development to determine the effectiveness of the above recommendations in the treatment of BPH as well as determining the actual practice patterns of clinicians in a variety of settings.[24] The information derived from this patient registry will be invaluable in the future direction of the medical management of this disease. The true efficacy of these medical interventions in a "real world" situation will then be established, as well as the ability to examine how strictly clinicians adhere to them. This will aid us in the future directions we, as urologists, need to move. This is especially important as more and more of these patients are being managed by primary care physicians. Our role may then be more useful as an educator, as opposed to the primary provider of care, for the actual patient in the appropriate medical management of BPH.

Disclosure

Dr. Cully Carson is a member of the Speakers' Bureau for Auxilium Pharmaceuticcals, Pfizer and Lilly. He is a consultant for Pfizer and Lilly. □

References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132(3):474-479.
2. McConnell JD. The Pathophysiology of benign prostatic hyperplasia. *J Androl* 1991;12:356-363.
3. Homma Y, Kawabe K, Tsukamoto T et al. Epidemiologic survey of lower urinary tract symptoms in Asia and Australia using the international prostate symptom score. *Int J Urol* 1997;4:40-46.
4. Girman CJ, Epstein RS, Jacobson SJ et al. Natural history of prostatism. Impact of urinary symptoms on quality of life in 2115 randomly selected community men. *Urology* 1994;44:825-831.
5. Foley CL, Taylor C, Kirby RS. Counting the cost of treating benign prostatic hyperplasia. *BJU Int* 2004;93:250-254.
6. Canadian Coordinating office for Health Technology Assessment. Cost effectiveness and cost-utility analyses of finasteride therapy for the treatment of benign prostatic hyperplasia. Ottawa;CCOHTA, 1995.
7. 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(5):547-554.
8. Wasson JH, Reda DJ, Bruskewitz RC et al. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on transurethral Resection of the Prostate. *N Engl J Med* 1995;332:75-79.
9. Denis L, McConnell J, Yoshida O et al. Recommendations of the international scientific committee: the evaluation and treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction; Proceedings of the 4th international consultation on benign prostatic hyperplasia; July 2-5, 1997;Plymouth, UK: Health Publications Ltd; 1998. Pp. 669-683.
10. Lam JS, Cooper KL, Kaplan SA. Changing aspects in the evaluation and treatment of patients with benign prostatic hyperplasia. *Med Clin North Am* 2004;88:281-308.
11. Kaplan S. Update on the American urological association guidelines for the treatment of benign prostatic hyperplasia. *Rev Urol* 2006;8(Suppl 4):S10-S17.
12. Wilt TJ, Mac Donald R, Rutks I. Tamsulosin for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2003;(1):CD002081.
13. Marberger M, Harkaway R, de la Rosette JJ. Optimizing the medical management of benign prostatic hyperplasia. *Eur Urol* 2004;45:411-419.
14. Roehrborn CG, Boyle P, Bergner D et al. Serum prostate-specific antigen and prostate volume predict long-term outcome in symptoms and flow rate: results of a 4 year, randomized trial comparing finasteride vs placebo. PLESS study Group. *Urology* 1999;54:662-669.
15. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Englemann U. Epidemiology of erectile dysfunction: results of the 'Cologne male survey'. *Int J Impot Res* 2000;12:305-311.

16. 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:G37-G49.
17. Carson CC. Combination of phosphodiesterase-5 inhibitors and alpha-blockers in patients with bengin prostatic hyperplasia: treatments of lower urinary tract symptoms, erectile dysfunction, or both? *BJU Int* 2006;97(2):39-43.
18. Lepor H, Williford WO, Barry MJ, Brawer MK, Dixon CM, Gormley G, Haakenson C, Machi M, Narayan P, Padely RJ. Veterans Affairs Cooperative Studies, benign prostatic hyperplasia study group. The effects of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med* 1996;335:533-539.
19. Debruyne FM, Jardin A, Colloi D, Resel L, Witjes WP, Delauche Cavallier MC et al. Sustained release alfuzosin, finasteride and the combination of both in the treatment of BPH. European ALFIN study group. *Eur Urol* 1998;34:169-175.
20. Kirby RS, Roehrborn C, Boyle P, Bartsch G, Jardin A, Cayr MN, Sweeney M, Grossman EB. Prospective European Doxazosin and Combination Therapy Study Investigators. Efficacy and toleratbility of doxazosin and finasteride, alone or in combination, in treatment of benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003;61:119-126.
21. McConnell JD, Roehrborn CJ, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, Lepor H, McVary KT, Nyberg LM Jr, Clarke HS, Crawford ED, Diokno A, Foley JP, Foster HE, Jacobs SC, Kaplan SA, Kreder KJ, Lieber MN, Lucia MS, Miller GJ, Menon M, Milam DF, Ramsdell JW, Schenkman NS, Slawin KM, Smith JA. Medical Therapy of Prostatic Symptoms Research Group. The long term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Eng J Med* 2003;349(25):2387-2398.
22. Crawford ED, Wilson SS, McConnell JD, Slawin KM, Lieber MC, Smith JA, Meehan AG, Bautista OM, Noble WR, Kusek JW, Nyberg LM, Roehrborn CG. Medical Therapy of Prostatic Symptoms Research Group. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. *J Urol* 2006;175(4):1422-1426.
23. Kaplan SA, McConnell JD, Roehrborn CG, Meehan AG, Lee MW, Noble WR, Kusek JW, Nyberg LM Jr. Medical Therapy of Prostatic Symptoms Research Group. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia for men with lower urinary tract symptoms and a baseline total prostate volume of 25ml or greater. *J Urol* 2006;175(1):217-220.
24. Roehrborn CG, Nuckolls JG, Wei JT, Steers W. BPH Registry and Patient Survey Steering Committee. The benign prostatic hyperplasia registry and patient survey: study design, methods, and patient baseline characteristics. *BJU Int* 2007;100(4):813-819.