Benign prostatic hyperplasia: from A – Z

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The management of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia over the last decade underwent many changes.
The introduction of many medical options including alpha blockers and 5 alpha reductase inhibitors provided alternatives to what used to be surgery or "watchful waiting".
Alpha blockers evolved over the years from non specific alpha blockers to alpha 1 selective and then to alpha 1a selective with a wider acceptance due to lack of need to titrate and a better safety profile.
5 alpha reductase inhibitor (finasteride) passed through a lot of changes from being the first medication directed at treating the disease process to less acceptance because of time to response and early data supporting no added benefit when combined to alpha blockers for a short period. Longer studies now demonstrate a benefit to combination causing a reduction of progression parameters and an advantage over 4 years in reducing endpoints, namely acute urinary retention and surgery. Surgical options have also undergone many changes over the last decade with introduction of minimally invasive options as well as the introduction of new energy sources to reduce complications and allow for management of larger glands such as Holmium laser enucleation of the prostate or the use of bipolar loops.
The journey has been long and exciting and we are sure Ernie Ramsey enjoyed being in the forefront of the evolution.

Key Words: benign prostatic hyperplasia, alpha blockers, 5 alpha reductase inhibitor

Remembrance

We have had the privilege to know and work with Ernest Ramsey for 2 decades. The experience has inspired and enriched our lives. He set a standard of excellence for all of us, one which we shall continue to aspire to. We are better people today for knowing and working with Ernie. We are proud and honored to be asked to write an article in this special issue of the CJU dedicated to the memory of Ernie Ramsey.

Ernie's special interest in urology, besides providing excellent urological care for his patients and teaching generations of students and residents was benign

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prostatic hyperplasia (BPH). He was there through all the dramatic changes in the BPH field that occurred over the last 2 decades; in fact he was responsible for many of them. We believe that if Ernie himself was asked to write an article for this special journal on some topic of urology that he had been intimately involved in, it would be BPH and how our understanding and treatment of this condition has evolved over the last decade or so.

The interlinked story of finasteride (its rise, fall and perhaps rise again), alpha-blockers and surgery for BPH is a fitting story to honor Ernie's memory.

Mostafa M. Elhilali and J. Curtis Nickel

Twenty years ago patients presenting with "prostatism" which we refer to now as Lower Urinary Tract Symptoms (LUTS) were offered some form of a prostatectomy. The "Gold Standard" for a moderate sized prostate was and still is transurethral prostatectomy (TURP). A Millin retropubic prostatectomy was indicated for large prostates. Few centers in Canada advocated perineal prostatectomy or transvesical prostatectomy for LUTS secondary to benign prostatic hyperplasia. TURP became the second most common surgical procedure in men over 65 years with 38 000 prostatectomies per year in Canada at an annual cost of 150 million Canadian dollars.

It does not seem that long ago that the patient had only two choices, watchful waiting or surgery, and physicians had no clear guidelines of when to treat, no objective assessment of symptoms, no bothersome assessment. It now appears very probable that many patients were operated on unnecessarily.

Non-ablative treatment of the prostate began in the late 19th century with two case reports of bilateral orchiectomy for the treatment of BPH; a rather radical approach for a benign condition.

The first attempt at medical therapy was introduced by Marco Caine when he suggested phenoxybenzamine as a treatment modality for the symptoms of BPH. This was followed by other more selective alpha-blockers such as prazosin, terazosin and doxazosin. These drugs were introduced as therapeutic agents for hypertension and were used by urologists off label for men with symptomatic BPH. While their efficacy for treating high blood pressure was proven to be limited, many studies confirmed the efficacy (and safety) of terazosin and doxazosin in the treatment of symptoms related to BPH.

The first drug to be primarily developed as a treatment modality for BPH was finasteride, a 5 alpha reductase inhibitor that resulted in the reduction of dihydrotestosterone (DHT), which was considered to be important in the development of BPH. The original studies demonstrated that it does reduce DHT in the serum and even to a larger extent in the prostate. This resulted in reduction of the size of the prostate associated with symptom and peak urinary flow improvement. A truly unique urological medical treatment (finasteride or Proscar) for BPH was born!!

The impact of introducing finasteride was quite significant and resulted in a dramatic increase in BPH awareness among urologists, physicians, and patients. The Canadian Prostate Health Council was created twelve years ago at the time when finasteride was about to be launched. Ernie Ramsey was the first chairman and led the group through its most productive years. Educational programs for urologists and family physicians, practice pattern studies, development of teaching aids, and finally patient education products successfully helped Canadians (both physicians and patients) through these turbulent early years. The patient pool multiplied; prostate cancer awareness increased yet the net outcome was a sharp but very appropriate decline in the frequency of surgical interventions for BPH. The AUA/IPSS Symptom Scores were introduced and then adopted globally. Guidelines for treatment with emphasis on bothersomeness and quality of life were established. The decade between 1986 and 1996 witnessed the introduction and acceptance of medical treatment for BPH.

The use of alpha-blockers as treatment modalities quickly gained ground in the race of medical therapies and soon surpassed finasteride. This was due to the rapid improvement in symptoms experienced by men bothered with BPH symptoms when they took this class of medical treatment. Finasteride's effect was found to be slow and it did not appear to work in as many patients as the alpha-blockers did. The need for titration to reach the therapeutic dose and the side effect profile were the limiting factors for using terazosin and dosazosin. Long term studies confirmed a high incidence of dropouts.

A logical step was to evaluate the possible synergistic effect of combining an alpha-blocker with a 5 alpha reductase inhibitor in the treatment of BPH. This combination seemed to make perfect sense as each agent acts through a different mechanism of action. Many urologists were already doing that in clinical

practice. The release of the surprising data from the Veterans Administration (VA) study that adding finasteride to terazosin did not show any advantage over the duration of the study (12 months) to terazosin alone and that finasteride efficacy was not very different to the placebo effect, changed everything overnight. It looked to everyone (including Merck Frosst in Canada who developed and distributed the drug) that finasteride's days as a treatment modality for BPH were numbered.

Urologists and researchers who had noted significant improvement in some patients over the years were taken by surprise by this study. Previous studies and combined data were re-analyzed in an attempt to explain this clinical paradox and to identify the factors that could influence response to finasteride. A large meta-analysis of all the previous finasteride trials held the answer. The most important factor appeared to be prostate size. Subsequent analyses then confirmed that PSA as a surrogate for the glandular component of the enlarged prostate was also important. These results led to a more rational approach to medical management of BPH with finasteride. Men with larger prostates (>30-40 cc) and/or higher PSA (≥1.4 ng/ml) benefit more from finasteride than men with smaller glands and lower PSA serum levels. These findings triggered a rebirth of interest in 5 alpha reductase inhibitors. But the urology profession in Canada remained skeptical. No company was actively promoting finasteride and alpha blockers were still considered by many urologists as the only medical option in BPH.

The release of the US PLESS study, a major multicenter randomized controlled study involving 3040 patients treated over 4 years with finasteride or placebo changed things yet again. The primary endpoint was symptoms, which were significantly improved with the difference between finasteride and placebo becoming more evident and important at 3 and 4 years. As predicted by the previously mentioned meta-analysis, the symptom improvement was also higher in the participants with larger prostates and higher baseline serum PSA levels. The most intriguing and impressive differences between finasteride and placebo were seen in the secondary endpoints; acute urinary retention (AUR) and/or surgery. Finasteride resulted in significant decrease in progression of BPH measured by these secondary outcomes. The difference was even more pronounced in patients with larger prostates and higher serum PSA's; placebo had the highest probability of experiencing AUR and/or surgery while finasteride treated patients had the most dramatic reduction in risk. It appeared 5 alpha reducatase inhibitors may have a long term role in prevention of BPH progression. Other 5 alpha reductase inhibitors, which are in their final stages of development, have produced clinical data very similar to that of finasteride. Dutasteride is an example of this, a dual inhibitor, inhibiting both types 1 and 2 - 5 alpha reductase enzymes.

The story of the alpha-blockers was not static during these years. Newer molecules and newer delivery systems were being explored to avoid the two major problems of titration and the side effect profiles. Two such drugs were eventually introduced; tamsulosin (Flomax) and alfuzosin (Xatral). Tamsulosin was introduced in the U.S. and Canada several years ago and quickly became the most prescribed drug for LUTS in North America. Alfuzosin was introduced in Europe many years ago as an immediate release formulation (2.5 mg T.I.D.) and then as a delayed (B.I.D.) and subsequently in Canada as a sustained release Geomatrix formulation 10 mg once daily. Both tamsulosin and alfuzosin are equally effective with low cardiovascular side effects. Tamsulosin having an alpha 1_a selective profile is associated with a higher incidence of ejaculatory problems than alfuzosin. The association of LUTS and sexual dysfunction was always thought to be coincidently encountered in older patients. Recent data suggest that the association is more significant with sexual dysfunction being associated with more severe LUTS. Improvement of both symptoms were seen to follow treatment with alpha blockers.

The quest for more selective alpha blockers resulted in the development of ultra selective alpha 1_a antagonists. Recent reports have indicated that this has resulted in less efficacy. Alpha blocker development may have come along as far as they are ever going to.

The story of finasteride, however, continues. The results from one of the most anticipated BPH studies ever attempted, the Medical Therapy On Progression BPH Study (MTOPS) were recently released. This study, undertaken in 3047 patients randomized to placebo, finasteride, doxazosin and the combination doxazosin and finasteride for 5 years, has significant ramifications for clinical practice. The primary end points were clinical progression which was defined as AUR, renal insufficiency due to BPH, recurrent U.T.I. or urosepsis, incontinence or an increase of >4

points in baseline AUA Symptom Score confirmed within 2-4 weeks. The results were quite different from the very much shorter VA study. In the MTOPS study, combination therapy resulted in significantly less progression than either drug alone and each drug alone was significantly less than placebo. The incidence of AUR was least with the combination and finasteride alone. The incidence of AUR was lower using doxazosin alone compard to placebo up to 2.5 years and then started to rise approaching placebo at 5.5 years presumably by the progressive increase in size of the prostate (the alpha blocker only delayed progression). The study for the first time showed that the combination therapy is the most effective in reducing progression but at the same time it was also confirmed for improving symptoms and flow rates. The use of combination therapy obviously adds a significant cost to the treatment of BPH. Data presented recently suggested that if the alpha-blockers were stopped between 6-9 months after initiation of combination therapy the majority of patients did not notice a significant difference. The MTOPS study could (and really should) significantly change the attitudes of physicians and patients in treating BPH.

What about that other benign prostate disease, chronic prostatitis. Both alpha blockers and 5 alph reducatase inhibitors are now being evaluated for the treatment of chronic nonbacterial prostatitis and early results show some modest treatment effect of both these agents (no combination trial is presently being done).

The finasteride story has not closed in on its final chapter just yet. Many researchers believe that long-term therapy with finasteride will result in risk reduction of prostate cancer. A large study designed to show a difference of 25% is presently being completed and will soon be analyzed. If such expectations materialize, 5 alpha reductase inhibitors may potentially be prescribed by urologists to treat LUTS associated with BPH, reduce progression of BPH (prevent AUR and the need for surgical intervention), treat prostatitis and potentially reduce the risk of prostate cancer.

Surgical options for BPH also changed dramatically at the same time medical therapy was becoming the primary therapy for most patients with BPH. Many minimally invasive options came, went or are going; balloon dilation, stents, ultrasound and transrectal hyperthermia. Transurethral thermotherapy (TUMT) and transurethral needle ablation of the prostate (TUNA) appear to be viable minimally invasive alternatives with data up to 5 years showing persistent benefit, but a high retreatment rate and higher incidence of alternative treatment. The improvement in symptoms with these treatments is not always matched by an increased flow. TURP remains the "Gold Standard" for ablation therapy of a reasonably sized prostate, but other techniques such as laser ablation, vaporization, roto-resection, interstitial thermal treatment etc may prove as effective with perhaps less side effects. The technique of TURP is also evolving with development of specialized electrocautery loops (including bipolar loops) and different energy sources which should result in more efficient resection and coagulation with less blood loss and other adverse problems associated with this procedure (TUR syndrome). Holmium laser enucleation of the prostate appears to be effective for treating any size prostate with no TUR syndrome (saline used), less bleeding (can even be done in anticoagulated patients), shorter hospitalization and less morbidity following a "steep" learning curve. But retropubic prostatectomy still remains as the "Gold Standard" for large prostate in relatively healthy individuals.

The BPH story has been an exciting adventure for all of us who were on the journey. We will always be happy that Ernie Ramsey chose to ride along. He will be missed. □