Management of symptomatic benign prostatic hyperplasia-today

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Symptomatic benign prostatic hyperplasia (BPH) is one of the commonest causes of men presenting with lower urinary tract symptoms (LUTS). We can find this in 50% of men over the age of fifty. If BPH is not treated, then one can expect that the disease will progress in a significant number of individuals. What we need to do is try to predict, based on certain baseline parameters such as International Prostate Score (IPSS), prostate volume, prostate-specific antigen (PSA) and the degree of bother, those men to whom we should offer therapy. The other consideration is that combination therapy of a 5-alpha reductase inhibitor (5-ARI) and an alpha blocker, may provide the best results for the prevention of progression of the disease or ultimately, the need for surgery. The final considerations are "if", for "how long" and "for whom" should combination therapy be utilized.

Key Words: BPH, LUTs, alpha blocker, 5-alpha reductase inhibitor, combination therapy

Introduction

By age 50, over 50% of men will have some degree of benign prostatic hyperplasia (BPH) as a cause of their lower urinary tract symptoms (LUTS). As they get older, their symptoms will only increase and the disease will probably progress if untreated. BPH is the most common cause of reported LUTS that clinicians see today. There has been a dramatic change in the management of BPH symptoms in patients who have clinical signs of an enlarged prostate, over the last few years. The first step is to make the correct diagnosis of an enlarged prostate. Clinicians no longer rely only on results of a digital rectal examination (DRE). Rather, the patient's serum prostate-specific antigen (PSA) level has been proven and used as a surrogate marker in order to guarantee that the patient's prostate volume is at least 30 cc. Research has shown that having a prostate volume of at least 30 cc greatly increases a man's chances of responding to BPH therapy with a 5-alpha reductase inhibitor (5-ARI).

It is commonly believed that alpha blockers do not provide early and significant short term relief from LUTS and may not decrease BPH progression. Two important recent trials have demonstrated that compared to monotherapy with an alpha blocker alone, combination therapy with an alpha blocker and a 5-ARI can be very effective for treating men with an enlarged prostate. The combination can provide both early symptom relief, as well as prevent disease progression. The problem for clinicians is how to identify appropriate patients for combination therapy.

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The other patient management decision is whether combination therapy should be provided on a long term or even permanent basis.

This article based on a presentation at "Current Concepts of Men's Health" for the Urological Institute of Northeastern New York and the Albany Medical College, given in August 2008, addresses these issues.

Diagnosis

Today, most patients with BPH first present with complaints associated with an enlarged prostate. These complaints can range from a small amount of urinary frequency and nocturia to some hesitancy in urine flow, or even complete urinary retention. Sometimes the symptoms are new, but often they have been present for a very long time. Often it is the patient's partner who suggests that the man should see a physician. Sometimes urgency incontinence is associated with the progression of BPH. The difficulty in making a diagnosis is that these symptoms are somewhat vague. BPH is one cause of LUTS. It is important for physicians to rule out some of the more serious causes of LUTS.

As with most medical conditions, the physician needs to take an adequate patient history and perform an appropriate physical examination. In the case of suspected BPH, a questionnaire can help quantify the patient's reported symptom severity as well as help predict the risk of disease progression.

In taking the patient history, the physician seeks to determine if the patient has aggravating factors that can worsen bladder function and to find out when the problem started and how rapidly the symptoms have evolved.

The American Urological Association-Symptom Index (AUA-SI) for BPH developed a few years ago is a questionnaire that deals specifically with LUTS and is virtually identical to the International Prostate Symptom Score (IPSS).[1] By asking seven questions about a patient's voiding function, the clinician can obtain a symptom score to quantify BPH and obtain a prognosis. If a patient has a score of 8 or less out of a maximum score of 35 on the AUA-SI questionnaire, he is classed as having mild BPH symptoms; if his score is between 8 and 20, he is classed as having moderate BPH symptoms; and if his score is between 20 and 35, he is classed as having severe BPH symptoms.

A final question, question "eight", on the AUA-SI for BPH questionnaire is about "quality of life". The question asks, "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" The patient responds by choosing a number from 0 to 6, where 0 indicates feeling "delighted" and 6 indicates feeling "terrible." This score is also described as the "bothersome index." I like to call it, the "motivational index," since the degree that the symptoms bother the patient is an indication of how motivated the patient will be to agree to medical therapy.

Work-up

Besides taking an adequate patient history, it is important to carefully examine the patient. By doing this, the physician will be able to rule out other physical conditions that may mimic or contribute to symptoms of BPH. As well, the physician will be able to detect the presence or absence of signs of significant BPH progression such as a distended bladder, hydronephrotic kidneys, or potentially some neurological condition with symptoms that mimic LUTS.

It is very important for the clinician to perform a digital rectal examination (DRE), determine the patient's serum prostate-specific antigen (PSA) level and obtain results from a urinalysis, in order to rule out most other causes of LUTS. The DRE will allow the physician to identify any obvious signs of prostate cancer and estimate the prostate's volume. It has been shown that the finger is not very accurate in determining prostate volume. Consequently, the PSA test has been proposed as a surrogate marker for prostate volume. Many studies have shown that a serum PSA value of approximately 1.5 ng/ml consistently corresponds to a prostate volume of at least 30 cc,[2] an important number in the management of BPH. If a physician is not sure about the significance of the symptoms of BPH, then he or she can also suggest that a patient undergoes a uroflow study, a postvoid ultrasound, and possibly an abdominal ultrasound to rule out hydronephrosis. The severity of the patient's symptoms, the size of the prostate, significant signs of progression of an enlarged prostate, and finally, the patient's motivation all help the physician determine appropriate patient management and treatment options.

Treatment

In order to assess treatment options, patients are usually stratified according to their severity of symptoms and their prostate volume, as indicated in guidelines published in the Canadian Journal of Urology.[3] If the patient is suffering from recurrent gross hematuria, significant and recurrent febrile urinary tract infections, renal failure, hydronephrosis, or any signs of moderate to severe or complete urinary retention, then aggressive

therapy — usually with surgery — is indicated. If the patient's PSA value is elevated for his age, or his PSA velocity or PSA density are abnormal, a prostate biopsy should be performed to rule out prostate cancer as a cause of his symptoms. Once the physician is satisfied that there is no prostate cancer, that the patient's symptoms are only the result of BPH and there are no absolute indications for surgical intervention, then the patient can be offered medical therapy.

Surgery

The objective of surgery is to physically debulk the prostate or to perform incision/resection of any bladder neck contracture or spasming that may create the physical obstruction as a cause of the patient's symptoms. Different approaches to debulking of the prostate that have evolved for the last number of years range from standard transurethral resection of the prostate (TURP), to the use of microwaves, holmium laser enucleation or to most recently, green/white light laser vaporization of the prostate. The problem with these approaches to the treatment of the enlarged prostate is that they can also lead to long term side effects such as erectile dysfunction, urinary incontinence, or even the need for repeat/correctional surgery within 5 years.[4] Today, in most cases, these surgeries can be done as either outpatient or short stay procedures. If the patient has not reached the stage where surgery is indicated, then he can be offered medical therapy as a first line option.

Medical therapy

"Obstruction" in BPH can be classified as being "dynamic" or "fixed". The "fixed" component is related to the bulk of the prostate, that is, the enlargement of the prostate that is causing obstruction and a squeezing pressure on the urethra. The "dynamic" component of prostatic obstruction is believed to be caused by the stimulation of alpha receptors of the smooth muscle at the bladder neck and within the prostate capsule. Increasing the tone of these smooth muscle fibers causes spasming at the bladder neck or a tightness that can sometimes be corrected or alleviated by utilizing alpha blocker therapy.[5]

The first type of alpha blocker therapy that was used for BPH was a nonselective alpha blocker that had the significant side effect of severe orthostatic hypotension. The drug that most significantly exhibited this side effect was a phenoxybenzamine. The incidence of fainting and severe hypotension was so prevalent with this drug that it was discontinued for this indication.

Over the years, physicians have trialed newer, more uroselective alpha blocking agents that specifically impact the bladder neck and areas within the prostate capsule, rather than to contribute to orthostatic hypotension. Therapeutic agents have evolved from drugs such as terazosin (Hytrin, Abbott Laboratories) and doxazosin (Cardura, Pfizer), which were nonselective alpha blockers, to newer agents such as tamsulosin (Flomax, Boehringer Ingelheim Pharmaceuticals) and alfuzosin (Xatral, sanofi-aventis).[6] Although these newer drugs do not cause hypotension, they can lead to another side effect that is sometimes very disconcerting for the patient: decreased or absent ejaculation. This is usually due to decreased propulsion from the seminal vesicles rather than retrograde ejaculation. The alpha blockers do not elicit significant differences in terms of efficacy, but exhibit some differences in their side effect profiles. The attractive characteristic of alpha blockers is that patients' voiding symptoms resolve very quickly. A patient who has significant urinary hesitancy, urgency, or urinary frequency, or lacks a strong urinary stream can see a significant improvement within 24 hours or at the most within a week. In the short term, resolution of symptoms can be very satisfying for the patient; however, alpha blockers do not prevent the progression of BPH.[7] Although the patient has less urinary frequency, increased urinary flow, and decreased hesitancy and nocturia in the short term, with time, his prostate will continue to grow, his symptoms will increase, and his response to alpha blocker therapy will diminish. Ultimately, he may go into retention or need surgery to alleviate the obstruction from the prostate.

A serendipitous scientific discovery based on a congenital biochemical deficiency, lead to the development of another family of medications that has become very important in the management of BPH. These drugs, the 5-ARIs (5-alpha reductase inhibitors), act on the "static" component of prostatic obstruction.

Testosterone is converted to dihydroxytestosterone (DHT) within the prostate cells and it is DHT that causes the growth of prostate cells and the prostate itself. It was discovered that individuals who lacked the 5-alpha reductase enzyme developed ambiguous genitalia, but did not develop BPH. Researchers hypothesized that if they could inhibit the 5-alpha reductase enzyme and prevent the conversion of testosterone to DHT after puberty, this would not only prevent the growth of the prostate, but would actually shrink the prostate. This concept was proven for finasteride (Proscar, Merck Inc.), the first 5-ARI to be marketed, and for dutasteride (Avodart, GlaxoSmithKline), the second 5-ARI to be produced.[8]

After the development of finasteride it was determined that there are actually two types of 5-alpha reductase enzymes, type 1 and type 2. Finasteride inhibits the type 2 enzyme, whereas dutasteride inhibits both, type 1 and type 2 enzymes.[8] Inhibiting these enzymes prevents the conversion of testosterone to DHT, which can be measured biochemically. It has been shown that finasteride will cause about a 70% reduction of DHT levels within the prostate, in contrast to dutasteride which results in more than a 90% reduction of DHT levels.[9] In the only head-to-head trial comparing finasteride to dutasteride, after a 1 year comparison, there were no statistical differences in patients' response to either medication. The side effect profiles were virtually identical. It has been suggested that a longer trial might have demonstrated some differences.[10] The other question that has not been addressed is "How much DHT suppression is enough to control or decrease BPH?"

Early monotherapy trials with finasteride and dutasteride showed that monotherapy could shrink the prostate by 23% to 27%. The only drawback was that it took up to 6 months for most patients to experience any perceived clinical benefit based on shrinkage of the prostate.

The Proscar Long-term Efficacy and Safety Study (PLESS) showed that there was a significant patient response to monotherapy with finasteride.[11] Similar results were seen in the Avodart regulatory agency approval trials where dutasteride monotherapy was taken for 4 years to manage symptomatic BPH.[12] Patients in both trials achieved significant shrinkage of the prostate as well as a good reduction in symptoms and decreased disease progression compared to placebo.

The next question was whether combination therapy with an alpha blocker plus a 5-ARI could provide more immediate, improved symptoms in the short term, and, could also prevent disease progression (e.g., advent of urinary retention) and/or the need for surgery in the long term.

Trials were developed to compare monotherapy with an alpha blocker or a 5-ARI versus combination therapy with both agents; some trials also had a placebo arm.

Two important earlier short term trials included the Veterans Administrative Cooperative Study (VA-Coop) in the United States, which investigated the 5-ARI finasteride and terazosin (Hytrin), and the Prospective European Doxazosin and Combination Therapy (PREDICT) trial, which investigated the alpha blocker doxazosin and finasteride. Both studies lasted only 1 year. Their results suggested that in order to respond to 5-ARI therapy, a patient had to have a prostate with a minimum volume of 30 cc. In patients with small volume prostates, there appeared to be no difference in the clinical responses when comparing the placebo to the 5-ARI therapy (finasteride). Some clinicians have wondered whether a longer duration trial would have resulted in a more pronounced difference in the responses in each monotherapy arm.

A few years ago, the first results from the Medical Therapy of Prostate Symptoms (MTOPS) trial were reported. This was a very unique trial in that it was sponsored by the National Institutes of Health rather than industry, and it included only American patients. The trial compared doxazosin and finasteride monotherapy to either combination therapy with both agents or to placebo. To be included in the study, men had to have had no evidence of prostate cancer (i.e., a PSA level of less than 4 ng/ml and a negative DRE), as well as at least "mild" symptoms on the International Prostate Symptom Score (IPSS) scale (< 8). There was no prerequisite for a minimum PSA level or a prostate volume documented by transrectal ultrasound.

The MTOPS study showed that patients taking combination therapy had a 67% decreased risk of progression of prostate disease to: urinary retention or the need for surgery. Treatment responses in both monotherapy arms were similar, but symptom control with the alpha blocker appeared to be more effective compared to the 5-ARI alone, up to 5 years.[11]

The Combination of Avodart and Tamsulosin (CombAT) trial was developed to further investigate this same hypothesis. In this trial, monotherapy with dutasteride or tamsulosin was compared to combination therapy with both agents in "high risk" BPH patients. High risk of disease progression was defined as a patient with a prostate volume of at least 30 cc determined by transrectal ultrasound, a PSA of at least 1.5 ng/ml with an upper limit of 10 ng/ml, and an IPSS score of at least 12 signifying moderate symptoms of BPH. The study's ethical review board determined that since each monotherapy had been previously proven to be more effective than placebo in other trials, it would not be ethical to allow these high risk patients to receive only placebo for 4 years.

Currently, only the 2 year interim results from the CombAT trial are available. Again, patients in the combination arm had greater symptom reduction than patients in either monotherapy arm. Surprisingly, by 15 months into this study, the 5-ARI dutasteride appeared to be even more effective than the alpha blocker tamsulosin in reducing the AUA-SI. The average prostate volume of the patients in the CombAT trial was 54 cc, which was much higher than in the MTOPS trial.[13]

The 2 year results from the CombAT trial showed that compared to patients in the monotherapy arms, patients in the combination arm showed a marked improvement in quality of life, as measured by their responses to question 8 on the AUA-SI questionnaire as well as the BPH Impact Index.[14]

After a clinician has elected to treat his patient with combination therapy, the final question to ponder is: How long to maintain the combination therapy?

The profile of a patient who should be offered combination therapy is that of a man who has prostate enlargement greater than 30 cc, no evidence of prostate cancer, and moderate to severe symptoms of BPH disease. Assuming that the patient will achieve response to the 5-ARI by approximately 6 months and that the alpha blocker will not prevent progression of the disease, the physician must determine when and if to stop the alpha blocker.

This question was addressed in two recent studies: the Symptom Management After Reducing Therapy-1 (SMART-1) trial and the PRoscar and alpha blOcker combinAtion followed by disContinuation Trial (PROACT) study. In SMART-1, all patients were given a combination of dutasteride and tamsulosin for 6 months. Then in a blinded monotherapy with dutasteride. Both at 3 months and 6 months later, the patients were asked: "Do you feel the same, better, or worse compared to how you felt 3 months ago?" The SMART-1 trial concluded that approximately 77% of patients who continued with dutasteride alone after only 6 months of combination therapy were very happy with their symptom response and their voiding function.[15]

In the PROACT trial, if a patient was already on an alpha blocker, all that the investigator did was to add finasteride for 9 months. If the patient was not on an alpha blocker, he was given tamsulosin and finasteride for 9 months. At 3 months and 9 months after the initial 9 month combination therapy, patients were asked a similar question about their satisfaction with their present treatment regimen compared to how they felt before. The answer here as well, was that most patients felt quite comfortable after completing a total of 9 months of combination therapy.[16]

Regardless of absolute symptom response, both MTOPS and CombAT suggest that long term combination therapy will prevent progression of BPH symptoms, urinary retention, and the need for surgery to a greater extent than either monotherapy.

Possible side effects from the 5-ARIs include gynecomastia, decreased libido, and erectile dysfunction. The only surprise was that the incidence of ejaculatory dysfunction was "more than additive" in the combination arm compared to the specific incidences in either monotherapy arm. This could be a concern for some patients.

We await the 4 year data from the CombAT trial to see how its final numbers for progression, retention and surgery, in this "higher risk" population compare to the MTOPS final results.

Recently it has been shown that patients who are either receiving an alpha blocker alone or combination therapy with a 5-ARI may still exhibit symptoms of bladder irritation as manifested by complaints of frequency, urgency, and possibly urgency incontinence. Some studies have demonstrated that adding an anticholinergic medication will not give these patients a higher risk of developing urinary retention, but could offer them additional symptom improvement.[17,18]

Another proposal for an additional type of combination therapy arises from the hypothesis of a common pathway that stimulates BPH symptoms and erectile dysfunction. It appears that some men who have mild to moderate irritative symptoms of BPH such as frequency and urgency also develop erectile dysfunction. Some men who are treated for BPH with alpha blockers can have improved erectile function. Conversely, men who use type 5 phosphodiesterase inhibitors to manage erectile dysfunction can also show some improvement in voiding symptoms associated with BPH. A possible explanation for this might be that increased oxygenation through the nitric oxide pathway which is also critical in the development of erections, can stabilize the prostate. The interesting result is that although urinary symptoms might improve, uroflow rate does not change.[19]

Conclusions

What would I do if I had BPH?

If I had significant symptoms of frequency, urgency, obstructive symptoms and a prostate volume greater than 30 cc as demonstrated by either transrectal ultrasound or a PSA level greater than 1.5 ng/ml, I would accept combination therapy with a 5-ARI and an alpha blocker for about 9 months. If after taking combination therapy for 3 months I was still experiencing frequency and urgency symptoms, I would add an anticholinergic medication to my treatment regimen. At the end of 9 months, I would attempt to discontinue the alpha blocker and monitor my symptoms. If there were no changes, I would consider stopping the anticholinergic medication. If after another 1 month there were no changes in my symptoms, I would continue treatment with only the 5-ARI.

What we have seen is that simultaneous combination therapy with an alpha blocker and a 5-ARI is definitely more effective than either type of monotherapy to prevent progression of BPH symptoms as well as urinary retention and the need for surgery. In a number of patients, after 6 or 9 months of combination therapy it appears that we may be able to stop alpha blocker therapy, but maintain symptom response while still preventing progression. If the symptoms return, it is easy to reintroduce the alpha blocker. Other additional therapeutic agents can be offered in response to a patient's symptoms.

With the development of newer, more selective alpha blockers, as well as combination therapy with the 5-ARIs, we have changed our approach to the management of BPH. Today, compared to a number of years ago, the frequency of doing the "gold standard" TURP (transurethral resection of the prostate) has diminished significantly as more and more men initially attempt BPH management by using medical therapy. These men can enjoy a long term response without disease progression while sustaining mild and in most cases very tolerable side effects.

Disclosure

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, GlaxoSmithKline, Merck Frosst, sanofi-aventis and Boeringer-Ingelheim. He has done the clinical research on Avodart, Flomax, Hytrin, Xatral and Proscar, both in monotherapy and combination. He has spoken all over the world for all of the companies outlined. □

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