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Review

Medical therapy for clinical benign prostatic hyperplasia: α1 Antagonists, 5α reductase inhibitors and their combination

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Abstract Medical therapy for clinical benign prostatic hyperplasia (BPH) has advanced significantly in the last 2 decades. Many new α1 antagonists and 5α reductase inhibitors (5ARi) are now commercially available. The practicing urologist must decide on the most appropriate medication for his patients, taking into consideration various factors like efficacy, dosing regime, adverse effects, cost, patient's socioeconomic background, expectations, drug availability and his own clinical experience. The use of combination therapy added further to the complexity in clinical judgment when prescribing. We highlight some of the key points in prescribing α1 antagonists, 5ARi and their combination, based on our viewpoints and experience as urologists in an Asian clinical setting.

1. Introduction

Benign prostatic hyperplasia (BPH) is often equated with prostatic enlargement in aging males, but "normal-sized" prostates below 20 mL may also cause bladder outlet obstruction. Such occurrence of prostatic obstruction, with or without significant symptoms, constitutes clinical BPH and its sequelae [1]. Cellular proliferations in the periurethral and transition zones lead to the formation of nodular adenomas, potentially distorting the bladder neck and prostatic urethra. A small adenoma located submucosally along the prostatic urethra may be sufficient to cause obstruction without significant enlargement of the remaining prostate gland [1].

Lower urinary tract symptoms (LUTS) from BPH can be classified into two groups. Voiding symptoms, such as hesitancy and intermittent/weak urinary stream, can be understood as the direct results from prostatic obstruction. Storage symptoms, such as frequency and urgency, may be

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secondary to a combination of factors like detrusor instability, detrusor hypertrophy, decreased bladder compliance and decompensation [2]. Non-urological factors, such as cardiac, neurological and hormonal dysfunctions, may also contribute to LUTS in BPH patients [2].

The choice of medications for BPH was limited in the past, and medications could only provide short-term symptomatic relief at the expense of significant adverse effects. One such example was phenoxybenzamine, a non-selective irreversible α antagonist. Patients risked postural hypotension, light-headedness, fainting spells and recurrent falls for several hours of symptomatic relief. Dose titration was a routine, since controlled release was not an option. BPH progression could not be halted and many patients, despite years of medications, eventually developed complications or required surgical interventions. The concurrent control of BPH-related sexual dysfunctions was almost never discussed.

However things have changed drastically, for the better. Many α1 antagonists are now commercially available, offering advantages of rapid onset, long-lasting efficacy, reduced adverse effects, convenient single daily dosing and many other perks. 5α Reductase inhibitors (5ARi) provide sustained improvements in LUTS and reduce BPH progression, so surgical interventions may be delayed or avoided [3—5]. α1 Antagonists and 5ARi are being used in combination to complement each other's pharmacological action, and the well-known MTOPS and ComBAT studies provided evidence for its success [4,5]. Muscarinic receptor antagonists, phosphodiesterase-5 inhibitors, phytotherapy and their combinations also play increasingly important roles in BPH treatment, though being outside the scope of this chapter.

With more choices in the pharmaceutical market, prescribing the appropriate medical therapy for BPH patients is an increasingly complicated task for the urologists. The fine balance between efficacy, adverse effects and costs is often difficult to achieve, and the different physiological and socioeconomic backgrounds of every BPH patient further complicate matters. In this chapter, we review the use of α1 antagonists, 5ARi and their combination for clinical BPH.

2. α1 Antagonists

2.1. Mechanism of action

BPH causes urinary obstruction by two main mechanisms. Firstly, the increase in prostatic stroma leads to nodular enlargement which, in turn, results in distortion of the prostatic urethra and obstruction to urinary flow [6]. Secondly, there is an increased smooth muscle tone in the prostate and bladder neck, mediated by α1 adrenoceptors [6,7]. These mechanisms account for the static and dynamic components of obstruction. α1 Antagonist, as the name implies, blocks the α1 adrenoceptors in the prostate and bladder neck, thus relieving the dynamic component of obstruction. Certain α1 antagonists, such as tamsulosin and silodosin, exhibit uroselectivity by having a high affinity for α1A adrenoceptors located in the prostate and bladder neck [8,9].

2.2. Efficacy

When dosed correctly, α1 antagonists improve International Prostate Symptom Score (IPSS) by 30%—45% and improve the urinary flow by 15%—30% [10]. They have fast onset of action and patients often experience their therapeutic effects within a week [11]. They improve both voiding and storage symptoms, with maintained efficacy for 4 years [4,5,12]. However, α1 antagonists do not reduce prostatic volume and do not prevent disease progression, so they do not reduce the risk of BPH complications or BPH-related surgery in the long term [4,5,13].

2.3. Adverse effects

α1 Adrenoceptors are found in many organ systems, including the genitourinary tract, the gastrointestinal tract, the vascular system and the iris. Thus the use of α1 antagonists is associated with systemic adverse effects, especially postural hypotension [4,5,14]. α1 Antagonists in the contemporary clinical setting are relatively long-acting, and many do not require dose titration. This reduces fluctuations in serum levels after each dose to reduce systemic adverse effects. Nasal congestion, another adverse effect due to the vasodilatory effect of α1 antagonists, may be bothersome for some patients. The peculiar problem of "floppy iris syndrome" is often overlooked by urologists [15]. While this does not usually cause problems, it may adversely impact on peri-operative outcomes when patients go for cataract surgery. Some α1 antagonists are uroselective, such as tamsulosin and silodosin, with preferential action on α1A adrenoceptors commonly found in the genitourinary tract. Their side effect profiles should, in theory, be safer than those of the other α1 antagonists [8,9]. However, it has been found that ejaculatory dysfunctions are more common among uroselective antagonists due to their concentrated action in the lower urinary tract [16]. α1 Antagonists do not affect libido, and may have a small benefit on erectile function [17]. In clinical practice, it is important to remember that efficacy of any medication is a double-edged sword, and mishaps usually happen when the urologist puts too much focus on the "therapeutic edge" without due consideration for adverse effects.

2.4. Clinical use and points for special mention

Since α1 antagonists have fast onset of action, they are often used as the first line medication in newly diagnosed BPH patients. However, there are several clinical points that deserve special mention:

- Since α1 antagonists do not reduce prostatic volume or prevent BPH progression, their use should be regularly monitored and reviewed [18]. This is especially true among patients who are at high risk of BPH progression, with very large prostates, high grade intravesical prostatic protrusion or clinically proven significant prostatic obstruction [18]. Many of these patients may not have bothersome LUTS, and simply continuing α1 antagonist for prolonged periods without appropriate monitoring

subjects them to the risk of irreversible obstructive uropathy. On the other hand, patients without significant prostatic obstruction may benefit from lifestyle changes alone to control LUTS. α1 Antagonists may be used for a short period and withheld once their LUTS are no longer bothersome [18].

- Various α1 antagonists have similar efficacy when dosed correctly [10], so the choice for a specific α1 antagonist often depends on factors like socioeconomic profile, drug availability and clinician's experience. The newer (and often more costly) ones should be chosen if their adverse effect profiles and dosing regimes truly fit the clinical context without excessive financial pressure to the patient. Otherwise, a correctly dosed generic α1 antagonist can be a more financially friendly alternative with similar efficacy.
- There should be extra vigilance when using α1 antagonists in certain groups of patients. These include the very old, those with cardiovascular comorbidities, those concurrently taking antihypertensive medications or vasodilators for erectile dysfunction, those with recent changes in their medications and those with mobility issues or high fall risks [19]. These patients have less reserves to buffer any postural hypotension caused by α1 antagonists.
- Among patients with acute urinary retention secondary to BPH, the use of α1 antagonists for at least 3 days prior to trial of catheter removal seems to improve the chance for successful resumption of micturition [20]. α1 Antagonists that have been studied in this aspect include alfuzosin, tamsulosin, silodosin and doxazosin [20]. However, there is insufficient evidence to conclude whether the use of α1 antagonists for this purpose may lead to significantly more adverse effects, though the overall occurrence of adverse effects appear low for both α1 antagonists and placebo [20].

3. 5-ARi

3.1. Mechanism of action

As part of the male reproductive system, the prostate is highly androgen sensitive. The prostatic stroma contains the enzyme 5α reductase, which converts testosterone to dihydrotestosterone. Dihydrotestosterone is more potent as an androgen receptor agonist than its precursor, and is the main mediator of androgenic effects. Inhibition of 5α reductase reduces androgenic stimulation to the prostate, resulting in epithelial atrophy and eventually a reduction in prostatic volume [21]. Thus, 5ARi reduces the static component of obstruction in BPH.

5α Reductase exists as 2 isozymes, type 1 and type 2. The predominant type in the prostatic stroma is the type 2 isozyme, while type 1 is mainly found in the liver and skin. Both finasteride and dutasteride, the 2 most commonly used 5ARi in clinical practice, effectively inhibit the type 2 isozyme. Dutasteride also inhibits the type 1 isozyme, and is often described as the 5ARi with more significant enzymatic inhibition. However, since only the type 2 isozyme predominates in the prostate, the actual clinical benefit of dutasteride over finasteride has been continuously debated [22,23].

3.2. Efficacy

When used as monotherapy, 5ARi provides 2 to 3 times better improvement in IPSS and 4 to 8 times better improvement in urinary flow than placebo, associated with a reduction in prostatic volume by about 20%—25% [3,24—26]. The 5ARi monotherapy arms in MTOPS and ComBAT studies showed a 30% improvement in IPSS and a 20% improvement in urinary flow at four years [4,5]. With a gradual onset of action, it takes approximately 6 months before patients experience the maximal efficacy of 5ARi [4,5]. One advantage of 5ARi over α1 antagonists is their ability to halt BPH progression, reducing the relative risks of BPH complications and BPH-related surgery in the long term. Finasteride reduced urinary retention by 57% and surgery by 55% in the PLESS study [3], and reduced such risks by 68% and 64% respectively in the finasteride arm of the MTOPS study [4]. Dutasteride showed similar risk reductions based on results from the ComBAT study [5].

Since 5ARis act via hormonal pathways to reduce prostatic volume, they work better among patients with a larger prostatic volume at baseline. Finasteride improves LUTS and urinary flow mainly in patients with a baseline prostatic volume above 40 mL [27]. One of the inclusion criteria in the ComBAT study was a baseline prostatic volume above 30 mL, so the sustained benefits from dutasteride treatment should not be extrapolated to patients with small prostatic volumes [5].

3.3. Adverse effects

Adverse effects of 5ARi are mainly related to sexual dysfunctions, including loss of libido and erectile dysfunction. Ejaculatory dysfunctions are less common, and a small proportion of patients may experience breast engorgement and gynecomastia [4,5]. In view of the hormonal nature of their mechanism of action, 5ARi were once evaluated for prostate cancer prevention. It was found that 5ARi reduced the overall incidence of prostate cancer, but the relative risk of high grade malignancy was increased [28,29]. The actual proportions of patients who developed high grade malignancy were small and there has been a heated debate on whether this statistically significant increase in relative risk can be translated into actual clinical significance. Nonetheless, there should be increased vigilance for prostate cancer when using 5ARi, since its association with high grade malignancy has not been excluded.

When a patient is taking 5ARi, his serum prostate specific antigen (PSA) level should be carefully interpreted. It is well known that 5ARi decreases serum PSA level, and it is common clinical practice to double the measured PSA level among patients on 5ARi for various clinical decisions. It should be noted that 5ARi do not always decrease serum PSA level by 50%, and the actual decrease can fluctuate very widely [30]. Thus observing the PSA trend among these patients over time may be more clinically relevant than simply doubling a single PSA level.

3.4. Clinical use and points for special mention

Some clinical points on the use of 5ARi that deserve special mention:

- 5ARi may be prescribed to BPH patients with a prostatic volume above 30 mL, who have not obtained satisfactory relief from α1 antagonist alone. It also helps to reduce BPH progression among these patients. However, when used as monotherapy, 5ARi has a relatively slow onset of action, so patients are unlikely to experience significant therapeutic benefits in the initial few months. This must be highlighted to the patients to ensure compliance, especially when 5ARi costs significantly more than α1 antagonists in most markets.
- The choice between finasteride and dutasteride should be based on the socioeconomic background of the patient and clinician's experience, since the clinical benefits of inhibiting type 2 isozyme only versus inhibiting both type 1 and 2 isozymes still remain controversial.
- Urologists should maintain vigilance about the small yet statistically significant risk of high grade prostate cancer associated with the use of 5ARi.
- As an off-label use, 5ARi may be prescribed for refractory hematuria secondary to BPH. Studies have found decreased prostatic expression of vascular endothelial growth factors and microvascular density among patients treated with finasteride for at least 2 weeks [31,32]. This change in prostatic vasculature occurs before any clinically significant decrease in prostatic volume is seen, and possibly by a separate mechanism from prostatic epithelial atrophy [33]. Prior to prescribing 5ARi for hematuria, thorough investigations should have been performed to exclude etiologies unrelated to BPH.

4. Combination therapy

Since α1 antagonist and 5ARi have different mechanisms of action, they have been used in combination to complement each other for faster, better and more sustained improvements in LUTS, urinary flow and prevention of BPH progression. Two commonly quoted studies, the MTOPS and the ComBAT, have provided evidence for the successful use of combination therapy among patients with moderate to severe LUTS or at high risk of disease progression. In the MTOPS study, the combination of doxazosin and finasteride led to a 64% risk reduction in IPSS progression, compared to 45% in doxazosin monotherapy or 30% in finasteride monotherapy [4]. Risks of urinary retention and BPH-related surgery were also reduced when combination therapy or finasteride monotherapy was used. In the ComBAT study, the combination of tamsulosin and dutasteride led to 40% risk reduction in IPSS progression and 70% risk reduction in urinary retention and surgery when compared to tamsulosin monotherapy, after a follow-up of four years [5]. It seems clear that combination therapy has both the advantages of α1 antagonist in providing early symptomatic relief and of 5ARi in prevention of BPH progression.

There are many practical questions on the use of combination therapy. One of them is whether to start a newly diagnosed BPH patient on combination therapy upfront or to start with α1 antagonist before adding a 5ARi when initial monotherapy fails. The CONDUCT study, which compared patients on lifestyle modification with possible escalation to tamsulosin against those prescribed combination therapy with tamsulosin and dutasteride upfront, showed that upfront combination therapy provided better improvements in LUTS and quality of life and reduced BPH progression at two years [34]. However, it is important to note that about 40% of patients who received lifestyle modification in the study did not require escalation to tamsulosin, and about 30% of men who were escalated to tamsulosin did not have LUTS deterioration, implying the possibility of overtreatment if combination therapy was to be indiscriminately used for all patients. And with overtreatment comes the issues about unnecessary adverse effects and excessive cost. Hopefully longer follow-ups in the CONDUCT study will be able to provide more convincing results for upfront combination therapy.

Another question is whether α1 antagonist may be stopped after an initial period of combination therapy. After all, many urologists have the perception that the role of α1 antagonist in combination therapy is to tide over the initial period when the maximal efficacy of 5ARi has yet to kick in, and subsequent withdrawal of α1 antagonist in combination therapy may mean less adverse effects and some cost savings. In the SMART-1 study, patients received 24 weeks of combination therapy followed by twelve weeks of dutasteride monotherapy [35]. It showed divergent outcomes based on LUTS severity. There are less than 20% of the patients with moderate LUTS, but nearly half of the patients with severe LUTS, who showed clinical deterioration. Choosing the suitable patients to stop α1 antagonist is made even more complicated, when LUTS severity and bothersomeness do not always correlate well with the degree of urinary obstruction. Therefore, stopping the α1 antagonist in combination therapy requires careful consideration, with monitoring to identify any clinical deterioration so necessary interventions can be initiated at the earliest moment.

While combination therapy combines the therapeutic benefits of α1 antagonist and 5ARi, it must be remembered that their adverse effects and costs are also combined [4,5]. So far, most studies on combination therapy included patients with at least moderate LUTS. Using combination therapy indiscriminately for all BPH patients may lead to significant overtreatment, and it is difficult to justify combination therapy among patients with mild LUTS. Even among patients with moderate LUTS, many of them remain happy with lifestyle changes or monotherapy [34].

5. Conclusion

Medical therapy for BPH has advanced significantly. When prescribing α1 antagonist, 5ARi or their combination, the decision making process should account for multiple factors, including efficacy, dosing regime, adverse effects, cost, patient's socioeconomic background, expectations, drug availability and clinician's experience. It is never a simple equation of a + b = c. Moreover, while many

available studies used LUTS severity as a guide to medical therapy, the practicing urologist should remember that symptom severity and bothersomeness do not always correlate with the degree of obstruction. The identification of patients with significant obstruction before zooming into a particular treatment option is the critical step in ensuring successful treatment.

Conflicts of interest

The authors declare no conflict of interest.

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