Management of benign prostate hyperplasia (BPH) by combinatorial approach using alpha-1-adrenergic antagonists and 5-alpha-reductase inhibitors

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ABSTRACT

Currently, the main available treatments for benign prostate hyperplasia (BPH) are alpha-1 adrenergic receptor antagonists (ARAs), 5-alpha reduce inhibitors (5-αRIs), anticholinergics, and Phosphodiesterase-5 inhibitors. Recent studies support the combined therapy approach using ARAs with 5-αRI for lower urinary tract symptoms (LUTS) in BPH patients at risk of clinical progression. We aimed to review BPH management in select group of randomized controlled trials by combination therapy with ARAs and 5-αRIs compared to monotherapy with either drug with respect to the safety and efficacy. A total of 6 randomized controlled trials (RCTs) involving comparison of combination therapy with monotherapy using ARAs and 5-αRIs were retrieved from PubMed Central and reviewed for international prostate symptom score (IPSS), quality of life (QoL), post-residual urinary flow rate (PUF), and clinical progression. The results significantly favour the treatment group that received the combination therapy in comparison with the groups receiving monotherapy. However, outcome with regard to prostate volume showed insignificant improvement when the combination therapy is compared with 5-αRIs alone, rather than ARAs. In conclusion, combination therapy using ARAs and 5-αRIs is better than monotherapy in the patients of BPH. Fixed dose combination (FDC), a type of combination, is also cost-effective and its side-effects profile resembles to that of monotherapy.

1. Introduction

Benign prostatic hyperplasia (BPH) is a common pathological condition of the aging men. It affects over 50% of men by the age of 50 and above and its prevalence increases further with the advancing age (Lim, 2017). It results from a non-cancerous enlargement of the prostate gland that is accompanied by multiple complications, including the lower urinary tract symptoms (LUTS), i.e., frequency, urgency, hesitancy, intermittency, and weak stream (Speakman and Cheng, 2014). The other risk factors, both modifiable and non-modifiable, that augment the risk of development as well as progression of BPH, besides others, include racial and genetic predisposition (Chughtai et al., 2016; Parsons, 2007). Genome-wise association study has revealed genetic correlation with serum levels of prostatic serum antigen (Gudmundsson et al., 2018). Aging incurs altered homeostasis due to physiological changes encompassing hormonal dysregulation to elevated oxidative stress that directly or indirectly impacts the prostate enlargement (Wen et al., 2015). Loeb et al. have reported a median increase of 0.6 ml in a prostatic volume that equals 2.5% growth in prostate size that included 278 patients (mean age = 58 years) (Loeb et al., 2009). On the same note, a recent study involving 40 patients (mean age = 64 years) with symptomatic BPH (PSA < 10 ng/ml PSA) has shown a significant but weak positive correlation between age and PSA and prostate volume (Deori et al., 2017) Besides aging, components of metabolic syndrome such as

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glucose intolerance, dyslipidaemia, hypertension, central obesity, and insulin resistance have been well-correlated with BPH relevant LUTS and IPSS (Lloyd et al., 2019; Sebastianelli and Gacci, 2018). Even though the average annual increase in total prostatic volume (TPV) is significantly higher in patients with metabolic syndrome elements, the relationship between metabolic syndrome and BPH might be only due to similarity in the sex hormones profile (Rastrelli et al., 2019).

2. Pathophysiology

The enlargement of the prostate is central to both BPH development and progression, which is characterized by hyperplastic process that sets in the peri-urethral region thus causing an increase in the cell size and number in the epithelial and stromal tissue (Lee and Kuo, 2017). These cellular-level changes culminate in increased prostatic intra-urethral pressure, as well as prostatic urethral resistance, thus developing into LUTS and symptomatic BPH. Although the underlying cause of hyperplasia remains less well-understood, the role of androgens and inflammation has been extensively studied in this regard (Bostanci et al., 2013; Wen et al., 2015). Dihydrotestosterone (DHT), a derivative of testosterone by the action of 5-α-reductase type-2, is the principal prostate androgen that accounts for 90% of the total prostatic androgens (Cannon and Rittmaster, 2003). It is pertinent to mention that unlike prostate growth during puberty, which is attributed to the increased levels of testosterone; prostate growth in the aged men is associated with low testosterone levels (Jarvis et al., 2015). These contrasting observations disprove 5α-reductase inhibitor (5α-RI) as the standard treatment option for BPH. While 5α-RI effectively shrink the prostate volume, it is attributed to a decrease in DHT levels which remain elevated even in the presence of low testosterone levels in BPH patients.

Besides the role of age and androgens, the presence of inflammatory cells, pro-inflammatory cytokines, and C-reactive protein support the development and progression of BPH (Fibbi et al., 2010). At the molecular level, AR activation and increased levels of reactive oxygen species (ROS) due to hypoxia developed from increased oxygen demand sets-in the inflammatory process (Vital et al., 2016). The inflammatory process may cause acute infection, which is then maintained beyond the acute phase into a chronic inflammatory phase (Kruslin et al., 2017). Mechanistically, the infiltrating Th1 cells secrete INF-γ and IL-2 during the early stages of BPH to stimulate the prostate stromal cells to produce IL-15 that leads to chronic inflammation which is dominated by Th2 and is characterized by elevated IL-4 and IL-13 levels thus characterizing the late stages of BPH. Also, IL-17 is found in BPH tissue which suggests a shift toward Th17 that speculates an autoimmune basis (Lloyd et al., 2019). Interestingly, a novel biomarker JM-27 also increases in clinically symptomatic BPH (Bechis et al., 2014). A serum-based enzyme-linked immunosorbent assay (ELISA) has been developed to measure serum levels of JM-27 to delineate symptomatic and asymptomatic BPH patients (Bechis et al., 2014).

According to the recently published molecular profiling, two biologically distinct BPH subtypes have been identified, which were referred to as BPH-A subgroup and BPH-B subgroup (Liu et al., 2020). While BPH-A subtype is characterised by stromal-tissue-like features, BPH-B subtype has specific dysregulations involving metabolic pathways in the patients with obesity (BMI >30) and hypertension. Abnormal metabolism is also reported in BPH-A subgroup when compared to age-matched control samples (Liu et al., 2020; Tomlins et al., 2007). BPH-A subtype has been correlated with mTOR inhibition in 50% of the nominated sample of BPH-A subgroup and has been investigated as a potential therapeutic option for BPH patients (Fingar et al., 2002; Tumaneng et al., 2012).

Contrary to the hypothesis that AR (androgen receptor) activation leads to vicious cycle of hypoxia and chronic inflammation, signalling disruption and subsequent downregulation of AR transduction cascade have been reported but the results get confounded by the exposure to medications affecting AR (Fenner, 2016; Zhang et al., 2016). Transcriptional analysis further identified KRAS gene signalling inactivation, bone morphogenetic protein 5 (BMP5) upregulation, and DNA hypermethylation, all disproving BPH as a neoplastic disease (Keszei et al., 2014; Köhler et al., 2012). KRAS gene signals the cells to mature, proliferate and differentiate and has been linked to multiple neoplastic processes (Keszei et al., 2014; Köhler et al., 2012). In addition, epigenetic analysis revealed that DNA hypomethylation was globally found in neoplastic diseases, whereas BPH epigenetic landscape has been dominated by DNA hypermethylation (Ehrlich, 2002; Jiang et al., 2008).

3. Diagnosis and diagnosis evaluation

The diagnosis of symptomatic BPH is generally based on the physical examination which reveals a diffusely enlarged, firm, and non-tender prostate supported by the storage and voiding symptoms (McConnell et al., 1994). Differential diagnosis of BPH includes urethral strictures, bladder neck contracture, prostate cancer, urinary tract infection, and neurogenic bladder. The criterion for clinical evaluation of BPH has been developed by the Agency for Health Care Policy and Research and updated by the American Urologic Association (AUA) in 2010 and 2019 (Deters et al., 2019; McVary et al., 2010; Nickel et al., 2010). AUA International Prostate Symptom Score (AUA/IPSS) assesses the severity of symptoms and requires the patient to respond to seven questions, i.e., frequency, nocturia, weak urinary stream, hesitancy, intermittency, incomplete emptying, and urgency. The score ranges from 0 to 5 (NOT present to almost ALWAYS present). This score aids in patients’ symptoms classification from mild (total score 0–7) to moderate (8–19), and severe (20–35) (Barry et al., 1992). Besides urologic conditions and symptoms, the history of patient about general health (i.e. diabetes mellitus is a BPH risk factor), family history about BPH or prostate cancer, and pharmacological history are important (Pearson and Williams, 2014).

A digital rectal examination assesses prostate size and consistency although the information about prostate size is unreliable until it should be large enough, i.e., >50 g to be recognized. A tender prostate is generally indicative of prostatitis while nodules are alarming for malignant transformation. Laboratory findings supportive in BPH diagnosis includes urine analysis, serum creatinine, and the detection of Prostate-specific antigen (PSA) in the patient’s serum samples. While urine analysis also is important for differential diagnosis of urinary tract infection (Nickel et al., 2010) and serum creatinine is part of the routine assessment for BPH, PSA levels in the serum screens the patients for prostate cancer especially in patients between the ages of 50–69 years. Some of the additional tests include urine cytology, post-void residual urine volume, and urethral cystoscopy.

4. Management of BPH patients

The management of BPH patients includes recommendations for lifestyle changes, pharmacological intervention and in the advanced cases with complications, it may necessitate surgical intervention. Lifestyle changes and watchful waiting without any pharmacological intervention is recommended for patients who have mild symptoms (IPSS ≤ 7), in addition to annual visits and evaluation of the patient history to see if there are any indications to start medication (Sarma and Wei, 2012). Similarly, advanced BPH necessitates surgical intervention that primarily involves transurethral resection of the prostate (TURP) or minimally invasive laparoscopic/robotic simple prostatectomy, and Holmium Laser Enucleation of the Prostate (HoLEP) (Williams et al., 2013). Please also see recent advances and guidelines by AUA, 2019 (Foster et al., 2018).

Advances in pharmacological management overtime have considerably reduced the rate of surgical intervention for BPH (Prescice et al., 2017). The contemporary approach of monotherapy (IMM) is generally employed to address lower urinary tract symptoms with drugs belonging to various pharmacological groups including ARAs, 5-alpha reductase
inhibitors (5α-RIs), anticholinergic agents, and phosphodiesterase-5 inhibitors (PDE5i). Treatment with ARAs generally suffices for patients with mild (IPSS ≤ 7) to moderate (IPSS 8–19) BPH.

4.1. Alpha-1 blockers (Alpha-1 adrenergic receptor antagonists)

Drugs from this group are the most commonly prescribed for BPH patient to relieve their lower urinary tract-related symptoms. Treatment with ARAs relaxes the smooth muscle tone in the bladder neck to decrease the flow along the bladder neck and prostate, thus facilitating the flow of urine. Treatment with ARAs decreases 4–6 points in the IPSS (Emberton et al., 2008). Drugs in this group may be non-selective ARAs (i.e., phenoxymenzamide), selective short-acting ARAs (i.e., prazosin, alfuzosin, and indoramin), selective long-acting ARAs (i.e., terazosin, doxazosin, and slow-release (SR) alfuzosin), and partially subtype (ARA-1a)–selective agents (i.e., tamsulosin, and silodosin) (Emberton et al., 2008; McVary et al., 2010). As the non-selective group shows an adverse side-effect profile i.e., drowsiness, depression, dizziness, dry mouth, ejaculatory failure, extrapyramidal signs, nasal congestion, and weight gain, it is out of clinical practice per current guidelines (McVary et al., 2010). On the contrary, the selective group specifically interacts with either of the receptor subtypes a, b, and c using respective ARAs.

Originally designed as anti-hypertensive agent, naftopidil has been used for the management of BPH symptom (Hara et al., 2013). Subsequent to the earlier reported success in the clinical studies (Yasuda et al., 1994; Yokoyama et al., 2006), Masumori et al., reported a three-year follow-up in a prospective study in 117 BPH patients who were treated with naftopidil (50 mg or 75 mg per day) (Masumori et al., 2015). The patients were aged 50 years and above were having IPSS score of 8 or more. A total of 25% patients successfully continued the medication 5α-RIs for three years. The results of the study showed long-term efficacy of the treatment; however, the beneficial effects were limited by older age, increased prostate volume and higher-level PSA at the start of the treatment. The same group has earlier published a 5-year follow-up data from a prospective study to show that monotherapy with ARA tamsulosin might not be appropriate for patients with a large prostate and high post-void residual urine volume. Nevertheless, symptomatic improvement continued despite stopping tamsulosin therapy in young patients (Masumori et al., 2013).

4.2. 5α-reductase inhibitor (5α-RI)

Two of the prototype drugs of this group, i.e., finasteride and dutasteride are particularly efficient in patients with enlarged prostate besides LUTS (McVary et al., 2010). The mechanism of action of 5α-RI is through approximately 80% reduction of testosterone conversion to DHT. This leads to a reduction in DHT concentration, which otherwise accumulates in prostate cells and is considered as responsible for prostate enlargement (Kim et al., 2005). The typical side-effects of 5α-RI include decreased libido, erectile dysfunction (ED), and ejaculation disorder as reported by long-term trial of finasteride versus placebo in 30–40 men with BPH (Wessells et al., 2003). Moreover, breast enlargement (gynecomastia), breast tenderness, general rash, and anxiety have also been reported (McConnell et al., 1998). With use of 5α-RI especially for periods longer than 4 years, the incidence of sexual adverse effects generally decreases with longer duration of therapy (Corona et al., 2017; Debruyne et al., 2004). Comorbidity status which is frequently correlated with elderly population, may adversely increase the risk of developing erectile dysfunction (ED) with 5α-RI inhibitor therapy (Fusco et al., 2015), although the exact underlying molecular mechanism remains less well-elucidated. However, it is generally attributed to decreased synthesis of neurotransmitters by 5αRI leading to reduced sexual desire and possible penile fibrosis due to cholinergic and nitrergic supra-sensitivity thus resulting in anatomical and physiological degeneration of penile tissue (Gur et al., 2013).

Additionally, 5α-RI has teratogenic potential (Traish et al., 2014). Treatment with 5α-RI for six months also causes up to 50% reduction in PSA with an associated shrinkage of prostate mass (Bell et al., 2009). Data from 2 RCTs showed that treatment with 5α-RI significantly reduced the incidence of prostatic cancer but may enhance the risk of high-grade prostatic cancer (McConnell et al., 1998). Although 5α-RI can reduce the volume of prostate in most patients, about one fourth (25%) of patients do not show any improvement and can experience worsening of their symptoms (Bechis et al., 2014). ARAs appear to be more effective than 5α-RIs for short- and long-term management of BPH. In a meta-analysis comparing ARAs monotherapy with 5α-RIs, doxazosin and terazosin were better in the management of urinary symptoms as compared to finasteride (Tacklind et al., 2010).

Table 1

The table summarizes in a chronological order the studies reviewed for combination therapy of BPH in terms of the aim, methodology, and results of each trial briefly.

| Objective | Methods | Results |
|-----------|---------|---------|
| Debruyne et al. (1998) | Study of the effects of combined treatment with alfuzosin & finasteride. | The study was double-blind, randomized, and multicenter trial involving 1051 BPH patients with LUTS. Reduction in IPSS was highest in alfuzosin group, followed by combination & finasteride groups. At end point of study, results were comparable in all groups. |
| McConnell et al. (2003) | Study the long-term effects of doxazosin, finasteride & combination therapy. | Double-blind, long-term trial with a mean follow-up of 4.5 years; 3047 patients. Primary outcome assessed by Intention to Treat analysis. Significant reduction in AUR, UI, UTI of doxazosin (39% RR) & finasteride (34% RR) vs placebo. Reduction with combined therapy (66% vs placebo) was more than monotherapy. Combination therapy has significantly greater improvements in symptoms when compared to dutasteride from month 3, and tamsulosin from month 9. |
| Roehrborn et al. (2008) | Comparing dutasteride, tamsulosin, & their combined therapy. | Multicenter, randomized, double-blind, parallel group study in BPH patients >50 years. LUTS & PUF assessed every 3 & 6 months respectively for 2 years. Combination therapy has significantly more improvement in symptoms compared to monotherapy. |
| Montorsi et al. (2011) | Comparing dutasteride & tamsulosin monotherapy vs combination therapy. | Multicenter, Double-blind, parallel-group study; 4644 patients aged >50 years; prostate volume >30 ml, 4 years duration. Combination therapy has significantly more improvement in symptoms than monotherapy. |
| Roehrborn et al. (2015) | Efficacy and safety of FDC of dutasteride & tamsulosin monotherapy. | Multicenter, randomized, open-label trial; 742 men with an IPSS of 8–19, Prostate volume >30 ml, and total serum PSA >1.5 ml. Significant reduction for FDC vs control group (~ 5.4 vs ~3.6 points, P < 0.001). FDC had a 43.1% (P < 0.001) reduction in risk of progression. Similar safety profile as monotherapy with each drug. |
| Shrestha and Karmacharya (2015) | Analyzing the usefulness of combination therapy of finasteride & tamsulosin. | 92 patients randomized into two groups (combined therapy tamsulosin + finasteride group and monotherapy with only Tamsulosin). Rx significantly reduced with combined therapy more than monotherapy. The sample of this study is smaller than other studies and have also proved its effectiveness. |

List of Abbreviations: AUA = American urological association; AUR = acute urinary retention; UI = urinary incontinence; UTI = urinary tract infection; BPH = benign prostate hyperplasia; FDC = fixed dose combination; IPSS = international prostate symptom score; PSA = prostate specific antigen; PUF = peak urinary flow; RR = Risk reduction; RV = residual volume.
4.3. Anti-cholinergic agents

Anticholinergics, i.e., flavoxate, propiverine, and oxybutynin, etc. serve as an alternative therapy for patients presenting largely with symptoms such as frequency, urgency, and incontinence related with the overactivity of detrusor muscle however without elevated post-void residual volume. Overactivity of detrusor is reported in virtually 40%–70% of patients with bladder outlet obstruction. Given the propensity of muscarinic receptor in the bladder smooth muscle, anticholinergics are an obvious choice for intervention in such patients. Although the use of anticholinergics is considered safe, their use in patients with BPH having LUTS is not without their side-effects (Blake-James et al., 2007). However, side-effects such as dry mouth, blurry vision, constipation, drowsiness, sedation, and possibility of acute retention of urine have allowed only limited use in BPH patients (Athanassopoulos et al., 2008). Combined therapy using anticholinergics with ARAs to treat LUTS symptoms in BPH patients has shown encouraging results in terms of safety and efficacy (Kim et al., 2017; Pung et al., 2016).

4.4. Phosphodiesterase-5 (PDE-5) inhibitors

Phosphodiesterase (PDE) is a superfamily of enzymes with extensive distribution in various body tissues including the prostate and bladder (Lin et al., 2013). The selectivity of PDE5 for cGMP makes it an attractive intracellular target to promote cGMP second messenger activity for various therapeutic benefits including cell survival, proliferation and cellular protection (Haider et al., 2010; Li et al., 2012). Inhibition of PDE-5 using PDE5 inhibitors allows vasodilation and relaxation of the smooth muscle that has been exploited for the treatment of BPH patients (Giuliano et al., 2013). The only approved PDE-5 inhibitor for the management of BPH is tadalafil (Gacci et al., 2013). However, its use is not without side-effects that include back pain, dyspepsia, headache, limb pain, myalgia, nausea, and flushing. Of note, tadalafil can be used either alone or combined with the 5α-RIs, i.e., finasteride, in patients with BPH/LUTS and erectile dysfunction (Olesovsky and Kapoor, 2016).

5. A combinatorial approach to treat BPH

A combined therapy approach using drugs from each group exploits the best of their unique mechanism of action. It allows interference with the disease process by simultaneous exploitation of a two-pronged strategy. The safety and effectiveness of the combinatorial approach have been extensively studied in randomized control trials some of which have been enlisted in Table 1. We have analyzed the data from 6 RCTs which was retrieved from the Advanced PubMed Search engine, using the terms: ((prostatic hyperplasia) AND (therapy) AND (combination)) and applying the filter (Clinical Trials) in the sidebar. However, we did not include all the published trials as it was beyond the scope of our mini-review. Our analysis plan for each RCT was to read the text thoroughly, describe the population, type of intervention and control groups, randomization process, the settings of the trial, and then cautiously analysing the results and report the conclusions.

According to the latest guidelines of the AUA, a combinatorial treatment approach based on ARAs and 5α-Ri would be more effective for the treatment of patients with LUTS and enlarged prostate than their individual use (Foster et al., 2018). Hence, the FDA approved formulation of Jalyn containing 0.4 g tamsulosin, and 0.5 dutasteride is more effective in providing symptomatic relief to the BPH patients than either of the two drugs used alone (Dimitropoulos and Gravas, 2016) and successfully improve IPSS (Madersbacher et al., 2007). While mono-therapy with ARAs alleviates BPH-associated LUTS symptoms by maximizing urinary flow rate, 5α-Ri treatment shrinks prostate size (McVary, 2007).

European ALFIN study group (1998) assessed the additive benefits of combining alfuzosin and finasteride in 1051 patients with LUTS due to BPH (Debruyne et al., 1998). The patients were randomized into three treatment groups including alfuzosin (n = 358), finasteride (n = 344), and combined treatment (n = 349) groups. The primary end-points of the study were improvement in IPSS and Maximum Flow Rate (Qmax), while the safety of the combined treatment was monitored by the reported adverse events. The treatment was continued for 6 months. The results in the three treatment groups showed symptomatic improvement insignificantly differing between the alfuzosin group and the combination treatment group in the first month. On the contrary, the finasteride treatment group significantly trailed behind the two groups with only 33% of patients showing a 50% improvement. Similarly, in the overall population, increases in Qmax were significantly larger with alfuzosin treatment and the combined treatment groups as compared to finasteride alone after 1 month of therapy. It was evident from the data that combination treatment using alfuzosin and finasteride did not offer a significantly higher benefit to the patients as compared to alfuzosin alone.

A subsequent study by McConnell et al. (2003) conducted a multi-centered double blind clinical trial Medical Therapy of Prostatic Symptoms (MTOPS) (McConnell et al., 2003). The study was designed to ascertain the beneficial effects combined treatment of BPH patients with doxazosin and finasteride in 3047 patients out of the total 4391 patients who were initially screened for the study. The average follow-up time duration for the patients was 4.5 years. The patients were randomized to receive their respective treatment using placebo-treated patients as a control. The drug treatment groups included doxazosin, finasteride, and combination therapy groups (n = 756 patients per group). The primary outcomes of the study were clinical progression of the disease which was defined as an increase of four points above the baseline of AUA symptom score, AUR, UI, and recurrent UTI) was assessed using ITT analysis. The assessment of the patients and their data were kept blinded. The data showed a significant risk reduction in the measures of the primary outcome in doxazosin (39%, P < 0.001), finasteride (34%, P = 0.002), and combination therapy (66%, P < 0.001) in comparison with the placebo treatment group (McConnell et al., 2003). The data thus generated evidenced the long-term safety and effectiveness of the combinatorial pharmacological intervention as a superior option as compared to monotherapy.

Roehrborn et al. (2008) compared dutasteride, tamsulosin, and their combination for the treatment of LUTS in men with BPH and prostate enlargement (Roehrborn et al., 2008). Sponsored by GlaxoSmithKline, the CombAT study (ClinicalTrials.gov Identifier: NCT00090103) was a multi-centered, double-blind, randomized, parallel group study performed in 503 centers. A total of 4844 men aged 50 and older were enrolled in the study. According to the Inclusion criteria set up for the study, participants had an IPSS of 12 or greater, a prostatic volume of 30 ml or greater, serum PSA 1.5–10 ng/ml, and PUF 5 ml–15 ml per second. The participants were randomized to receive dutasteride, tamsulosin or combination therapy and were followed-up for 4 years (Roehrborn et al., 2010). The primary outcome data published at 2 years of daily treatment showed a significant change in IPSS from baseline. The combination therapy resulted in significant improvement in the symptoms when compared to dutasteride from month 3, and tamsulosin from month 9. The change from baseline post-rectal urinary flow-rate showed significant improvement in the combination group as compared to both monotherapy groups after 6-months of treatment. However, the rate of adverse drug reactions was significantly increased in the combined treatment group as compared to the monotherapy treated patients. The results from the 4-year follow-up revealed the safety and effectiveness of the combinatorial approach although the study lacked a placebo-treated group of patients (Roehrborn et al., 2010). Montorsi et al. (2011) analyzed the mean changes of the storage and voiding symptoms at 4 years as compared to their baseline values in the sub-scales of IPSS patients (Montorsi et al., 2011). The results showed a mean reduction both in the storage and voiding symptoms in the combination treatment group as compared to the monotherapy groups of patients (P < 0.001). Nevertheless, patients with a baseline prostate volume of more than 58
ml failed to benefit from the combined therapy as compared with monotherapy with dutasteride. These observations show the limitations of the combined therapy approach in patients for baseline prostate size (Montorsi et al., 2011).

Subsequently, the same group assessed the safety and efficacy of a fixed-dose combined (FDC) administration of dutasteride and tamsulosin treatment (Duodart®) for the management of men with moderately symptomatic BPH at risk of progression. The study was a multi-centered, randomized open-label trial conducted in 742 men with an IPSS of 8–19, the prostate volume of more than 30 ml, and total serum PSA of more than 1.5 ml (Roehrborn et al., 2015). The primary outcome was a symptomatic improvement from baseline to 24 months that was measured by IPSS. Therapeutic benefits in the FDC administration group were significantly more as compared to the control group taking tamsulosin alone. For example, the FDC administration group showed 43.1% (P < 0.001) risk reduction in the progression as compared to the control group. The safety profile of FDC administration was consistent with the profiles of dutasteride and tamsulosin as monotherapy (Roehrborn et al., 2015). These data support that the FDC administration of dutasteride and tamsulosin along with lifestyle changes leads to continued and therapeutically stable improvement in men with moderate BPH at risk of progression and significantly reduced risk of BPH progression.

Shrestha et al. (2015) used a combination of tamsulosin with finasteride to treat benign prostate enlargement (Shrestha and Karmacharya, 2015). The primary aim of the study was to ascertain the usefulness of combined therapy with finasteride and tamsulosin in comparison with monotherapy with each of the two drugs. The study included men aged 45 and above (n = 92) and diagnosed with BPH. The patients were grouped equally to receive combination therapy or monotherapy with tamsulosin once daily at bedtime. AUA symptom score decreased significantly in the combination therapy group of patients (P < 0.0001) as compared to tamsulosin treated group with a concomitant reduction in residual volume with combination therapy as compared to the monotherapy treatment (P < 0.0001 vs. P = 0.1271). These data validated the findings of the prior studies to conclude that combination therapy is more effective in decreasing LUTS as compared to the monotherapy treatment strategy.

6. Discussion and conclusion

Unlike to the earlier trials had found that combined treatment of ARAs and 5-αRIs therapy was not superior to monotherapy with an ARAs (Debruyne et al., 1998), subsequent randomized trials have demonstrated the benefits of long-term use of combination therapy (Montorsi et al., 2011; Roehrborn et al., 2008). Nearly 84% of the articles we reviewed favoured dual therapy over monotherapy while the remaining 16% showed that monotherapy with some drugs like alfuzosin has comparable results with combination therapy. As inclusion criteria require a prostatic volume of equal to or more than 30 ml in the participants, the results show that efficacy of such comparison may be only specific to a certain population of BPH patients. Besides being pharmacologically more effective, combination therapy is more cost effective as compared to the monotherapy. Walker et al. (2013) have reported the long-term cost-effectiveness of single-dose of dutasteride and tamsulosin combination therapy as a first-line treatment for BPH from the perspective of the UK National Health Service and concluded that combination therapy has a higher probability of being cost-effective as compared to either monotherapy and compared with the two therapies taken separately (Walker et al., 2013).

Secondary outcomes on side-effect profile of dual therapy showed that patients mostly suffered from sexual dysfunction (e.g. decreased ejaculation, erectile dysfunction, etc.), which was comparable to that of monotherapy, suggesting no significant difference. In conclusion, combined treatment with ARAs and 5-αRIs has been the most widely investigated combination for BPH which shows that the approach is safe, more efficacious and cost-effective as compared to the monotherapy. The data support the inference that it causes significant reduction in IPSS (Figure-1), improvement in Qol, and other subjective and objective measures of BPH suggesting a synergistic effect of the drug combination, especially in patients who have a moderate enlargement of the prostate (prostate volume <30 ml). With excellent long-term outcomes, combination therapy can be started as soon as patients are found to have prostate enlargement causing moderate to severe symptoms.

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