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ORIGINAL RESEARCH

Comparison of Characteristics of Benign Prostatic Hyperplasia (BPH) Patients Treated with Finasteride and Alpha Blocker Combination Therapy Versus Alpha Blocker Monotherapy in China: An Analysis of Electronic Medical Record Data

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ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is commonly treated with 5-alpha-reductase inhibitor/alpha blocker combination therapy or with alpha blocker monotherapy. However, in China, the characteristics of BPH patients receiving 5-alpha-reductase inhibitor/alpha blocker combination therapy or alpha blocker monotherapy remain largely unknown. Therefore, this study compared the characteristics of BPH patients receiving either the 5-alpha-reductase inhibitor finasteride in combination with an alpha blocker or an alpha blocker as monotherapy in clinical practice in China.

Methods: Data were obtained from a large electronic medical record database from four tertiary hospitals in major cities in China (2009–2016). BPH patients aged ≥ 50 years with ≥ 1 alpha blocker fill on/after the first BPH diagnosis were selected. Patients were further classified as receiving combination therapy (≥ 1 overlapping day of supply for finasteride and an alpha blocker) or alpha blocker monotherapy (did not receive any 5-alpha-reductase inhibitor). Patient characteristics, visit type (in- vs. outpatient) at treatment initiation, and comorbidities were evaluated during the 6-month baseline period and compared between the two groups using two sample *t* tests and chi-square tests/Fisher's exact tests.

Results: A total of 2666 and 2738 patients received combination therapy and monotherapy, respectively. The combination group was older (70.3 vs. 67.3 years, $p < 0.0001$) and had more patients initiated in an inpatient setting (46.0% vs. 26.4%, $p < 0.0001$). Compared with the monotherapy group, the combination group had more comorbidities, such as hypertension (48.3% vs. 35.6%, $p < 0.0001$), cardiovascular disease (65.3% vs. 48.0%, $p < 0.0001$), and diabetes (21.1% vs. 15.7%, $p < 0.0001$), and a higher Charlson comorbidity index (0.9 vs. 0.7, $p < 0.0001$).

Conclusion: Chinese BPH patients using finasteride/alpha blocker combination therapy were older and had a higher comorbidity burden than those using alpha blocker monotherapy. These findings provide Chinese healthcare decision-makers with a better understanding of

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the patient characteristics generally associated with BPH combination therapy vs. alpha blocker monotherapy.

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Keywords: 5-Alpha-reductase inhibitors; Alpha blockers; Benign prostatic hyperplasia; China; Combination therapy; Patient characteristics; Urology

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a non-cancerous enlargement or growth of the prostate gland [1]. As its size increases, the prostate obstructs the bladder outlet and urethra, leading to a number of lower urinary tract symptoms (LUTS) such as urinary urgency or retention, weak urinary stream, nocturnal polyuria, and infections [1–3]. The prevalence of BPH has been shown to progressively increase with age, making BPH one of the most common urologic diseases in older men worldwide [1, 2, 4]. In China, a meta-analysis comprising epidemiologic data from 1989 to 2014 estimated the average prevalence of BPH to be 36.6% in men aged 40 years and older [5]. In the same study, the prevalence of BPH in Chinese urban and rural areas was found to be 41.5% and 38.6%, respectively [5].

The management of BPH is mainly based on the severity of LUTS [6]. Treatments include pharmacotherapy and, in the most severe cases, surgery [6, 7]. The most commonly used pharmacologic options are alpha blockers, which improve urinary flow by promoting prostate smooth-muscle relaxation, and 5-alpha-reductase inhibitors, which limit the growth or reduce the size of the prostate by downregulating the conversion of testosterone to dihydrotestosterone [6, 7]. Typically, alpha blockers take effect quickly, generally within days or weeks, and are most effective in men with a smaller prostate [7]. On the other hand, 5-alpha-reductase inhibitors are most effective in men with a larger prostate and a higher baseline prostate-specific antigen (PSA) value, as they have been shown to act faster and have longer term effects in this patient population; however, they may take up to 6 months to have symptomatic effects [8, 9]. The current Chinese Guidelines on the Diagnosis and Treatment of Urological Diseases recommend the use of alpha blockers as monotherapy or in combination with a 5-alpha-reductase inhibitor [10]. Because of their different, but potentially complementary, mechanisms of action, the combination of alpha blockers and 5-alpha-reductase inhibitors in treating BPH patients has been investigated in several studies. In the Medical Therapy of Prostatic Symptoms (MTOPS) study conducted in the US, the combination of the two drugs was shown to be more effective than either drug alone in reducing the risk of clinical progression of BPH [9]. Combination therapy also resulted in a greater improvement in the American Urological Association (AUA) symptom score and urinary flow rate compared with either drug alone [9].

Despite mounting evidence of its effectiveness compared with alpha blocker monotherapy, the combination of alpha blockers and 5-alpha-reductase inhibitors has been underutilized in China even though included in Chinese treatment guideline recommendations. Indeed, in one study, only 52.6% of Chinese patients with moderate-to-severe BPH and high risk of progression, for whom 5-alpha-reductase inhibitor/alpha blocker combination therapy should be used based on Chinese treatment guidelines, actually received this combination therapy [11]. Importantly, the characteristics of patients with BPH receiving combination therapy vs. monotherapy in clinical practice in China have not been described in the literature. A better understanding of these characteristics would help guide and optimize real-world treatment decisions and, potentially, improve clinical outcomes among Chinese patients with BPH. Therefore, this study aimed to examine and compare the characteristics of BPH patients receiving the 5-alpha-reductase inhibitor finasteride in combination with an alpha blocker with those of BPH patients receiving an alpha blocker alone in four major hospitals in China.

METHODS

Data Source

Data were obtained from a multicenter database containing de-identified electronic medical records (EMR) from four major hospitals located in Southern and Northern China in the cities of Guangzhou, Tianjin, Beijing, and Hebei. The database contains in- and outpatient records (2009–2016) and includes diagnosis, medications, procedures, laboratory values, imaging tests, and pharmacy and medical costs.

Statement of Ethics Compliance

This article does not contain any new studies with human or animal subjects performed by any of the authors.

Patient Selection

To be eligible for inclusion, patients were required to have at least one inpatient stay associated with a diagnosis of BPH in any position or at least two outpatient visits associated with a diagnosis of BPH that were at least 30 days apart, and have at least one alpha blocker prescribed on or after a diagnosis of BPH. A diagnosis of BPH was identified based on both Chinese diagnostic description and ICD-9/10 codes.

The patients meeting the above selection criteria were classified into two treatment groups: (1) *combination therapy*, comprising patients with at least one overlapping day of supply of an alpha blocker and the 5-alpha-reductase inhibitor finasteride; for this treatment group, the date of the first finasteride prescription fill, as part of the combination therapy, was defined as the *index date*; (2) *alpha-blocker monotherapy group*, comprising patients who received an alpha-blocker but did not receive any 5α-reductase inhibitor (including finasteride) during the entire available data history; for this treatment group, the index date was a randomly selected date among all the alpha blocker prescription fill dates.

For both treatment groups, patients were required to be at least 50 years of age as of the index date. The 6-month period before the index date was defined as the *baseline period*. Treatments were identified in the database using both their generic and brand names. To increase the confidence that patients used only one hospital for medical services, patients in both treatment groups were further required to have at least one in- or outpatient visit in the same hospital any time before the index date. Patients with a prior treatment of finasteride monotherapy were excluded from both treatment groups.

Outcomes

Patient demographics were measured at the index date and included age and geographic location (i.e., Guangzhou, Tianjin, Hebei, or Beijing). The type (i.e., in- vs. outpatient) of hospital visit at the time of the index date was also reported (*index visit type*). The comorbidities measured during the baseline period included the Charlson Comorbidity Index (CCI) [12] and individual comorbidities [13], including hypertension, cardiovascular disease, chronic prostatitis, diabetes, metabolic syndrome, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, hemiplegia or paraplegia, renal disease, any malignancy including lymphoma and leukemia except malignant neoplasm of skin, moderate or severe liver disease, metastatic solid tumor, AIDS/HIV, diabetes with chronic complication, and diabetes without chronic complication.

All comorbidities were identified based on the ICD-9/10 codes for inpatient records and Chinese description for outpatient records.

Statistical Methods

Patient demographics, index visit type, individual comorbidities, and CCI were described and compared between the two treatment groups. Means and standard deviations (SD)

were reported for continuous variables; frequency counts and percentages were reported for categorical variables. Wilcoxon rank sum test was used to compare continuous variables. Categorical variables were compared using Fisher's exact test for expected frequencies of less than five, while a Chi-square test was used in all other instances.

All the statistical analyses for this study were conducted using SAS software 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 2666 eligible patients receiving an alpha blocker and finasteride (combination therapy group) and 2738 patients receiving an alpha blocker alone (monotherapy group) were identified (Fig. 1).

The combination therapy group was significantly older (70.3 ± 9.8 vs. 67.3 ± 10.4 years, $p < 0.0001$) and had a significantly different geographic distribution (89.1% vs. 57.6% for Tianjin, 10.4% vs. 26.2% for Guangzhou, 0.0% vs. 2.4% for Beijing, and 0.4% vs. 13.8% for Hebei; $p < 0.0001$) compared with the monotherapy group (Table 1).

The combination therapy group comprised a significantly higher percentage of patients who initiated treatment in an inpatient setting compared with the monotherapy group (46.0% vs. 26.4%, $p < 0.0001$). Moreover, the combination therapy group had a significantly higher CCI (0.9 ± 1.5 vs. 0.7 ± 1.4, $p < 0.0001$) and more comorbidities, including hypertension (48.3% vs. 35.6%, $p < 0.0001$), cardiovascular disease (65.3% vs. 48.0%, $p < 0.0001$), diabetes (21.1% vs. 15.7%, $p < 0.0001$), cerebrovascular disease (28.1% vs. 23.6%, $p = 0.0002$), chronic

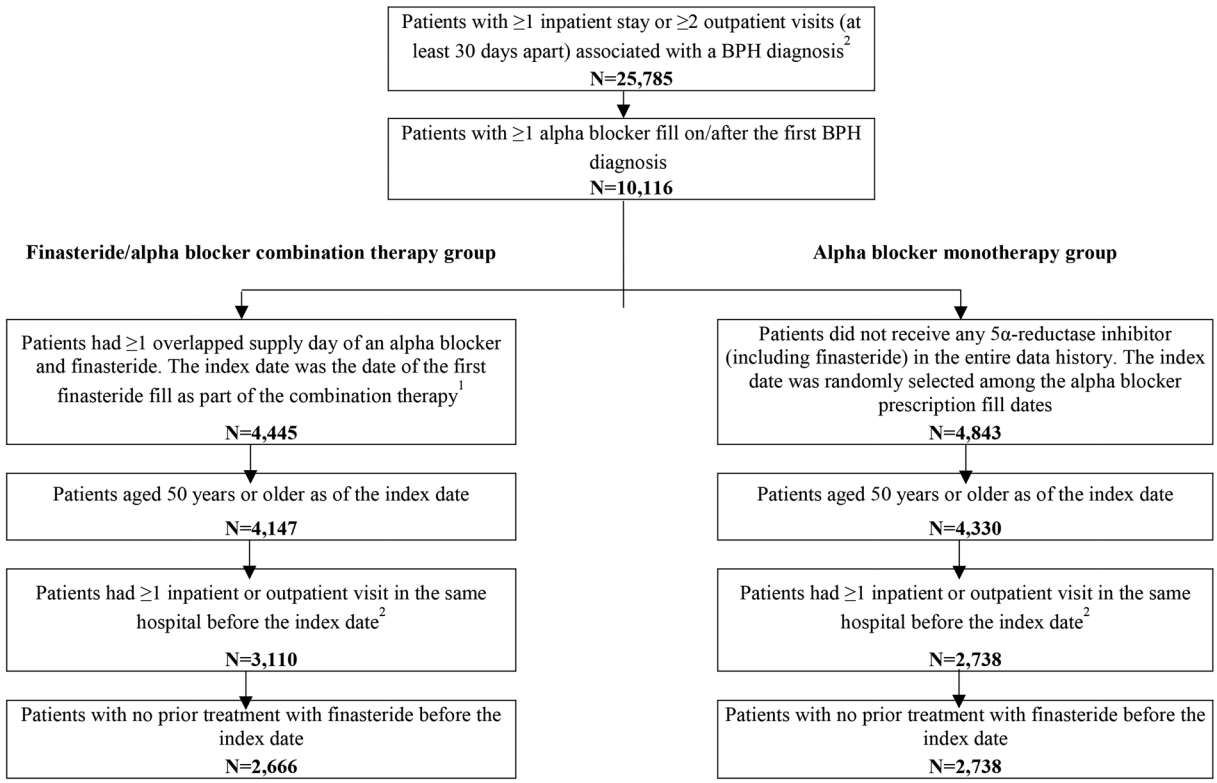

Fig. 1 Sample selection flow chart. *BPH* Benign prostatic hyperplasia. [1]Days of supply for inpatient treatments were derived based on the treatment start and stop dates. Days of supply for outpatient treatments were derived based on the dose and amount of treatments prescribed. Days of supply was assumed to be 1 if it was not indicated in the database. [2]The hospital visits before the index date were not restricted to occur during the year 2009 or later as information on hospital visits (excluding clinical, pharmacy, and costs information) was available before 2009

Table 1 Patient characteristics

Baseline characteristics	Combination therapy (*N* = 2666)	Monotherapy (*N* = 2738)	*p* value
Demographics			
Age at index, mean (SD)	70.3 (9.8)	67.3 (10.4)	< 0.0001*
Location of hospital visits, n (%)			< 0.0001*
Tianjin	2376 (89.1%)	1578 (57.6%)	
Guangzhou	278 (10.4%)	717 (26.2%)	
Beijing	1 (0.0%)	66 (2.4%)	
Hebei	11 (0.4%)	377 (13.8%)	
Index visit type			< 0.0001*
Inpatient	1227 (46.0%)	723 (26.4%)	
Outpatient	1439 (54.0%)	2015 (73.6%)	
Comorbidities[a], *n* (%)			
Cardiovascular diseases	1742 (65.3%)	1314 (48.0%)	< 0.0001*
Hypertension	1289 (48.3%)	975 (35.6%)	< 0.0001*
Cardiovascular diseases excluding hypertension	1335 (50.1%)	969 (35.4%)	< 0.0001*
Chronic prostatitis	7 (0.3%)	15 (0.5%)	0.0996
Diabetes	562 (21.1%)	430 (15.7%)	< 0.0001*
Metabolic syndrome	0 (0.0%)	0 (0.0%)	NA
Charlson comorbidity index (CCI), mean (SD)	0.9 (1.5)	0.7 (1.4)	< 0.0001*
AIDS/HIV	0 (0.0%)	0 (0.0%)	NA
Any malignancy excluding metastatic solid tumors, including leukemia and lymphoma	89 (3.3%)	79 (2.9%)	0.3374
Cerebrovascular disease	750 (28.1%)	647 (23.6%)	0.0002*
Chronic pulmonary disease	338 (12.7%)	215 (7.9%)	< 0.0001*
Congestive heart failure	190 (7.1%)	131 (4.8%)	0.0003*
Dementia	30 (1.1%)	25 (0.9%)	0.4371
Diabetes with chronic complication	258 (9.7%)	177 (6.5%)	< 0.0001*
Diabetes without chronic complication	304 (11.4%)	253 (9.2%)	0.0089*
Hemiplegia or paraplegia	144 (5.4%)	76 (2.8%)	< 0.0001*
Mild liver disease	210 (7.9%)	204 (7.5%)	0.5558
Moderate or severe liver disease	10 (0.4%)	14 (0.5%)	0.4515
Metastatic solid tumor	53 (2.0%)	47 (1.7%)	0.4592

Table 1 continued

Baseline characteristics	Combination therapy ($N = 2666$)	Monotherapy ($N = 2738$)	p value
Myocardial infarction	83 (3.1%)	68 (2.5%)	0.1602
Peptic ulcer disease	92 (3.5%)	70 (2.6%)	0.0539
Peripheral vascular disease	258 (9.7%)	240 (8.8%)	0.2466
Renal disease	184 (6.9%)	112 (4.1%)	< 0.0001*
Rheumatologic disease	8 (0.3%)	13 (0.5%)	0.3020

AIDS acquired immunodeficiency syndrome, *BPH* benign prostatic hyperplasia, *CCI* Charlson Comorbidity Index, *HIV* human immunodeficiency virus, *PSA* prostate-specific antigen, *SD* standard deviation

*p value < 0.05

[a] The following comorbid conditions were mutually exclusive: diabetes with chronic complications and diabetes without chronic complications; mild liver disease and moderate or severe liver disease; any malignancy (excluding metastatic solid tumors, including leukemia and lymphoma) and metastatic solid tumor

pulmonary disease (12.7% vs. 7.9%, $p < 0.0001$), congestive heart failure (7.1% vs. 4.8%, $p = 0.0003$), diabetes with chronic complications (9.7% vs. 6.5%, $p < 0.0001$), diabetes without chronic complications (11.4% vs. 9.2%, $p = 0.0089$), hemiplegia or paraplegia (5.4% vs. 2.8%, $p < 0.0001$), and renal disease (6.9% vs. 4.1%, $p = 0.0001$) compared with the monotherapy group. Metabolic syndrome was not observed in either group, and the other comorbidities used to calculate CCI were comparable between the two treatment groups.

DISCUSSION

Abundant evidence suggests that combination therapy with an alpha blocker and a 5-alpha-reductase inhibitor is a more effective treatment for BPH than either drug alone [9]. However, in China, the use of combination therapy for BPH appears to be suboptimal [11], and the characteristics of Chinese patients with BPH who receive combination therapy or monotherapy in clinical practice have not been reported in the literature. This study addressed this knowledge gap by examining and comparing, for the first time, the characteristics of patients with BPH who received the 5-alpha-reductase inhibitor finasteride in combination with an alpha blocker with those of patients with BPH who received an alpha blocker in monotherapy in multiple major hospitals in China.

The results of this study showed that, compared with the monotherapy group, the combination therapy group was older, comprised a higher percentage of patients who initiated treatment in an inpatient setting, had a higher CCI, and had more comorbidities (including cardiovascular disease, hypertension, diabetes, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, diabetes with chronic complications, diabetes without chronic complications, hemiplegia or paraplegia, and renal disease). These findings suggest that physicians in China tend to prescribe combination therapy with an alpha blocker and finasteride to older patients with more comorbidities more often than to younger patients with fewer comorbidities. This may be due to the fact that combining the different mechanisms of action of an alpha blocker and finasteride, as well as the different times it takes for each of them to be effective, may be seen as more beneficial to older patients. Since the size of the prostate increases with age [14] and finasteride has been shown to have a faster effect on patients with a larger prostate [9], physicians may deem finasteride to be a more effective treatment choice in older patients, who are likely to have a larger prostate. Therefore, in older patients, combining an alpha

blocker with finasteride could be seen as a way to improve the urinary flow rate while controlling prostate growth. However, it is worth noting that this strategy may work just as well in younger patients. Indeed, the results of the MTOPS study, a US-based study including patients with BPH aged 50 years and older who were mostly Caucasian, indicate that combination therapy is more effective than monotherapy with either an alpha blocker or a 5-alpha-reductase inhibitor alone in reducing the risk of BPH clinical progression [9]. To ameliorate the symptoms of BPH and improve quality of life, combination therapy could thus be prescribed to patients when they are younger and have fewer and less severe comorbidities to manage. However, the current study was not designed to compare the effectiveness of BPH combination therapy and monotherapy in younger patients with fewer comorbidities vs. older patients with more comorbidities in China. Further studies are warranted to evaluate the benefits of initiating combination therapy in Chinese patients with BPH at an earlier age and/or when the comorbidity burden is lower. Nevertheless, the results of this study provide healthcare decision-makers with important information regarding the use of available treatment options for BPH based on the characteristics of patients treated in clinical practice in China and highlight the importance of evaluating the benefits of combination therapy vs. monotherapy to prevent and delay the clinical progression of BPH.

The present study has some limitations. First, since patients were from a limited number of Chinese hospitals, the study results may have limited national generalizability; however, patients were selected from a large geographic area in China. Furthermore, since the study included only Chinese patients, the results may not be fully generalizable to other countries. Second, complete records on in- and outpatient visits may not be available in our data if patients filled their prescriptions for finasteride or an alpha blocker or received medical treatments in other hospitals. To increase the confidence that patients used only one hospital for medical services, we required at least one in- or outpatient visit in the same hospital before the index date. Lastly, eligible patients in the outpatient setting may have been underestimated given that diagnoses made in outpatient settings may not be documented for all visits.

CONCLUSION

This study showed that Chinese BPH patients receiving finasteride in combination with an alpha blocker were older and had a higher comorbidity burden than those receiving an alpha blocker alone. This finding may help optimize real-world treatment decisions and therefore improve clinical outcomes in Chinese BPH patients. Future studies are warranted to evaluate the real-world benefits of 5-alpha-reductase inhibitor/alpha blocker combination therapy vs. alpha blocker monotherapy in Chinese BPH patients who are younger or have fewer and less severe comorbidities.

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Data Availability. The manuscript has no associated data or the data will not be deposited.

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