The use of Phosphodiesterase 5 Inhibitors (PDE-5-Is) alone or in Combination with Alpha-blockers for Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH)

Thesis

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List of Abbreviations

Abb.	Full term
AEs	*Adverse events.*
ANOVA	*Analysis of variance.*
BOO	*Bladder Outlet Obstruction.*
BPH	*Benign prostatic hyperplasia.*
cAMP	*Cyclic adenosine monophosphate.*
cGKI	*Cyclic guanosine monophosphate (cGMP - dependent protein kinase I).*
DRE	*Digital rectal examination.*
IIEF	*International Index of Erectile Function.*
IPSS	*International Prostate Symptom Score.*
LUTS	*Lower urinary tract symptoms.*
MetS	*Metabolic syndrome.*
NAION	*Non-arteritic anterior ischemic optic neuropathy.*
nNOS	*Neuronal nitric oxide synthase.*
NVCs	*Non-voiding contractions.*
OAB	*Over-active bladder.*
PDE5-Is	*Phosphodiesterase type 5 inhibitors.*
Qmax	*Maximum flow rate at uroflowmetry.*
RCTs	*Randomized controlled trials.*
RT-PCR	*Reverse transcriptase - polymerase chain reaction.*
SCI	*Spinal cord injury.*
sGC	*Soluble guanylyl cyclase.*
SNP	*Sodium nitroprusside.*
VIP	*Vasoactive intestinal polypeptide.*

INTRODUCTION

Lower urinary tract symptoms *(LUTS)* associated with benign prostatic hyperplasia *(BPH)* are common conditions in middle-age or older men. LUTS range from mild to severe, and include ***obstructive*** symptoms such as hesitancy, incomplete emptying, and weak stream, and ***irritative*** symptoms such as frequency, urgency, and nocturia, that can strongly worsen the quality of life *(QoL)*. For several years, surgery has represented the gold standard of care for this condition, allowing the relief of urinary symptoms and the consequent improvement in QoL ***(Gacci et al., 2007)***.

BPH is a non-malignant enlargement of the prostate caused by cellular hyperplasia of both glandular and stromal elements, and is a common progressive disease among men, with an incidence that is age-dependent. Histological BPH, which typically develop after the age of 40 years, ranges in prevalence from >50% at 60 years to as high as 90% by 85 years of age ***(Chapple et al., 2008)***.

BPH contribute to, but is not the single cause of, bothersome LUTS that may affect QoL. The prevalence of troublesome symptoms increases with age, typically occurring in men aged ≥50 years. Approximately 50% of patients with BPH report moderate to severe LUTS, consisting of storage and voiding symptoms. Although bothersome LUTS may affect QoL by altering normal daily activities and sleep patterns,

mortality associated with BPH is rare. Although uncommon, serious complications of BPH may occur, including acute urinary retention, renal insufficiency, urinary tract infection, hematuria, bladder stone, and renal failure ***(Yoshida et al., 2011)***.

These complications may be triggered or worsened by inadequate management of BPH. The incidence of acute urinary retention in untreated patients ranges from 0.3% to 3.5% per year; the risk of developing other long-term complication is unclear ***(O' Leary, 2003)***.

However, since the 1990's, there has been a substantial shift in the management of BPH from surgical to medical therapy. The current standard of care for LUTS/BPH includes alpha- adrenergic blockers, 5 alpha-reductase inhibitors, and phytotherapies, used alone or in combination. These therapies are associated with bothering sexual side effects ***(Morelli et al., 2009).***

Sexual dysfunction is a highly prevalent comorbidity in aging men with LUTS associated with BPH, common links such as the nitric oxide-cyclic guanosine mono-phosphate (NO/cGMP) pathway, RhoA/Rho-kinase signaling, pelvic atherosclerosis, and autonomic adrenergic hyperactivity can be potential targets for phosphodiesterase type 5 inhibitors (PDE5-Is) ***(Ho et al., 1998)***.

The management of patients with BPH includes non-pharmacological, pharmacological, and surgical option, with the choice of therapy typically depending on the presence and severity of symptoms. Watchful waiting is the preferred management strategy for patients with mild LUTS and those who do not perceive their symptoms to be particularly bothersome. Pharmacological treatment include α1- adrenergic receptor blockers, and 5 α-reductase inhibitors, which are recommended for use alone or in combination in moderate to severe LUTS. Currently, adrenergic receptor antagonists are commonly used as the first-line treatment for LUTS associated with BPH. The α1-adrenergic receptor antagonists cause vasodilatory symptoms, including postural hypotension and dizziness. Tamsulosin has relative selectivity for the α1A-adrenergic receptor ***(Yoshida et al., 2011)***.

The α1- adrenergic receptor blockers increases the incidence of the hip fractures (clinically important orthostatic hypotension). Avoidance of α1B- adrenergic receptor blockade may result in fewer overall hip fractures ***(Thorpe and Neal, 2003)***.

PDE5 tissue distribution and activity in the human prostatic urethra, prostate, and bladder indicate that in LUTS, PDE5 is mostly expressed and biologically active in the muscular compartment with the following rank order of activity: bladder neck more than prostatic urethra more than prostate ***(Fibbi et al., 2010).***

This selective distribution and activity of PDE5 in LUTS, along with inhibition of the RhoA/Rho-kinase contractile mechanism induced by PDE5-Is in the bladder, could be the mechanistic rationale for the use of PDE5-Is treatment to ameliorate the dynamic component (bladder dysfunction and urethral contractions) of male LUTS ***(Morelli et al., 2009).***

The importance of the bladder as a target of PDE5-Is in LUTS is further underlined by the significant improvement of urodynamic parameters in spinal cord injury patients after PDE5-Is administration, and the efficacy of PDE5-Is on continence recovery after radical prostatectomy for prostate cancer ***(Gacci et al., 2010)***.

The pathophysiology of male LUTS is highly complex, multifactorial, including an impaired NO/cGMP signaling, an increased RhoA/Rho-kinase pathway activation, pelvic ischemia, autonomic overactivity, and increased bladder/ prostate afferent activity, all these major mechanisms of BPH/LUTS could be counteracted by PDE5-Is. The mechanism of action of PDE-5-Is on LUTS includes several potential targets such as prostate, urethra, bladder, and LUTS vasculature ***(Zhao et al., 2011).***

PDE 5 is also highly expressed in the LUTS vasculature. Chronic ischemia due to pelvic artery insufficiency, caused by metabolic syndrome (MetS) or hypertension, can induce

functional and morphologic changes in the bladder and prostate that can be restored by the use of PDE5-Is ***(Morelli et al., 2011).***

It was confirmed that PDE-5 could improve urinary symptom scores in a population of men with comorbid ED and mild to moderate LUTS ***(Mulhall et al., 2006)***. The following year, with a randomized double-blind placebo-controlled study on BPH men (with or without ED), it was conclusively established the emerging role of PDE5-Is as an effective and well-tolerated treatment for LUTS ***(McVary et al., 2007)***.

Although the underlying pathophysiological links between LUTS and ED are not completely understood, both conditions are amenable to therapy with (PDE5-Is). Recently, several studies have suggested that metabolic factors could be important for contributing to both prostate inflammation and enlargement in men with LUTS ***(Gacci et al., 2015).*** PDE5-Is could reduce inflammation with the associated fibrosis and improve the oxygenation of the human prostate, with a normalization of prostatic structural anatomy and physiologic activity ***(Vignozzi et al., 2013).***

Aim of the Work

To determine the relative efficacy and safety of PDE5-Is alone or in combination with alpha-1 adrenergic blockers in LUTS due to BPH.