Rev Mex Urol. 2016;76(6):360–369

Revista Mexicana de
UROLOGIA
ÓRGANO OFICIAL DE DIFUSIÓN DE LA SOCIEDAD MEXICANA DE UROLOGÍA
www.elsevier.es/uromx

REVIEW ARTICLE

Combination therapy for the treatment of lower urinary tract symptoms in men

I. Barragán-Arteaga[a], **L. Reyes-Vallejo**[b,*]

[a] *Hospital Puerta de Hierro & Universidad de Guadalajara, Zapopan, Mexico*
[b] *Eli Lilly México, México DF, Mexico*

Received 19 November 2015; accepted 23 May 2016
Available online 21 August 2016

KEYWORDS
Lower urinary tract symptoms;
Combination therapy;
5α-Reductase inhibitors;
α-Blockers;
Phosphodiesterase-5-inhibitors;
Antimuscarinics

Abstract Recent interest in the coadministration of approved pharmaceutical agents has resulted in a wealth of emerging data on the safety and efficacy of dual pharmacological treatment for lower urinary tract symptoms (LUTS). Much evidence supports the coadministration of α-blockers with 5-alpha-reductase inhibitors (5-ARIs) in patients at risk for clinical progression. The use of phosphodiesterase-5 inhibitors (PDE5Is) in combination with 5-ARIs has also demonstrated a good safety and efficacy profile, providing early symptomatic relief and reduction of sexual side effects associated with 5-ARI use, although longer-term studies are needed. Studies investigating the combination of PDE5Is with α-blockers have shown additive effects on each of the individual agents with respect to the International Prostate Symptom Score (IPSS) and the International Index of Erectile Function (IIEF), which holds promise for patients who have shown a poor response to monotherapy. The coadministration of α-blockers and antimuscarinic agents provides an alternative for treatment of storage symptoms in patients who have failed to respond to monotherapy. This review aims to summarize and comment on available evidence regarding the safety and efficacy of combination treatment for LUTS.

PALABRAS CLAVE
Síntomas del tracto urinario inferior;
Terapia de combinación;
Inhibidores de la 5α-reductasa;

Combinación de terapias para el tratamiento de los síntomas del tracto urinario inferior en hombres

Resumen El reciente interés en la administración conjunta de agentes farmacéuticos aprobados ha dado lugar a una gran cantidad de nuevos datos sobre la seguridad y eficacia del tratamiento dual farmacológico para los síntomas del tracto urinario inferior. La evidencia científica apoya la co-administración de bloqueadores alfa con inhibidores de la 5-alfa-reductasa (5-ARI) en pacientes con riesgo de progresión clínica.

* Corresponding author at: Eli Lilly y Compañía de México, S.A. de C.V. Barranca del muerto 329 2o. Piso Col. San José Insurgentes México D.F. C.P. 03900, Mexico. Tel.: +52 55 1719 4739; fax: +52 55 1719 4739.
E-mail address: reyes_vallejo_luis_antonio@lilly.com (L. Reyes-Vallejo).

http://dx.doi.org/10.1016/j.uromx.2016.05.007

Bloqueadores alfa;
Inhibidores de la fosfodiesterasa 5;
Antimuscarínicos

El uso de inhibidores de la fosfodiesterasa-5 en combinación con 5-ARI también ha demostrado un adecuado perfil de seguridad y eficacia, proporcionando mejoría sintomática y reducción de los efectos sexuales secundarios asociados al uso de 5-ARI, aunque se necesitan estudios a largo plazo. Los estudios de combinación de inhibidores de la fosfodiesterasa-5 con bloqueadores alfa han mostrado efectos aditivos con respecto al Índice Internacional de Síntomas Prostáticos (IPSS) y al Índice Internacional de Función Eréctil (IIEF) sobre cualquiera de los agentes en forma individual, lo que mantiene la eficacia clínica para los pacientes que han mostrado una pobre respuesta a la monoterapia. Además la coadministración de bloqueadores alfa y agentes antimuscarínicos ofrece una alternativa para el tratamiento de los síntomas de almacenamiento en pacientes que no han respondido a la monoterapia. Esta revisión tiene como objetivo resumir y comentar la evidencia disponible sobre la seguridad y eficacia del tratamiento combinado para síntomas del tracto urinario inferior.

Introduction

The causal link between the prostate and lower urinary tract symptoms (LUTS) has come into question during the past decade, and the correlation between prostate size and symptoms, measured by the International Prostate Symptom Score (IPSS), has been shown to be weak.[1] Because of these recent findings and because patients seek help for LUTS rather than for a particular underlying contributing factor such as benign prostatic hyperplasia (BPH) or benign prostatic obstruction (BPO), more recent updates to international clinical management guidelines are now written from the perspective of men who suffer from LUTS, which incorporates a variety of bladder storage, voiding, and/or post-micturition symptoms.[2] Storage symptoms typically include daytime urinary frequency, nocturia, urgency, or urinary incontinence; voiding symptoms include slow stream, splitting or spraying, intermittency, hesitancy, straining, and terminal dribble; and post-micturition symptoms refer to the sensation of incomplete emptying or post-micturition dribble.

The evolving understanding about factors that may contribute to LUTS has led to increased interest in the combination of existing treatment approaches, so that multiple modes of action can be used to best manage symptoms. The mainstay of current treatment approaches for LUTS includes the four main drug classes used as monotherapies, and the combination of 5α-reductase inhibitors (5-ARIs) with α-adrenoceptor antagonists (α-blockers).[2] The α-blockers are traditionally the first-line treatment for managing signs or symptoms of BPH/LUTS, and this class of agent includes alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin. The 5-ARIs are used to manage benign prostatic enlargement (BPE), and the two key agents are dutasteride and finasteride. Antimuscarinic agents are primarily used to treat overactive bladder (OAB) and other storage symptoms, and the most common in this class include oxybutynin, propiverine, solifenacin, and tolteroidine. The phosphodiesterase-5 inhibitors (PDE5Is) are used for treating the signs or symptoms or BPH with or without erectile dysfunction. The only agent licensed for this indication is tadalafil; the other PDE5Is, vardenafil and sildenafil, are licensed as on-demand erectile dysfunction agents.

The Multinational Survey of the Aging Male-7 reported that among men $\geq$50 years of age, 43% with mild LUTS, 65.8% with moderate LUTS, and 82.5% with severe LUTS, also suffer from erectile problems.[3] This multinational survey concluded that sexual activity is common in a majority of men $\geq$50 years of age and is an important component of overall quality of life, highlighting the need to consider sexual issues in the management of patients with LUTS.[3] Because of the positive impact of PDE5Is on erectile dysfunction, there has been considerable interest in therapeutic regimens that include this class of agent. The purpose of this article is to review evidence on the efficacy and safety of dual pharmacological treatment for LUTS, with the aim of making evidence-based decisions about the suitability of patients with particular symptoms or risk profiles for different types of combination therapy.

α-Blocker/5-ARI combination therapy

This is the most widely investigated combination therapy for LUTS, with many clinical trials building the evidence for efficacy of treatment combinations in this class. The key initial studies were the Prospective European Doxazosin and Combination Therapy (PREDICT) study,[4] which investigated finasteride with terazosin, the Alfuzosin Finasteride (ALFIN) study,[5] which investigated finasteride with alfuzosin, and the Veterans Affairs Cooperative (VA-COOP) study,[6] which investigated finasteride with doxazosin, for 6 or 12 months. All three studies reported significantly improved symptom scores (American Urological Association symptom score [AUA-SS] or IPSS) in the combination therapy groups compared with the baseline and 5-ARI monotherapy groups, with reductions from the baseline between 6.1 and 8.5 points.[4–6]

Three studies lasted longer than 1 year, the first of which was the Medical Therapy of Prostatic Symptoms (MTOPS) study. It investigated the long-term effects of placebo, doxazosin 1 to 8 mg once daily [QD] monotherapy (doxazosin dose was 1 mg QD for the first week, increasing to 4 mg or 8 mg QD, depending on tolerability), finasteride 5 mg QD monotherapy, and finasteride/doxazosin combination therapy on BPH clinical progression in 3047 symptomatic