

Sexuality and disease progression: the cutting edge of BPH management

Highlights of a satellite symposium held during the XIXth Congress
of the European Association of Urology

25 March 2004, Vienna, Austria

Introduction

This Sanofi-Synthelabo-sponsored symposium introduced the latest concepts in the management of benign prostatic hyperplasia (BPH).

Over the past 15 to 20 years, the management of BPH has evolved from an essentially surgical role to a more prominent role for medical treatment.

Today, the two main objectives of BPH medical treatment are improvement of symptoms and prevention of disease progression. It is becoming clear that the benefit/risk ratio differs between the classes of drugs used for the treatment of BPH, as well as between drugs within each class. These differences impact on quality of life, most notably sexual function. The final treatment choice must take into account the patient's perspective and priorities.

During this symposium, Dr Mark Emberton, UK, provided an overview of acute urinary retention (AUR), its epidemiology, aetiology and treatment options including the benefits of selective α_1 -adrenergic receptor blockers (α -blockers). Dr Michael O'Leary, USA, discussed the relationship between urinary symptoms and sexual function and the impact of treatment choices on sexual function. Finally, Prof François Desgrandchamps, France, summarized data from recent clinical trials on BPH and their potential impact on BPH treatment guidelines.

Chair

Dr Steven Kaplan, New York, USA

Speakers

Dr Mark Emberton, London, UK

Dr Michael O'Leary, Boston, USA

Prof François Desgrandchamps, Paris, France

HIGHLIGHTS





Treating acute urinary retention: medicine and/or surgery

AUR is a frequent complication of BPH, with an estimated 5-year risk of one in three for men in their 80s.¹ Also, AUR is reported by up to one third of patients who undergo transurethral resection of the prostate (TURP) for BPH. As Dr Mark Emberton, UK, concluded, AUR is an important public health issue for men with BPH.

Acute urinary retention

AUR can be spontaneous (65% of cases) or precipitated (35%).² Aetiological factors include α -adrenergic activity, mechanical obstruction, bladder distension and sensory/motor deficit, though we don't yet have a unifying hypothesis for these factors.

Management of AUR varies greatly between countries, as shown by recent data from *Alf-One* – a large, real-life practice study of 8000 patients conducted in 29 countries in four continents. Variable healthcare access and a lack of harmonization in the management of BPH complications might account for these differences.^{2,3}

Management options for BPH/AUR

Until recently, prostatectomy was the only method for managing AUR, though surgery following AUR is associated with increased morbidity and mortality. Current treatment options include a trial without catheter (TWOC) and α -blockers.

Trial without catheter

The need for BPH surgery to be performed in an emergency setting can be reduced by TWOC. This enables appropriate planning for surgery, and the surgical procedure may be performed in the absence of a urinary catheter. Factors that influence the success of a TWOC include the duration of catheterization, age, drained volume and detrusor pressure.

α -blockers

Recent clinical studies have assessed the role of α -blockers in the management of AUR, in particular alfuzosin. α -blockers could influence the AUR outcome by reducing bladder outlet obstruction and post-void residual urine volume (PVR).⁴⁻⁶

ALFAUR is a double-blind, placebo-controlled trial of alfuzosin, 10 mg o.d., and a TWOC in patients (n=363) with a first AUR episode related to BPH. ALFAUR comprised two phases:

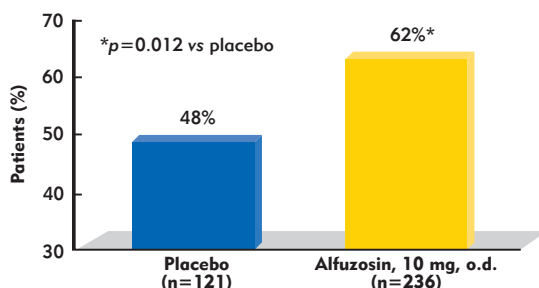
Phase 1: patients were randomized to receive alfuzosin, 10 mg o.d., or placebo for 2 to 3 days from the beginning of catheterization until a TWOC. Alfuzosin increased the rate of successful voiding after catheter removal (61.9% vs 47.9% for placebo, $p=0.012$; Figure 1).

Alfuzosin almost doubled the likelihood of a successful TWOC and its beneficial effects were particularly marked in patients at high risk of TWOC failure (men over 65 years of age and/or with a retention volume greater than 1000 ml).

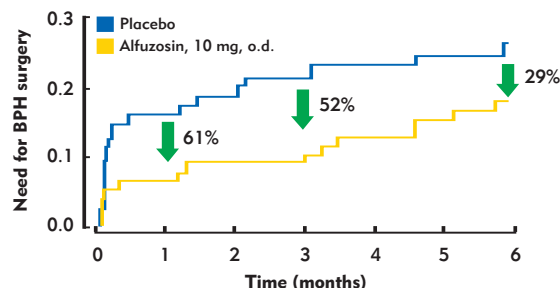
Phase 2: patients who successfully voided in phase 1 were re-randomized to receive alfuzosin, 10 mg o.d., or placebo for a further 6 months. Following a successful TWOC, alfuzosin reduced the need for BPH surgery by almost 30% compared to placebo at 6 months. Improvements over placebo were even more marked at months 1 and 3 (61% and 52% risk reduction, respectively, $p=0.04$; Figure 2).

Overall, alfuzosin significantly increased the success rate of a TWOC compared to placebo (39% vs 25%, $p=0.02$). The ALFAUR data show that alfuzosin, which affects risk factors and sympathetic overactivity, allows rapid catheter removal in patients with AUR. Alfuzosin also significantly reduces recurrence of AUR and the need for BPH-related surgery, compared with placebo, over the medium term.⁷

Alfuzosin, 10 mg once daily, over 6 months following a successful TWOC reduces the need for BPH surgery without increased risk of adverse events



1 Alfuzosin increases the incidence of successful voiding after catheter removal.



2 Alfuzosin reduces the need for BPH surgery within 6 months after a successful TWOC.

Sexual function: the new focus of BPH

Sexual function is an important element of quality of life and, as highlighted by Dr Michael O'Leary, USA, many men are sexually active into their 80s. We are now becoming aware of how significantly BPH and its treatment can affect sexual function in the older male.

LUTS and sexual function

Lower urinary tract symptoms (LUTS) cause sexual dysfunction, as revealed by the Multinational Survey of the Aging Male (MSAM-7).⁸ The severity of sexual dysfunction is closely related to the severity of LUTS, and both erection and ejaculation are affected (Figure 3). The severity of LUTS is independent of other risk factors (hypertension, diabetes, cardiac diseases) and patients' perceptions are that ejaculatory disorders (EjD) are as bothersome as erectile disorders (ED).

MSHQ: measuring men's sexual health

The MSAM-7 study highlights the need to consider sexual function in the older male. Evaluation tools are needed that consider both ED and EjD. The Male Sexual Health Questionnaire (MSHQ) is a psychometrically-validated tool for evaluating sexual function in BPH patients and includes questions about both erection and ejaculation, as well as satisfaction, activity and desire. The MSHQ is well suited to clinical trials in BPH/LUTS and their use will further our

understanding of the effects of age, BPH and associated management strategies on sexual function.⁹

BPH treatments and sexual function

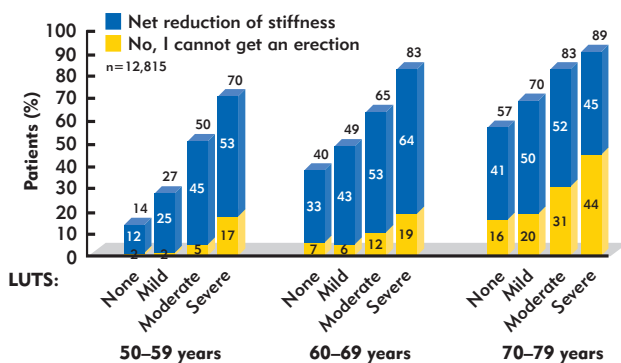
Not only BPH/LUTS themselves, but some of the strategies for managing BPH affect sexual function. Differences in these effects are observed between surgical and medical interventions and also within drug classes. Currently available drugs differ significantly in their sexual side-effect profiles. 5 α -reductase inhibitors, such as finasteride or dutasteride, are associated with increased impotence and decreased libido. Tamsulosin, a selective α_{1a} -blocker, is also associated with increased EjD (6% at 0.4 mg; 18% at 0.8 mg).^{9,10} Conversely, EjDs appear negligible with alfuzosin (Figure 4).^{11,12}

These differences between α -blockers are being investigated. Potential explanations include effects on different targets that affect the bladder neck and seminal vesicle, and the potential role of 5HT_{1A} receptors for tamsulosin.^{13,14}

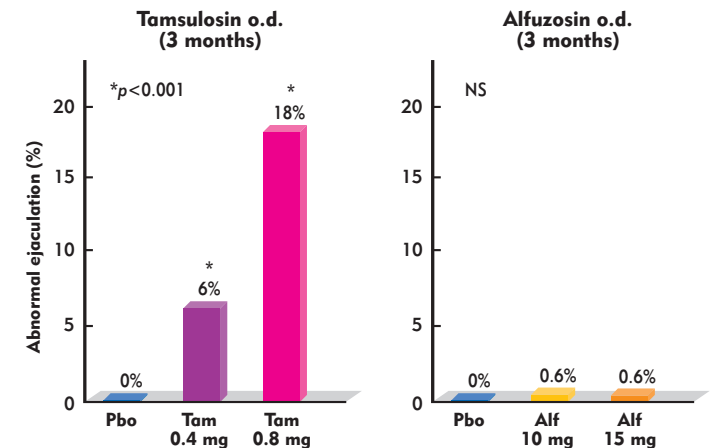
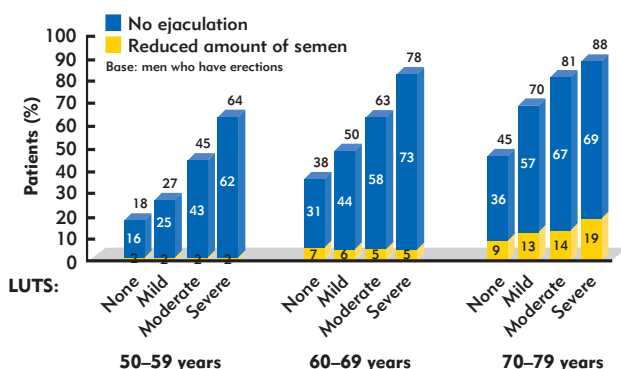
Clinical data show that alfuzosin has a positive impact on sexual function after 12 months' treatment, compared with the pre-treatment state (Figure 5).

It is clear from these data that sexual function must be considered when choosing treatment options for BPH and LUTS.

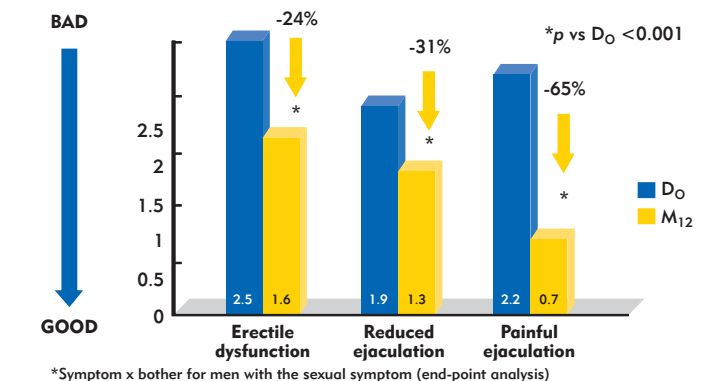
(a) DAN-PSSsex: erectile dysfunction



(b) DAN-PSSsex: ejaculatory dysfunction



4 α -Blockers and EjD: tamsulosin & alfuzosin US pivotal studies.^{11,12} (Tamsulosin, 0.8 mg, is only approved in the USA).



*Symptom x bother for men with the sexual symptom (end-point analysis)

3 Effects of severe LUTS on sexual function are independent of age.

5 Alfuzosin improves sexual function.¹⁵

Everyday practice for BPH patients: impact of recent results

Until recently, the standard view of medical treatment for BPH was simply the control of symptoms until surgery. However, recent data show the importance of managing disease progression. Prof Desgrandchamps, France, reviewed these data and their impact on the management of BPH, based on four key factors:

- interfere with the natural history of BPH
- interfere with sexual life
- combination therapy
- interfere with the risk of prostate cancer.

Interfere with natural history of BPH

Reducing the risk of AUR is a primary goal of treatment. For patients with a prostate greater than 40 g and PVR greater than 50 ml, risk of AUR increases three-fold during follow-up for 3 to 4 years. 5 α -reductase inhibitors, such as finasteride, significantly reduce this risk.¹⁶

Alfuzosin acts on risk factors such as PVR (Figure 6), thereby reducing the incidence of AUR in patients with LUTS.^{17,18} The exact role of alfuzosin and other α -blockers in the prevention of AUR requires long term placebo-controlled studies.

Interfere with sexual life

Prof Desgrandchamps reiterated the impact of LUTS on sexual function in old age and the negative effect of some BPH treatments on ED and/or EjD (e.g. tamsulosin, finasteride). Unlike these treatments, alfuzosin does not negatively affect sexual function; in fact, alfuzosin has been shown to improve it (Figure 5).

Combination therapy

Combination therapies are common for multifactorial diseases such as hypertension and diabetes. Combination treatments for BPH, e.g. α -blockers and 5 α -reductase inhibitors, could have an impact on the dynamic and anatomic components of LUTS, respectively. The Medical Therapy of Prostatic Symptoms (MTOPS) trial has demonstrated that combined doxazosin plus finasteride significantly delays disease progression compared to monotherapy.

In this trial, patients who may benefit from combination therapy, i.e. at high risk of disease progression, are those with prostate-specific

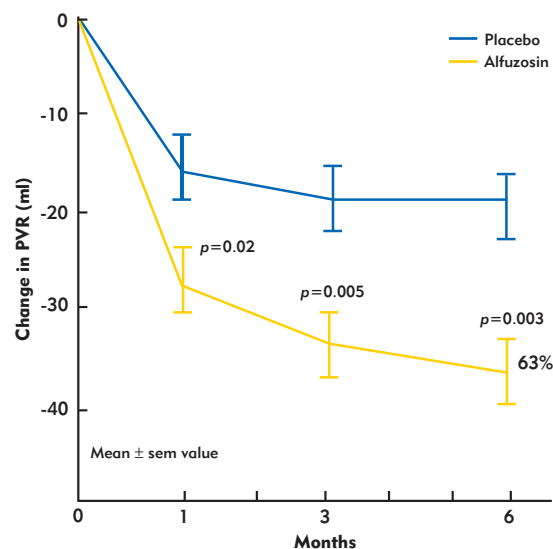
antigen (PSA) median levels greater than 1.6 ng/ml and a prostate greater than 31 g. However, caution must be exercised when choosing a combination therapy because of potential safety problems as well as the cost of combining treatments – approximately double the financial cost for less than 10% reduction in risk of progression.

Currently, α -blockers offer the best monotherapy choice for BPH, while combination therapy should be reserved for patients at high risk of disease progression. The exact characteristics of these patients remain to be defined.

Interfere with risk of prostate cancer

Risk of prostate cancer is high among patients with BPH. The Prostate Cancer Prevention Trial (PCPT) of nearly 19,000 men treated with finasteride showed a 6% global reduction in prostate cancer incidence after 7 years' treatment compared to placebo. However, finasteride appeared to increase the risk of high-grade prostate cancer. The significance of these data is not clearly understood, so we must carefully monitor patients taking this drug.

Each of the four factors discussed by Prof Desgrandchamps must be considered when choosing the best treatment for each patient. Individualizing patient treatment based on these factors will maximize the alleviation of symptoms, delay disease progression and minimize the side-effects that affect quality of life of the older man with BPH.



6 Alfuzosin reduces PVR, a risk factor for AUR.¹⁵

Sexual function should be taken into account in the initial evaluation of BPH patients and the choice of treatment

BPH treatment choice must consider the risk of disease progression and the benefit-risk ratio for each treatment as well as the patient's perspective





Overall conclusions

In the past, medical treatment of BPH was limited to symptom management until surgery. Today, improved treatment options enable us to control disease progression as well as symptoms.

Sexual function is an important element of quality of life and must be considered when making treatment choices for patients with BPH. In addition to age and LUTS, some medical treatments affect sexual function. While some treatments have a negative effect, alfuzosin appears to improve sexual function.

The combination of α -blockers and 5α -reductase inhibitors prevents disease progression, but care should be exercised when selecting patients to receive combination therapy. Currently, α -blockers remain the monotherapy of choice.

Undoubtedly, our treatment options for BPH are increasing. As a result, we can now control both the symptoms and progression of BPH. More research into disease progression cut-off points will enable treatment choices to be made with greater confidence, thereby improving further the patient's quality of life.

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Abbreviated prescribing information

Trade name of the medicinal product: XATRAL OD

Presentation: Three-layer tablets containing 10 mg of alfuzosin hydrochloride – prolonged release tablets.

Therapeutic Indications: Treatment of functional symptoms of benign prostatic hyperplasia.

Adjuvant therapy with urethral catheterization for acute urinary retention (AUR) related to BPH*

Posology and Method of Administration: The recommended dose is 10 mg tablet daily to be taken after the meal. The tablets should be swallowed whole.

Contra-indications: Hypersensitivity to alfuzosin. Combination with other α_1 -blockers. Hepatic insufficiency.

Special Warnings: Postural hypotension may occur transiently at the beginning of treatment in patients receiving antihypertensive medications within a few hours following administration. The patient should be warned of the possible occurrence of such events.

Special Precautions for Use: Patients with known hypersensitivity to α_1 -blockers. Specific treatment for coronary insufficiency, if any, should be continued. If an angina pectoris reappears or gets worse, alfuzosin should be discontinued.

Interaction with other Medicaments and other Forms of Interaction: Combinations to be taken into account: Antihypertensive drugs, nitrates.

Effects on Ability to Drive and Use Machines: Be aware of the risk of postural hypotension, especially at the beginning of treatment.

Undesirable Effects: CNS and psychiatric disorders: Faintness, dizziness, headache; Gastrointestinal disorders: Nausea, abdominal pain; Body as whole: asthenia. For uncommon effects, please refer to full prescribing information.

Overdose: In case of overdosage, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension should take place. Alfuzosin is highly proteinbound, therefore, dialysis may not be of benefit.

Pharmacodynamic Properties: Alfuzosin is a selective peripherally α -adrenoceptor antagonist.

Marketing authorisation number: Depending on the country.

Date Of First Authorisation: 23/02/2001.

Date Of (Partial) Revision Of The Text: June 2003.

More detailed information on request: SANOFI-SYNTHELABO, 174 Avenue de France, 75635 PARIS, Cedex 13, France. Tel: 33153774000

*Adjunctive therapy for AUR granted in some countries, please check the prescribing information in your country.

*Prescribing information and available presentations may differ according to the countries.
Readers are advised to carefully read the full Prescribing Information in force in their country.*