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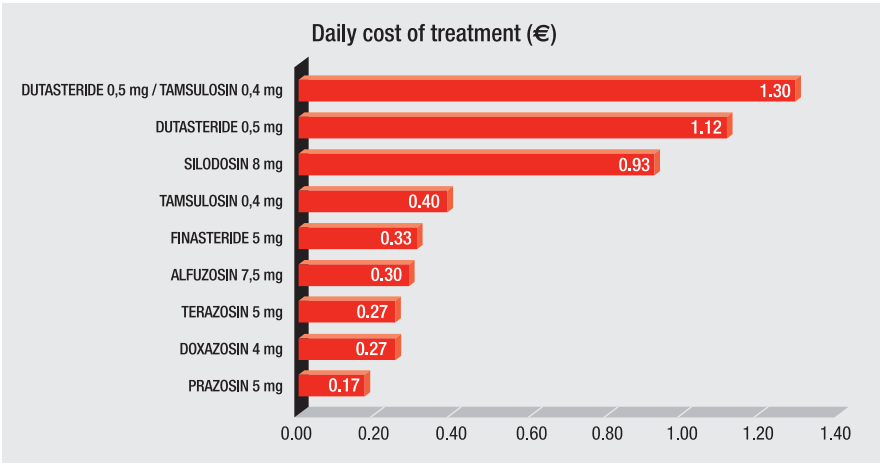
09/2011

Dutasteride/Tamsulosin (Duodart®) in benign prostatic hyperplasia

Why associate?



The combination has similar efficacy to dutasteride alone and presents more undesirable effects

- The combination dutasteride/tamsulosin is indicated in the management of moderate to severe symptoms of BPH and in the reduction of the risk of acute urinary retention and surgery in these patients.
- In the only published study, the combination did not clearly demonstrate the superiority of the combination when compared to dutasteride in monotherapy with regard to the reduction of acute urinary retention or the need for surgery.
- Adverse reactions were more frequent in the group under combined therapy compared to monotherapy, and no differences were seen with regard to treatment withdrawal due to adverse effects in either group. The incidence of heart failure was higher in patients treated with tamsulosin alone or combined while the incidence of ejaculation disorders and erectile dysfunction was higher in patients who were treated with dutasteride either alone or in combination.

Therapeutic indications[1]

It is indicated for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH) and for the reduction in the risk of acute urinary retention and surgery in patients with moderate to severe symptoms of BPH.

Mechanism of action and pharmacokinetics[1]

Dutasteride acts as an inhibitor of the 5-alpha-reductase which converts testosterone into 5-alpha-dihydrotestosterone, the main androgen responsible for prostate growth. Tamsulosin is an alpha blocker that acts by relaxing the smooth muscle tone of the prostate gland and the neck of the bladder.

Bioequivalence of the combination of the two drugs and the concomitant administration of each drug separately has been shown.

Posology and administration[1]

The recommended dose is 1 capsule a day, 30 minutes after the same meal every day.

Clinical efficacy

The CombAT trial, which lasted 4 years, included 4,844 men ≥50 years, with an IPSS (*International Prostate Symptom Score*) ≥12, prostate volume ≥ 30 mL and PSA ≥1,5 ng/mL. These patients were randomly assigned to receive either 0.5 mg dutasteride+ 0.4mg tamsulosin in separate formulations[1] or dutasteride+placebo or tamsulosin+placebo[2-4]. After 2 years, an average modification in the IPSS of -6.2 was observed in patients under dutasteride+tamsulosin compared to -4.3 with tamsulosin and -4.9 in the case of dutas-

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

teride[3]. These differences, although statistically significant, were not considered clinically relevant (NICE establishes that the minimum differences in IPSS should be 3 points)[5]. After 4 years, a statistically significant difference was observed in the incidence of acute urinary retention or the need for surgery in the patients under dutasteride-tamsulosin (4.2%) vs tamsulosin (11.9%, p<0.001) but not when compared to dutasteride (5.2%). The average modification of the IPSS was similar to that after 2 years: -6.3 points with dutasteride-tamsulosin compared to -3.8 tamsulosin and -5.3 points with dutasteride (p<0.001)[4].

There are no comparative studies available with other combinations of 5-alpha-reductase inhibitors and alpha blockers.

Safety

Adverse reactions

During the CombAT trial the incidence of adverse reactions was considerably higher in the dutasteride-tamsulosin group (28% vs 21% in those treated with dutasteride and 19% in the tamsulosin group). Treatment withdrawal due to adverse effects was similar in all groups. With regard to cardiovascular reactions, there was a greater incidence of heart failure in patients under the combination of dutasteride-tamsulosin, or tamsulosin alone, vs dutasteride alone: 0.9%, 0.6% and 0.2% respectively[6,10].

Dutasteride can produce a reduction in libido and erectile dysfunction, and a reduction in ejaculation volume and gynecomastia in some patients. Tamsulosin can produce dizziness, orthostatic hypotension, syncope and ejaculation disorders. The combination of both drugs seems to increase the frequency of ejaculation disorders[1,3,7].

In June 2011, the FDA issued an alert with regard to the increased risk of high grade prostate cancer related to the use of 5-alpha reductase inhibitors (dutasteride, finasteride).

Contraindications y precautions[1]

This combination should not be employed in women, children and adolescents, patients with hypersensitivity to any of the components (contains S (E110), yellow-orange colorant) and those patients with a history of orthostatic hypotension and severe liver impairment.

Before initiating treatment with the combination, screening for prostate cancer should be carried out which may produce similar symptoms to BPH.

In patients with programmed cataract surgery, treatment onset is not recommended due to the risk of "intraoperative floppy iris syndrome".

Dutasteride is absorbed through the skin and women in child bearing age, children and adolescents should avoid any contact with broken capsules and should this mishap occur, then the affected area should be thoroughly washed immediately with soap and water. Men under treatment with dutasteride should use a condom and should not donate blood for a 6 month period after interrupting treatment to avoid transmission to pregnant women[7].

The dutasteride-tamsulosin combination produces a 50% reduction in serum PSA levels in patients with BPH after 6 months, even in the presence of prostate cancer. Therefore given any isolated value of PSA in a patient under combined therapy the value should be doubled to correctly interpret the result as in normal values in untreated men.

Use in special situations[1]

Renal impairment: severe, use with precaution. **Liver impairment:** mild to moderate, use with precaution. **Elderly:** no dose adjustments required.

Interactions[1]

Plasma concentrations of dutasteride can increase with the concomitant administration of potent CYP3A4 enzyme inhibitors such as ritonavir, nefazodone and itraconazole. Tamsulosin can increase the hypotensor effect of other drugs. The combination of dutasteride-tamsulosin should not be employed with other alpha blockers.

Place in therapeutics

Management of BPH includes the use of alpha blockers and 5-alpha reductase inhibitors. Alpha blockers are the elective option in preventing acute urinary retention, by producing relaxation of smooth muscle of the prostate gland and the neck of the bladder. Relief comes about after 4-6 weeks of treatment and urine stream improves, with the reduction in urethral resistance to urine outflow[3-5].There is no effect on prostate volume or on growth[2-4]. Currently there are 6 alpha blockers available: doxazosin, prazosin, terazosin, silodosin, alfuzosin and tamsulosin and there is no evidence on the existence of differences among them. Orthostatic hypotension is minimised by nocturnal administration and initial low doses, and disappears after withdrawing treatment[3,5].

The 5-alpha reductase inhibitors (finasteride, dutasteride) present a comparable efficacy and safety profile[6], and could be an adequate alternative for patients with BPH who present moderate to severe symptoms and a prostate gland volume of over 50 mL. These agents relieve obstructive symptoms (reduction in the force and size of urine stream, difficulty on initiating bladder emptying, intermittent pauses of urine flow once started, incomplete voiding of the bladder, terminal dribbling, etc.)[8,9]. The response to the 5-alpha reductase inhibitors can take up to 6 months[3-5].

Some management guidelines on BPH consider indicating the combination of both drugs when moderate to severe symptoms are present (IPSS between 8 and 20), a large prostate gland on rectal examination (>30 g) and PSA >1.4-1.5 ng/mL, and when patients do not respond sufficiently to previous monotherapy, with an expected long term treatment duration (more than one year) and the absence of cardiovascular conditions (mainly heart failure)[5,6,12].

Studies carried out on combined treatments for BPH (finasteride+doxazosin and finasteride+terazosin) showed hardly conclusive results[7]. In the CombAT study there was a reduction in acute urinary retention or the need for prostate surgery due to the significantly lower BPH for the dutasteride-tamsulosin combination compared to tamsulosin in monotherapy[10]. There is no evidence that justifies that the combination of dutasteride with tamsulosin has more advantages over the combination of finasteride and any other alpha blocker. The cost of this combination (dutasteride + tamsulosin) is higher than the other alternative combinations of alpha blockers and 5-alpha reductase inhibitors administered separately such as finasteride+doxazosin or finasteride+tamsulosin.

On the other hand, given that the periods established to review patients with BPH who start treatment with alpha blockers and 5-alpha reductase inhibitors are different, the use of combined treatments at fixed doses does not seem advisable, at least during the initial phases of treatment. In addition, some trials have indicated that the withdrawal of the alpha blocker from the combined treatment is possible after 6-12 months with no recurrence of symptoms[5,6].

Presentations

Duodart® (GlaxoSmithKline S.A.) (0.5/0.4) mg 30 capsules (39.07 €).

References

A complete report on dutasteride/tamsulosin is available at: http://www.dtb.navarra.es

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