Overview of off-label use of 5-apha reductase inhibitors in women

Introduction

Finasteride (Proscar®, 5 mg) [1] and dutasteride (Avodart®) [2] are 5 alpha-reductase inhibitors indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.
Finasteride (Propecia®, 1 mg) is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in *men only* [3]. Finasteride 5 mg has been available on the Dutch market since 28 July 1992 and finasteride 1 mg since 28 June 2002. Dutasteride has been granted marketing authorization in the Netherlands on 16 December 2002.
Treatment with finateride and dutasteride is also used in practice as a pharmacologic option for women with alopecia who do not achieve satisfactory responses to topical minoxidil solution [4,5]. Also hirsutism is one of the off-label indications [6].

The drug dutasteride is contraindicated for use in pregnancy and women of childbearing potential [2]. Finasteride 5 mg use is contraindicated in women when they are or may potentially be pregnant [1]. The contraindication in the SmPC of finasteride 1 mg is even stricter; Propecia® is contraindicated for use in women [3].
Because of the ability of Type II 5α-reductase inhibitors to inhibit the conversion of testosterone to 5α-dihydrotestosterone (DHT), these drugs may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives them [1].

Even though the SmPCs of finasteride and dutasteride contraindicate these drugs for use in women or more specifically who are pregnant or of childbearing potential [1-3], the Netherlands Pharmacovigilance Centre Lareb has received multiple reports of adverse drug reaction in women. The use of finasteride and dutasteride these women is off-label use.

The purpose of this overview is to give insight in the reports Lareb has received associated with 5 alpha-reductase inhibitors in women.

Reports

In a period from 16-03-2005 to 28-11-2014 Lareb received 10 reports about the use of 5 alpha-reductase inhibitors in women. Six reports considered finasteride (both Proscar® and Propecia®), four reports considered dutasteride.

Table 1: reports of use of 5-apha reductase inhibitors in women

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 49622 F, 69, pharmacist	finasteride (Proscar®) 5mg 1dd hair loss	dexamethasone/ gentamicine eyedrops, ketorolac eyedrops, metformine tablet, insulin (Actrapid & Isulatard), miconazole ointment	blood glucose decreased (2.5)	8.5 hours drug withdrawn, recovered
B 55097 F, 40, physician via the MAH	finasteride (Proscar®) 2.5 mg 1dd hirsutism and polycystic ovaries with acne methyldopa 250 mg	metformin	exposure during pregnancy ,off label use, wrong technique in drug usage process (5 mg tablet split incorrectly)	latency unknown, used until 18.5 weeks pregnant, withdrawn, child born with hypospadias

C 82446 F, 65, specialist doctor	finasteride (Proscar®), 1,25 mg 1dd alopecia androgenetica cyproteron tablet 10mg alopecia androgenetica		benign polyp of uterus	finasteride: latency 11 months, used 7 months, drug withdrawn 4 months before diagnosis, cyproterone latency 4 months, drug withdrawn, unknown (two months after withdrawal of cyproterone the polyps had almost disappeared)
D 111962 F, 58, pharmacist	finasteride (Propecia®) 1mg 1dd alopecia		dry skin and hair	days, dose not changed, not recovered
E 85771 F, 43, pharmacist	finasteride (Propecia®) 1mg 1dd alopecia		localized skin reaction	1 day, unknown, unknown
F 118565 F, 29, pharmacist via the MAH	finasteride (Propecia®) 1 mg 1dd hair loss	unknown hormonal contraception	drug administration error, exposure during, pregnancy abortion induced	unknown, withdrawn, unknown
G 13831 F, 44, general practitioner	dutasteride 0,5mg alopecia		dysmenorrhoea	3 months, unknown, recovered with sequel
H 158122 F, 64, consumer	dutasteride 0.5 mg 1dd alopecia androgenetica	metoprolol tablet 50mg	breast cancer ,off label use	3 years, dose not changed, recovered
I 133992 F, 57, specialist doctor	dutasteride 0,5mg	venlafaxine, timolol eyedrops, acetylsalicylic acid	mood swings	week, drug withdrawn, recovering
J 121241 F, 55, pharmacist	dutasteride 0,5mg 1dd		muscle spasms, vomiting, abdominal pain upper	1 day, drug withdrawn, recovered/resolved

Addition information about the serious cases is listed below:
In Case B the patient took finasteride till she was 18,5 week pregnant. Somewhere in December 2004 the patient underwent an amniocentesis, no abnormalities were found. At 38 weeks of pregnancy she gave birth (caesarian section) to a son with hypospadias. After she gave birth to her baby she started therapy with finasteride again. The baby will be treated surgically when he is 1,5 years old. Subsequently, the patient recovered from drug exposure during pregnancy. The reporter considered hypospadias to be related to therapy with finasteride.
Assessment of this case by the Lareb Teratology Information Service (TIS) concluded that it was possible that there was an association between finasteride and the hypospadias based on the time-course. The development of external genitalia occur late in the first trimester of pregnancy, from about week 10 of embryonic development with the formation of the distal part of the urethra from week 12 [7]. In this period finasteride was used.

The patient in Case C was extensively examined in hospital, a malignant neoplasm was suspected. Hysteroscopy was performed twice with biopsy. The polyps turned out to be benign. Two months after withdrawal of cyproterone (and six months after finasteride had been withdrawn), the polyps had almost disappeared. This was still the case 3.5 months later. The patients gynecologist thinks that finasteride is the cause of the polyps while her dermatologist thinks that cyproterone is a more likely cause.

In Case of the patient was placed on therapy with finasteride by her dermatologist). Stopdate of finasteride was half December 2010. The first day of her last menstruation was January 25 2011. The patient has decided to do an elective abortion.
No further information is present about the reported 'drug administration error'. We suspect that this was meant as an indicator of the contraindicated use in this patient.
Assessment of this case by the Lareb Teratology Information Service (TIS) concluded that it was unlikely that finasteride could do damage in this case. The exposure was more than 5 ½ week before the last menstrual period, and therefore more than 7 ½ weeks before conception. The elimination half-life of finasteride is 3-14 hours [8]. TIS uses the rule of thumb that approximately 5 times the elimination half-life is needed in order to remove a substance from the body; 5 times is 14 hours to 90 hours. Because much more time had passed, no influence of finasteride on the developing fetus is expected.

In Case H the patient was hospitalized and underwent surgery, chemotherapy and radiation. In the report, the action taken with the drug is 'Dose not changed', however the correctness of this information is unknown.

Other sources of information

SmPC

Finasteride and dutasteride are indicated for the use in men. Some of the reported ADRs like the benign polyp of uterus are only applicable to women.
For the reported reactions that can occur in both sexes; an increase in blood glucose is not labeled for finasteride [1]. Dry skin is not labeled for finasteride, the SmPC mentions hypersensitivity reactions including rash that could be applicable to the localized skin reaction [3].
For dutasteride *male* breast cancer is labeled. Also a somber mood is a labeled ADR. Gastro-intestinal ADRs and myalgia are not labeled [2].

Literature

There are some descriptions of off-label use of finasteride and dutasteride in women for indications alopecia and hirsutism [4,9-13]. Reports on dutasteride are more scarce than for finasteride. Reported adverse drug reactions were maintained libido reduction (n=4) and liver enzymes increase (n=1) in a study with 40 normoandrogenic postmenopausal women with female pattern androgenetic alopecia [9]. In a study with 87 normoandrogenic, pre and post-menopausal women with female pattern hair loss (FPHL), four patients (4.6%) reported adverse events (headache, menstrual irregularity, dizziness and increased body hair growth). However, these adverse events were mild and disappeared soon [10].
No adverse effects were noted in a small study with five postmenopausal women without clinical or laboratory signs of hyperandrogenism that were given 2.5 or 5 mg/day oral finasteride for the treatment of pattern hair loss [11]. Finasteride was reported as well tolerated in other (small) studies in women [4,12].
Congenital adverse effects of finasteride and dutasteride are mainly described in animal studies [14-16]. A case report of a congenital anomaly possibly associated with the use of finasteride in early pregnancy was found. The baby was found to have deformities in the right hand in the form of a small hand with short fingers and absent phalangial bones in all five fingers (aphalangia), and in the left foot in the form of short second and third toes with absent distal phalanges. Two cafe au lait spots were seen also on the back. No other abnormalities could be identified [17].

Databases

On 13-11-2014, in the database of the Uppsala Monitoring Centre of the WHO [18] there are 389 reports of finasteride use in women. In the MedDRA® System Organ Class (SOC) Pregnancy, puerperium and perinatal conditions there are 77 reports in total for women using finasteride. For dutasteride there 157 cases of use in women. In the SOC Pregnancy, puerperium and perinatal conditions there are 41 reports in total for women using dutasteride.

On 17-11-2014, in the Eudravigilance database of the European Medicines Agency (EMA) [19] there are 211 reports of finasteride use in women. In the MedDRA® System Organ Class (SOC) Pregnancy, puerperium and perinatal conditions there are 67 reports in total for women using finasteride. For dutasteride there 17 cases of use in women. In the SOC Pregnancy, puerperium and perinatal conditions there are four reports in total for women using dutasteride.

Prescription data

According to the Drug Information System of the Dutch Health Care Insurance Board (GIP-database) in 2013 there were 366 women using finasteride 5 mg. Of these women, 90 were aged 15-44 years. For finasteride 1 mg there is no information available. In 2013 there were 104 women using dutasteride. Of these 19 were aged 15-44 [20].

Discussion and conclusion

Looking at the age of the women in the reports Lareb received, most of them are likely past the age of child-bearing potential. Therefore, the most important reason for contraindicating this drug in women (hazard to the male fetus during pregnancy) is no longer relevant to them. However, Lareb did receive one report of the use during pregnancy and one of use shortly prior to pregnancy.
Patient H suffered from breast cancer associated with the use of dutasteride. Male breast cancer is described as a possible ADR in the SmPC of dutasteride [2]. No cases of female breast cancer associated with the use of dutasteride were found in the literature. However, the MHRA describe four cases of female breast cancer for finasteride, received until 2009. Exposure periods to finasteride were relatively short and their hypotheses is that while there may be some unknown contributory factors, the difference in endogenous hormone levels between men and women, in particular for oestrogen, may mean that a lower dose of finasteride over a shorter period of time in women may be equivalent to a higher dose of finasteride over a longer time period in men to reach similar levels of risk for breast cancer [21].
No information was found regarding a relation between finasteride and the development of a benign polyp of the uterus.
The use of 5 alpha-reductase inhibitors.in women is an example of off-label use where in some cases patients have contra-indications mentioned in the SmPC.
Risks involved with this off-label use should be monitored. Lareb will stay vigilant of incoming reports of off-label use in women with 5 alpha-reductase inhibitors.

The Dutch Healthcare Inspectorate (IGZ) had advised negatively about the off-label use of both finasteride and dutasteride to treat female hair loss [22]. Also the Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV) has issued a position paper stating that based on the low quality of the RCTs performed , uncertainty about the effect , various potential side effects and unfamiliarity with impact and long-term safety the use of finasteride and in androgenic alopecia in women is not recommended, unless this is prescribed in the context of a medical research [23].

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This overview was published in March 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl