

Goserelin and psychiatric disorders in treatment of prostate cancer

Introduction

In the Netherlands several synthetic analogues of Luteinizing Hormone-Releasing Hormone (LH-RH) - also known as Gonadotropin-releasing Hormone (GnRH) - are approved for the treatment of prostate cancer. These GnRH receptor agonists such as goserelin, buserelin, and leuprorelin (leuprolide acetate) cause the inhibition of luteinizing hormone production during chronic administration. This in turn causes suppression of the synthesis of testosterone and dihydrotestosterone, on which continued growth of prostate cancer cells depends.

Goserelin is indicated for the suppression of testosterone production in the treatment of metastasized prostate carcinoma, for adjuvant hormonal therapy to radiotherapeutical treatment of locally extended prostate carcinoma, for treatment of receptor positive metastasized mamma carcinoma in combination with tamoxifen in pre- and perimenopausal women, and for the management of endometriosis and uterine fibroids. It is also given before surgery for endometrial reduction [1]

Buserelin is indicated for the suppression of testosterone production in the treatment of metastasized prostate carcinoma[2]

Leuprorelin is indicated for the suppression of testosterone production in the treatment of metastasized prostate carcinoma, for the management of endometriosis and as pre-operative treatment of leiomyomata uteri and for the management of ideopathic central precocious puberty [3]

These indications imply that in the Netherlands goserelin and leuprorelin will be prescribed to both men and women and that buserelin will be prescribed to men only.

Reports

Until 20 May 2006, the Netherlands Pharmacovigilance Centre Lareb received 5 reports of a psychiatric disorder associated with the use of GnRH receptor agonists in male patients: one report associated with the use of buserelin and four reports associated with goserelin. We received no reports of psychiatric disorders associated with the use of leuprorelin in male patients.

The time to onset for buserelin in patient A was 7 months and varied from one week to 5 months for goserelin treated patients. Two patients required treatment with antidepressants or antipsychotics. Hormone levels (testosterone) were not reported in all reports. However, about patient A it was reported that he recovered from the depressive symptoms after withdrawal of buserelin but before the rise of his testosterone levels. Patient E was the only individual with a reported medical history of a psychiatric disorder (depression).

Table 1. reports of psychiatric disorders associated with the use of goserelin and buserelin by male patients.

Patient, Sex, age	Dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A M, 56	9.45 mg buserelin prostate carcinoma	not reported	depression, emotional lability	7 months, recovered (dechallenge positive)
B M, 67	10.8 mg goserelin prostate carcinoma	vitamin C, terphenadin, opticrom, finimal, lomusol nasal spray	emotional lability	1 week, not reported
C M, 63	10.8 mg goserelin prostate carcinoma	triamterene/hydrochlorothiazide, pindolol, cyproterone	insomnia, constipation	3 weeks not recovered after 4 months
D M, 74	10.8 mg goserelin prostate carcinoma	tamsulosin	depression, psychosis, sleep disorder, pruritus	not reported, not recovered (treated with mirtazapine and oxazepam)
E M, 80	10.8 mg goserelin prostate carcinoma	bicalutamide, clonidine	psychosis	5 months recovered (treated with haloperidol and oxazepam, next with olanzapine and oxazepam)

Other sources of information

SPC

Mood disorders, i.e. depressed feelings, are described in the SPC of goserelin, but specifically in relation to reduced estradiol levels in females[1]. In the SPC of buserelin nervousness, emotional lability, anxiety and depression (newly diagnosed or aggravated) are listed as rarely (0.01 – 0.1%) occurring adverse reactions [2]. Depression, insomnia, irritability are some of the psychiatric disorders listed as adverse reactions in men in the SPC of leuprorelin. In addition the same SPC of leuprorelin separately lists depression, emotional lability, insomnia, nervousness, anxiety and delusions as some of the psychiatric adverse reactions in women [3].

Literature

Declining male testosterone levels are associated with symptoms such as weakness, fatigue, decreased libido, depressive mood, lack of motivation and energy, lower psychological vitality, anxiety, irritability, insomnia, decreased work and sport performances, difficulty in concentrating, and memory impairment. [4]. Forty men with prostate cancer were treated with androgen blockade therapy (flutamide and leuprolide) which was clinically associated with increased scores in depression and anxiety tests [5]. However, it has been difficult to establish a therapeutic effect of testosterone substitution on the symptoms of depression [6].

Prescription data

Table 2. Total number of patients treated with GnRH receptor agonists in the Netherlands.

	2001	2002	2003	2004	2005
Goserelin (Zoladex [®])	11.032	11.766	12.324	13.128	13.554
Buserelin (Suprefact [®])	7.352	6.258	5.151	4.225	3.528
Leuprorelin (Lucrin [®])	7.575	8.039	8.497	7.864	8.279

Source: GIP/College voor zorgverzekeringen 2006 (<http://www.gipdatabank.nl/>)
Updated: 22-04-2006

Discussion and conclusion

The exact mechanism by which sex hormones influence mood and other psychiatric disorders in men remains elusive. A factor that may be of influence in pharmacological castration is that compared to natural gonadorelin (LHRH) goserelin is 100 times as powerful and buserelin is 16 times as powerful [7]. Lareb received one report of depression in a man in association with treatment with buserelin and four reports of psychiatric disorders in men in association with treatment with goserelin, including psychosis and depression. Psychiatric adverse reactions are described in the SPC of goserelin, but specifically in relation to reduced estradiol levels in females. The association between GnRH receptor agonists and psychiatric adverse reactions in men is listed in the SPCs of buserelin and leuprorelin, the two other GnRH receptor agonists licensed for treatment of men in the Netherlands.

References

1. Dutch SPC Zoladex[®]. (version date 27-06-2003) <http://www.cbg-meb.nl/IB-teksten/12277-18562.pdf>
2. Dutch SPC Suprefact[®]. (version date 02-12-2005) <http://www.cbg-meb.nl/IB-teksten/21170.pdf>.
3. Dutch SPC Lucrin[®]. (version date 21-03-2006) <http://www.cbg-meb.nl/IB-teksten/30198.pdf>
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5. Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. *Psychoneuroendocrinology.* 2004 Sep;29(8):1071-81
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