Use of degarelix among patients with prostate cancer in daily practice

A population-based cohort study describing the characteristics, cardio events and urinary tract infections among patients with prostate cancer using degarelix or other gonadotropin-releasing hormone agonists in UK's primary care

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1.0 Content Page

2.0 Background

Androgen deprivation therapy (ADT) has been used as a primary treatment for advanced prostate cancer and in combination with radiotherapy in patients with earlier stages of disease [1]. For several years gonadotropin-releasing hormones (GnRHs) agonists such as leuprorelin, goserelin and triptorelin were the standard of care for ADT. Recently, GnRH antagonists, degarelix, provide an alternative form of ADT [1,2]. Degarelix has a more direct mode of action by binding to GnRH receptors in the pituitary gland, thereby blocking their interaction with GnRH. This induces a rapid suppression of testosterone (and prostate-specific antigen (PSA)) [3]. In general, degarelix is well tolerated, with no reports of systemic allergic reactions in any clinical studies [4].

It has been suggested that GnRH antagonists may be associated with lower risks of cardiovascular effects. A meta-analysis of three clinical trials reported severe cardiovascular side effects (QT interval increase, angina pectoris, atrial fibrillation, cardiac failure, and myocardial ischemia) in 1.6% and 3.6% of patients using degarelix and GnRH agonists (leuprorelin or goserelin), respectively [5]. One pooled study of six Phase II and III studies suggested that patients with pre-existing cardiovascular disease, the risks of a subsequent cardiovascular event or death were approximately half in patients treated with degarelix compared with patients treated with leuprolide [6]. Another randomised trial comparing degarelix with leuprorelin showed, however, no difference in the rates of cardiac arrhythmias, incident ischemic heart disease, cardiac failure, and stroke [7]. Similar results were observed when six Phase II and III studies on the same drugs were pooled [8].

Another potential complication of degarelix is the risk of urinary tract infections (UTIs). In a one-year comparative, randomised phase III study comprising patients with prostate cancer [9], UTI (9% versus 3%, respectively; $p<0.01$) were more common among the leuprorelin users than the degarelix users. Another phase III study comparing degarelix with goserelin showed, lower incidence of urinary tract infection among degarelix users [10].

Treatment with degarelix in patients with prostate cancer has been studied in clinical trials. Because of their short duration and relatively small sample sizes, clinical trials cannot predict the safety of degeralix in daily practice. Participants in clinical trials often differ substantially from patients who use the drug once it is used in daily practice, because participants from clinical trials are highly selected in terms of comorbidities and concomitant medications. To date, it is not clear what the characteristics, and the number of cardio events and urinary tract infections are among patients with prostate cancer using degarelix in daily practice..

3.0 Study Aims & Objectives

3.1 Study Aim

The aim of the study is to describe the use of degarelix among patients with prostate cancer in UK's primary care.

3.2 Study Objectives

- To **describe the characteristics** of prostate cancer patients using degarelix, leuprorelin, goserelin and triptorelin at time of initiation.
- To **describe the number of switchers** to degarelix, leuprorelin, goserelin or triptorelin after initiation of one of these therapies in patients with prostate cancer.
- To **describe the number of degarelix users** who will switch to second line treatment (leuprorelin, goserelin or triptorelin).
- To **describe the number of cardio events** among prostate cancer patients treated with degarelix, leuprorelin, goserelin or triptorelin.
- To **describe the number of UTIs** among prostate cancer patients treated with degarelix, leuprorelin, goserelin or triptorelin.

4.0 Methods

4.1 Study Cohort

The study cohort comprises patients with prostate cancer who are new users of degarelix, leuprorelin, goserelin or triptorelin and are registered at a general practice from 2010 till present.

4.2 Study Design

A population-based cohort study will be carried out using the UK's general practitioner database, Optimum Patient Care Research Database (OPCRD), which includes prostate cancer patients initiating treatment of degarelix, leuprorelin, goserelin or triptorelin from 2010 till present.

Index prescription date (IPD): is defined as the date (day/month/year) at which patients receive either:

- A first prescription for degarelix;
- A first prescription for leuprorelin;
- A first prescription for goserelin;
- A first prescription for triptorelin.

The first prescription of each drug will be assessed between 2010 till present to ensure that all prostate cancer patients initiating treatment are assessed in the same period. In this case, the characteristics of the patients may be more comparable.

Baseline period: is used to estimate patient characteristics, and to prevent user bias as we will identify only new users of degarelix, leuprorelin, goserelin or triptorelin. The baseline period is at least one-year prior to the IPD.

Study end: All patients will be followed from the IPD up to the date they died, transferred out of general practice, switched to second line treatment, the date of the cardio event, the date of the UTI, or the end date of data collection, whichever date will come first.

4.3 Study Population

4.3.1 Inclusion Criteria

- Evidence of prostate cancer: an ever diagnostic code (Quality Outcomes Framework (QOF) defined) for prostate cancer or a diagnostic code for surgery, chemotherapy or radiotherapy plus a prescription of degarelix, leuprorelin, goserelin or triptorelin before or at IPD;
- Patients who have at least one record of degarelix, leuprorelin, goserelin or triptorelin;
- Each patient has to be registered with a general practitioner (GP) for at least one year before the IPD;
- Patients have to be actively registered from 2010 till present, i.e. until latest available data.

4.3.2 Exclusion Criteria

- Patients with a diagnosis of prostate hyperplasia at any time;
- Patients with a diagnosis of benign prostate cancer at any time.

4.4 Data Sources

This study will use data from the OPCRD which is a bespoke computerised primary care database and comprises anonymised data collected from over 600 general practices across the UK [11].

The OPCRD is approved by Trent Multi Centre Research Ethics Committee for clinical research use. Two types of anonymised patient data are typically included in this database:

- Routine clinical data: a dedicated software interfaces with primary care practice management systems and extracts anonymised, patient-level diagnostic, clinical and prescribing information.

- Patient reported outcomes: eligible respiratory patients (e.g. those with diagnoses and/or prescriptions for obstructive lung disease and approved for participation by the GP) are invited to complete validated disease assessment questionnaires to capture patient reported data on disease status and (where present) possible reasons for sub-optimal control/disease status.

5.0 Methods of Analysis

5.1 Demographic & Baseline Characteristics

Patient characteristics will be based on the variables listed below.

a) Variables examined at or closest to the IPD (where data available):

- Age (years), categorised as: <70, 70-80, >80 (at IPD)
- Sex
- Body Mass Index (BMI, kg/m^2) (calculated from height and weight data if available, taken from practice recorded BMI value if not, categorised as: underweight < 18.5, normal weight 18.5 -<25, overweight 25 - <30, obese ≥30 (within 5 years prior to IPD))
- Smoking status, categorised as never smokers, current smokers, former smokers (closest to IPD)
- Level of prostate specific antigens (PSA, ng/ml), categorised as: <20 and ≥20 (at OR closest to IPD)
- Level of testosterone (ng/ml) (at OR closest to IPD)

b) Variables examined in the year prior to the IPD or ever prior to IPD):

- Presence of comorbid condition: heart failure (diagnosis ever prior to IPD)
- Presence of comorbid condition: myocardial infarction (diagnosis ever prior to IPD)
- Presence of comorbid condition: arrhythmia (diagnosis ever prior to IPD)
- Presence of comorbid condition: chronic kidney disease (diagnosis ever prior to IPD)
- Presence of comorbid condition: hepatic impairment (diagnosis ever prior to IPD)
- Presence of comorbid condition: osteoporosis (diagnosis ever prior to IPD)
- Presence of comorbid condition: urticaria (diagnosis ever prior to IPD)
- Presence of comorbid condition: diabetes mellitus (diagnosis ever prior to IPD)
- Presence of comorbid condition: cardiovascular disease (diagnosis ever prior to IPD)
- Presence of comorbid condition: the number of 'active' UTIs, categorised as: 0, 1, 2, >2 UTIs in one year (diagnosis in year prior to IPD)

c) Variables examined in six months prior to the IPD or at IPD:

- Use of co-medication: antithrombotic treatment, including anti-platelets and anticoagulants (prescriptions six months prior to IPD OR at IPD)
- Use of co-medication: anti-androgens, including non-steroidal anti-androgens (bicalutamide, enzalutamide, flutamide, nilutamide) and androgen synthesis inhibitor (abiraterone acetate) (prescriptions six months prior to IPD OR at IPD)

5.2 Study Outcomes

The outcomes of this study are 'switchers' to second line treatment (leuprorelin, goserelin, triptorelin or degarelix), cardio events and UTIs from 2010 till present. The outcomes will be defined as follows:

1) 'switchers' to second line treatment

'Switchers' to second line treatment will be defined as either:
1) Patients who switched to degarelix after they initiated leuprorelin, goserelin or triptorelin (IPD),
2) Patients who switched to leuprorelin after they initiated degarelix, goserelin or triptorelin (IPD),
3) Patients who switched to goserelin after they initiated degarelix, leuprorelin or triptorelin (IPD), or
4) Patients who switched to triptorelin after they initiated degarelix, leuprorelin or goserelin (IPD).

The date of the first prescription of second line treatment will be defined as the switching date. When there is a gap of 2 to 6 months before the switching date, the start date of this gap will then be defined as the switching date. We hypothesise that patients with a gap between two prescriptions for different treatments (GnRH agonists or degarelix) may have been hospitalised and received during their stay another treatment.

a. descriptive of the number of switchers to second line treatment and time to switch from IPD to the date of second line treatment (in days).
b. descriptive of the number of switchers to a specific second line treatment and time to switch from IPD to the date of a specific second line treatment (in days).
c. when degarelix users switch to leuprorelin, goserelin or triptorelin, the number of patients who switched to one of these drugs at 3, 6, 9 or 12 months will be described.

2) cardio events

Incident cardio events after initiating degarelix, leuprorelin, goserelin or triptorelin will be defined as:

1) Patients with a first medical record of heart failure,
2) Patients with a first medical record of myocardial infarction, or

3) Patients with a first medical record of arrhythmia.

a. descriptive of the number of patients with an incident cardio event after initiation treatment.
b. descriptive of time from IPD to the date of the first cardio event (in days).
c. descriptive of the number of patients who switched to second line treatment before the first cardio event.

3) UTIs

Incident UTIs after initiating degarelix, leuprorelin, goserelin or triptorelin will be defined as:

1) Patients with a first medical record of an UTI,

a. descriptive of the number of patients with an incident UTI after IPD.
b. descriptive of time from IPD to the date of the first UTI (in days).

6.0 Statistical Analysis

6.1 Exploratory Analysis

An exploratory analysis of variables at baseline or during follow-up (switching to second line treatment, cardio events or urinary tract infections) will be carried out:

Results are reported as:

- Continuous variables:
  - Sample size (n) (standard deviation (SD)) and percentage non-missing
  - Median and Interquartile Range (25th and 75th percentiles)
- Categorical variables:
  - Sample size (n) and percentage non-missing
  - Count and percentage by category (distribution)

6.2 Feasibility: OPCRD

In our initial feasibility study we assessed the number of patients that will be included in the study based on the read codes as listed in Appendix I.

- The number of patients with prostate cancer is 34,286
- The number of patients with prostate cancer using degarelix is 111

The number of patients and time of using degarelix per practice are described in below table:

Year	Patients
2010	1
2011	2
2012	14
2013	22
2014	15
2015	21
2016	21
2017	14
2018	1

7.0 References

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11. Optimum Patient Care Research Database (OPCRD). http://optimumpatientcare.org/database-overview/ (accessed April 2018).

Appendix I: Read Codes

Prostate cancer:

id	read_term_v2	read_term_v3
4M0..	Gleason grading of prostate cancer	
4M00.	Gleason prostate grade 2-4 (low)	
4M01.	Gleason prostate grade 5-7 (medium)	
4M02.	Gleason prostate grade 8-10 (high)	
8BAV0	Prostate cancer care review	
B46..	Malignant neoplasm of prostate	Malignant tumour of prostate
B915.		Neoplasm of uncertain behaviour of prostate
X30Ot		Tumour of prostate
X78Fx		TNM Prostate tumour staging
X78Y6		Carcinoma of prostate
Xa0bb		Endometrioid carcinoma of prostate
XaB1M		Gleason's microscopic prostatic carcinoma grading system
XaFrM		Local recurrence of malignant tumour of prostate
XaFrk		Metastasis from malignant tumour of prostate
XaIma		Gleason grading of prostate cancer
XaImb		Gleason prostate grade 2-4 (low)
XaImc		Gleason prostate grade 5-7 (medium)
XaImd		Gleason prostate grade 8-10 (high)
XacSF		Prostate cancer care review

Degarelix:

id	read_term_v2	read_term_v3
heI..	DEGARELIX	DEGARELIX
heI1.	FIRMAGON 80mg powder and solvent for solution for injection	FIRMAGON 80mg powder and solvent for solution for injection
heI2.	DEGARELIX 80mg powder and solvent for solution for injection	DEGARELIX 80mg powder and solvent for solution for injection
heI3.	FIRMAGON 120mg powder and solvent for solution for injection	FIRMAGON 120mg powder and solvent for solution for injection
heI4.	DEGARELIX 120mg powder+solvent for solution for injection	DEGARELIX 120mg powder+solvent for solution for injection

Leuprorelin

id	read_term_v2	read_term_v3
he8..	LEUPRORELIN ACETATE	Leuprorelin acetate
he81.	*LEUPRORELIN 3.75mg injection	Leuprorelin acetate 3.75mg injection (pdr for recon)+diluent
he82.	*PROSTAP SR 3.75mg injection	Prostap SR 3.75mg injection (pdr for recon)+diluent+kit
he83.	LEUPRORELIN ACETATE 11.25mg injection (pdr for recon)+dil	Leuprorelin acetate 11.25mg injection (pdr for recon)+dil
he84.	PROSTAP 3 injection (pdr for recon)+diluent	Prostap 3 injection (pdr for recon)+diluent
he85.	PROSTAP SR DCS 3.75mg powder+solvent for susp injection pfs	PROSTAP SR DCS 3.75mg powder+solvent for susp injection pfs
he86.	LEUPRORELIN ACETATE 3.75mg pdr+solv for susp injection pfs	LEUPRORELIN ACETATE 3.75mg pdr+solv for susp injection pfs
he87.	PROSTAP 3 DCS 11.25mg powder+solvent for susp injection pfs	PROSTAP 3 DCS 11.25mg powder+solvent for susp injection pfs
he88.	LEUPRORELIN ACETATE 11.25mg pdr+solv for susp injection pfs	LEUPRORELIN ACETATE 11.25mg pdr+solv for susp injection pfs
he89.	LUTRATE 1 MONTH DEPOT 3.75mg powder+solvent for susp for inj	LUTRATE 1 MONTH DEPOT 3.75mg powder+solvent for susp for inj
he8A.	LEUPRORELIN ACETATE 3.75mg pdr+solv for susp for injection	LEUPRORELIN ACETATE 3.75mg pdr+solv for susp for injection
he8B.	LUTRATE 3 MONTH DEPOT 22.5mg powder+solvent for susp for inj	LUTRATE 3 MONTH DEPOT 22.5mg powder+solvent for susp for inj
he8C.	LEUPRORELIN ACETATE 22.5mg pdr+solv for susp for injection	LEUPRORELIN ACETATE 22.5mg pdr+solv for susp for injection
puf3.	*LEUPRORELIN 3.75mg injection	
puf4.	*PROSTAP SR 3.75mg injection	
x01Lu		Leuprorelin
x02oa		Prostap SR
x03n1		Prostap 3

Goserelin

id	read_term_v2	read_term_v3
he5..	GOSERELIN	Goserelin product
he51.	*ZOLADEX 3.6mg implant	Zoladex 3.6mg implant
he52.	GOSERELIN 3.6mg implant	Goserelin 3.6mg implant
he53.	GOSERELIN 10.8mg implant	Goserelin 10.8mg implant
he54.	*ZOLADEX LA 10.8mg implant	Zoladex LA 10.8mg implant
he56.	ZOLADEX 3.6mg SafeSystem implant	Zoladex 3.6mg SafeSystem implant

he57.	ZOLADEX LA 10.8mg SafeSystem implant	Zoladex LA 10.8mg SafeSystem implant
x02vB		Zoladex
x04A4		Zoladex LA

Triptorelin

id	read_term_v2	read_term_v3
heB..	TRIPTORELIN	Triptorelin
heB1.	TRIPTORELIN 3mg injection (pdr for recon)+diluent	Triptorelin 4.2mg injection (pdr for recon)+diluent
heB2.	DECAPEPTYL SR 3mg injection (pdr for recon)+diluent	Decapeptyl SR 3mg injection (pdr for recon)+diluent
heB3.	TRIPTORELIN 3.75mg inj(pdr for recon)+solvent p/f syringe	Triptorelin 3.75mg inj (pdr for recon)+solvent p/f syringe
heB4.	GONAPEPTYL DEPOT 3.75mg inj(pdr for recon)+solv p/f syringe	Gonapeptyl Depot 3.75mg inj (pdr for recon)+solv p/f syringe
heB5.	TRIPTORELIN 11.25mg injection (pdr for recon)+diluent	Triptorelin 15mg injection (pdr for recon)+diluent
heB6.	DECAPEPTYL SR 11.25mg injection (pdr for recon)+diluent	Decapeptyl SR 11.25mg injection (pdr for recon)+diluent
heB7.	TRIPTORELIN 11.25mg pdr+solv for suspension for injection	TRIPTORELIN 11.25mg pdr+solv for suspension for injection
heB9.	DECAPEPTYL SR 22.5mg injection (pdr for recon)+diluent	DECAPEPTYL SR 22.5mg injection (pdr for recon)+diluent
heBA.	TRIPTORELIN 22.5mg injection (pdr for recon)+diluent	TRIPTORELIN 28mg injection (pdr for recon)+diluent
x05rq		Gonapeptyl

Appendix II: Research Outputs

Baseline characteristics	Degarelix users n =	Leuprorelin users n =	Goserelin users n=	Triptorelin users n=
Age, year Mean (SD)				
BMI, kg/m^2, n (%) Mean (SD) Non-Missing Underweight: <20 Normal weight: 20-24.9 Overweight: 25-30 Obese: >30				
Smoking Status, n (%) Non-smoker Current smoker Ex-smoker Non-Missing				
PSA, ng/ml, n (%) Median [IQR] Non-missing <20 ≥20				
Testosterone, ng/ml Mean (SD) Non-missing, n (%)				
Type of prostate cancer, n (%) Localised Low risk of recurrence High risk of recurrence Metastatic				
Comorbidity ever before/at baseline, n Cardiovascular disease Heart Failure Myocardial Infarction Arrhythmia Chronic Kidney Disease Hepatic Impairment Osteoporosis Urticaria UTIs* 0 1 2 >2 Diabetes Mellitus				
Drug use in the 6 months before/at baseline Antithrombotic treatment Anti-androgens -Non-steroidal anti-androgens (Bicalutamide, Enzalutamide, Flutamide, Nilutamide, -Androgen synthesis inhibitor (abiraterone acetate, aminoglutethimide)				

Table 1. Characteristics of prostate cancer patients using degarelix, leuprorelin, goserelin or triptorelin at time of initiation

SD: standard deviation; IQR: interquartile range; BMI: Body Mass Index; PSA: Prostate-specific antigen; GnRH agonist: gonadotropin releasing hormone agonist; UTIs: urinary tract infections
* in the year before/at baseline

Characteristics	Degarelix users n=	Leuprorelin n=	Goserelin n=	Triptorelin n=
Switched to second line treatment, N (%)				
Time to switch from initiation therapy to second line treatment, days Mean (SD) Median [IQR]				
Switched to a specific second line treatment **Degarelix, N (%)** Time to switch from initiation therapy to degarelix, days Mean (SD) Median [IQR] **Leuprorelin, N (%)** Time to switch from initiation therapy to leuprorelin, days Mean (SD) Median [IQR] **Goserelin, N (%)** Time to switch from initiation therapy to goserelin, days Mean (SD) Median [IQR] **Triptorelin, N (%)** Time to switch from initiation therapy to triptorelin, days Mean (SD) Median [IQR]	-	-	-	-

Table 2. Switch to degarelix, leuprorelin, goserelin or triptorelin use after initiation of one of these therapies in patents with prostate cancer

SD: standard deviation; IQR: interquartile range; second line treatment: switch to Degarelix or other GnRH agonists after initiation of one these drugs.

Characteristics	3 months	6 months	9 months	12 months
Number of degarelix users, N (%)				
Switched to second line treatment, N (%)				
Switched to a specific second line treatment, N (%) Leuprorelin Triptorelin Goserelin				

Table 3. Prostate cancer patients who switched to second line treatment (leuprorelin, goserelin or triptorelin) after using degarelix

second line treatment: switch to leuprorelin, triptorelin or goserelin treatment after initiation of degarelix.

Characteristics	Degarelix users n=	Leuprorelin n=	Goserelin n=	Triptorelin n=
Number of patients with an incident cardio event after initiation of therapy, N (%) Heart failure, N (%) Myocardial infarction, N (%) Arrhythmia, N (%)				
Time from initiation therapy to the first cardio event, days Mean (SD) Median [IQR]				
Number patients who switched to second line treatment before the first cardio event, N (%)				
Number of patients who remained on treatment before the first cardio event, N (%)				

Table 4. Cardio events in prostate cancer patients treated with degarelix, leuprorelin, goserelin or triptorelin

SD: standard deviation; IQR: interquartile range; second line treatment: switch to leuprorelin, triptorelin or goserelin treatment after initiation of degarelix.

Characteristics	Degarelix users n=	Leuprorelin n=	Goserelin n=	Triptorelin n=
Number of patients with an incident UTIs after initiation of therapy, N (%)				
Time from initiation therapy to the first UTI, days Mean (SD) Median [IQR]				

Table 5. Urinary tract infection in prostate cancer patients treated with degarelix, leuprorelin, goserelin or triptorelin

UTIs: urinary tract infections; SD: standard deviation; IQR: interquartile range; second line treatment: switch to leuprorelin, triptorelin or goserelin treatment after initiation of degarelix.