An Audit to Evaluate the Clinical Safety and PSA Response of *Firmagon*® (*Degarelix*) in Patients with Advanced Metastatic Prostate Cancer

Nikhil Vasdev*, Patricia McClurey, Debra Gray, Aftab Bhatti and David Chadwick

Department of Urology, James Cook University Hospital, Middlesbrough, UK

Abstract: *Objectives*: To evaluate the clinical safety and PSA response in patients with metastatic prostate cancer being treated with *Firmagon*® (*Degarelix*) and to assess the drug's safety profile.

Patients and Methods: This was an audit of 35 patients with PSA levels >50 and advanced metastatic prostate cancer at presentation who received *Firmagon*® (*Degarelix*) as per our North East & Cumbria Cancer Drug Approvals Group (NECDAG), UK guidelines. The audit was conducted using results from three hospitals in North East England with an aim to evaluate the safety profile, clinical and PSA response with this new drug. Baseline symptoms at diagnosis, presenting PSA and post treatment parameters on the commencement of with *Firmagon*® (*Degarelix*) were recorded. All patients in our cohort were homogenous having had not received any previous treatment including any form of LHRH analogue therapy. PSA levels were measured at 6 weekly intervals initially followed by 3 monthly intervals to evaluate initial and long term response to treatment with *Firmagon*® (*Degarelix*).

Results: There was no incidence of anaphylaxis or injection site complications on immediate administration of *Firmagon*® (*Degarelix*). No of our patients had renal or liver toxicity in our series. There was no incidence of tumour flare in any patient. A total of 23% of patients who presented primarily with severe bone pain described a complete resolution of *Firmagon*® (*Degarelix*) and required no adjuvant treatment such as bisphosphonates or palliative radiotherapy. A significant reduction in PSA levels were noted immediately at 6 weeks and 3 months following treatment with *Firmagon*® (*Degarelix*) (p=0.0038).

Conclusions: *Firmagon*® (*Degarelix*) is a safe drug is well tolerated in patients with advanced metastatic prostate cancer. The reason of how bone pain completely resolves in some patients with extensive bone metastasis on the commencement of *Firmagon*® (*Degarelix*) needs to be evaluated.

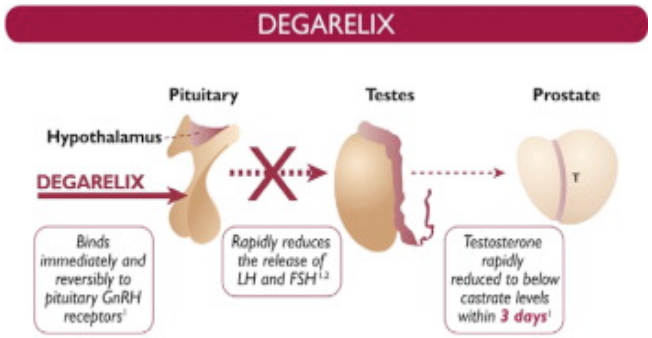
Keywords: *Firmagon*® (*Degarelix*), prostate cancer, PSA response, bone pain.

INTRODUCTION

Prostate cancer is the most common cancer in men in the UK and accounts for a quarter of all new cancer diagnoses in men [1]. Hormonal therapy is recommended as first-line treatment of locally advanced or metastatic disease [2]. The goal of this treatment is to reduce testosterone to castrate levels. The hormonal agents that are currently used as first-line therapy are normally luteinising hormone-releasing hormone (LHRH) agonists such as goserelin, leuprorelin acetate and triptorelin. At initiation of treatment, these agents produce a transient testosterone surge, which can lead to symptoms of flare. Anti-androgen therapy for flare protection is, therefore, usually co-prescribed during the first month of treatment.

Prostate Cancer can metastasize to bones (90%), lungs (46%), and liver (25%) [3]. A few patients present with significant bone pain at the time of diagnosis of prostate cancer and can have squealae of bone metastasis such as pathological fractures and spinal cord compression [4].

Firmagon® (*Degarelix*) is a gonadotrophin-releasing hormone (GnRH) antagonist for the treatment of prostate cancer. In contrast with LHRH agonist therapies, *Firmagon*® (*Degarelix*) acts by blocking GnRH receptors. Through this direct mechanism of action, *Firmagon*® (*Degarelix*) reduces testosterone to castrate levels, without any initial surge in hormone levels, thereby avoiding the risk of clinical flare and the need for concomitant anti-androgen therapy (Figure **1**).



[1]Klotz L, Boccon-Gibod L, Shore ND, et al. *BJU Int*. 2008;102 (11):1531-1538.
[2]Van Poppel, H, et al. *Eur Urol*. 2008;54(4):805-813.

Figure 1: Mechanism of action of *Firmagon*® (*Degarelix*).

*Address correspondence to this author at the Department of Urology, James Cook University Hospital, Middlesbrough, UK; Tel: + 44-(0) 1642 850 850; Fax: +44 (0) 1642 854 712; E-mail: nikhilvasdev@doctors.org.uk

ISSN: 1929-2260 / E-ISSN: 1929-2279/13

We present the results of our audit on the safety profile, clinical and PSA response use of *Firmagon*® (*Degarelix*) in three hospitals in our region (James Cook University Hospital, Middlesbrough, UK; Darlington Memorial Hospital, Darlington, UK and *Friarage Hospital*, *Northallerton, UK.* All patient presentation who received *Firmagon*® (*Degarelix*) as per our North East & Cumbria Cancer Drug Approvals Group (NECDAG), UK, guidelines.

PATIENT AND METHODS

Firmagon® (*Degarelix*) was introduced to the pharmaceutical formulary at our centre in 2010, following its approval in February 2009 by the North East & Cumbria Cancer Drug Approvals Group (NECDAG). The NECDAG recommended the use of *Firmagon*® (*Degarelix*) to be prescribed in patients with advanced hormone-dependent prostate cancer with at least one of the following clinical/biochemical criteria:

1. PSA >50 ng/ml

2. Ureteric obstruction

3. Symptoms of spinal cord compression (as per the National Institute for Health and Clinical Excellence's [NICE] guideline: Metastatic spinal cord compression: Diagnosis and management of adults at risk of and with metastatic spinal cord compression. Clinical guideline CG75) [5].

Patients were eligible if they met the NECDAG criteria. Our retrospective evaluated the details of 35 consecutive patients who commenced treatment with *Firmagon*® (*Degarelix*) between May 2010 and August 2011. These patient data was archived retrospectively from three hospitals in the North east of England and included James Cook University Hospital, Middlesbrough, UK; Darlington Memorial Hospital, Darlington, UK and *Friarage Hospital*, *Northallerton, UK*. All data were collected from patient case notes.

The mean age of the patients at diagnosis was 70.9 years, with a range of 49.2–89.6. The mean baseline creatinine level was 111 µmol/l, with 28 (80%) patients having normal renal function; mean baseline ALT levels were 43 µmol/, with 29 (83%) patients having normal liver function). The mean PSA level at presentation was 759 ng/ml, with 82.9% of patients having PSA >50 ng/ml (Table **1**).

A number of symptoms at diagnosis were also recorded, with five (14.2%) patients having acute urinary retention and one (2.8%) spinal cord compression. Bone pain was the most common symptom in 14 (39.9%) of patients (Table **2**).

A transrectal ultrasound (TRUS) biopsy was carried out on 31 (88%) patients. The remainder of the patients were not biopsied as they were deemed high risk for possible consequences of a prostate biopsy. The mean prostate volume indicated from the TRUS was 56.5 cm^3, with a range of 20–361 cm^3. The mean tumour volume measured by the biopsies was 56% (Range 10-100), with a range of 10–100. The Gleason scores in these 31 patients are summarized in Table **3**. Bone scans found metastasis in all 35 patients and superscans were seen in 11 (31%) patients.

All 35 patients were to receive an initial dose of *Firmagon*® (*Degarelix*) of 240 mg, given as two subcutaneous injections of 120 mg at a concentration of 40 mg/ml. This was to be followed by a maintenance dose of 80 mg given as one subcutaneous injection at a concentration of 20 mg/ml every 28 day. None of the

Table 1: Mean Presenting PSA

Mean PSA at presentation = 759 µmol / L (Range – 27.1 - 5798)		
PSA levels	**N**	**%**
20 – 50	6	17.1 %
50 – 100	6	17.1 %
100 – 200	6	17.1 %
200 – 500	8	22.8 %
500 – 1000	3	8.5 %
1000 – 2000	3	8.5 %
2000 – 5000	1	2.8 %
≥ 5000	2	5.7 %

Table 2: Presenting Symptoms of Patients

Symptoms	N	%
1. Acute Renal Failure	1	2.8 %
2. Acute Urinary Retention and Renal Impairment (High pressure chronic retention)	4	11.4 %
3. Asymptomatic (On PSA reading)	5	14.2 %
4. Bone pain	13	37.1 %
5. Cord Compression	1	2.8 %
6. Bone pain and acute retention	1	2.8 %
7. Hydronephrosis and renal impairment	1	2.8 %
8. Incidental * * Lung patch consistent with Metastasis	1	2.8 %
9. LUTS	4	11.4 %
10. Weight loss / cachexia	3	8.5 %

patients had received any previous treatment including LHRH Analogue therapies.

Table 3: Gleason Score of TRUS Biopsies

Gleason Score	N	%
3 + 4 = 7	1	3.2 %
4 + 3 = 7	4	12.9 %
5 + 3 = 8	3	9.6 %
4 + 4 = 8	1	3.2 %
4 + 5 = 9	10	32.2 %
5 + 4 = 9	9	29.1 %
5 + 5 = 10	3	9.6 %

RESULTS

All 35 patients had their first *Firmagon*® (*Degarelix*) injection in their respective hospital department. Eighteen (51.6%) of the patients continued with further injections in general practice as per the 'Shared Care Pathway'. One patient received only one injection of *Firmagon*® (*Degarelix*) and died within three weeks from a acute myocardial infarction. The incidence of anaphylaxis on immediate administration, tumour flare or immediate injection site reaction within four weeks of first injection was 0%.

PSA Response

The mean time from the first injection of *Firmagon*® (*Degarelix*) to the first PSA check was 5.8 weeks (range 1–14.3 weeks). The mean time from first injection to achievement of PSA nadir was 14.4 weeks (range 1.7–27.2 weeks). The mean follow-up was 37.1 weeks (range 1.8–117.8). All 35 patients had an initial biochemical PSA response. Figure **2** displays the mean drop in PSA levels: initial drop, nadir PSA and PSA at latest follow-up. PSA levels at the latest follow-up (from nadir) rose in 14 (40%) patients. The mean time for the rise of PSA from nadir was 37.1 weeks (range 6.4–47.8 weeks).

A significant reduction in PSA immediately following treatment with *Firmagon*® (*Degarelix*) (Table **4** and Figure **2**).

A significant reduction from initial test before treatment is still significant by the last PSA test carried out (Table **5**).

Of the total number of patients, 21 (60%) are currently on *Firmagon*® (*Degarelix*) only and continue to respond to treatment. Of the 13 patients with bone pain, three (23%) were noted to have a reduction in bone pain after treatment with only *Firmagon*® (*Degarelix*) this is based on patients reporting symptomatic response, without receiving bisphosphonates or palliative radiotherapy. One patient had a myocardial infarction while receiving *Firmagon*® (*Degarelix*), although this patient had a previous history of ischaemic heart disease.

DISCUSSION

Firmagon® (*Degarelix*) has a unique chemical characteristics and a novel mechanism of action, different from traditionally used hormonal therapies. Administered as a subcutaneous injection, *Firmagon*®

Table 4: PSA Reduction at Last Follow Up

	PSA before treatment (n=34)	First PSA following treatment (n=34)	Last PSA following treatment (n=34)
Mean	781	81	98
St dev	1433	203	205
95% CI	(15.5, 500)	(2.2, 70.8)	(2.2, 71.4)
Min, Max	27.1, 5798	0.8,1100	0.1, 1100

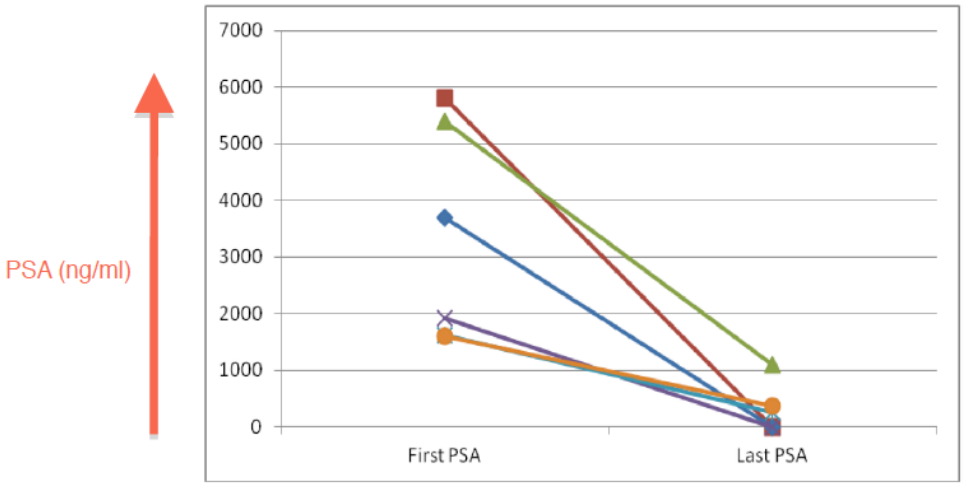


Figure 2: Graphical representation of First PSA at presentation and last PSA on follow up on the commencement of Firmagon® (Degarelix).

Table 5: Degree of PSA Reduction at Last Follow Up

	Change in PSA from before treatment to first test following treatment (n=34)	Change in PSA from first test following treatment to last test following treatment (n=34)	Change in PSA from before treatment to last test following treatment (n=34)
Mean change	700.30	-16.99	683.31
St dev change	225.06	93.01	1341.90
95% CI change	(242.42, 1158.18)	(-49.44, 15.46)	(-215.10,1 151.52)
p value	0.0038	0.2945	0.0055

(*Degarelix*) rapidly reduces levels of testosterone by immediately blocking the GnRH receptors in the pituitary gland. Blocking the receptors suppresses the release of the luteinizing hormone and follicle-stimulating hormone, resulting in a decrease in production of testosterone by the testicles to castration levels within three days. Prostate cancer is dependent on testosterone for its growth, and reducing testosterone levels slows the growth of cancer cells.

In clinical trials, *Firmagon*® (*Degarelix*) decreased the production of testosterone very rapidly, profoundly and in a sustained way [6]. In our series we noted a significant reduction in PSA levels within 3 days on the commencement of *Firmagon*® (*Degarelix*). At a mean follow up 27.5 weeks *Firmagon*® (*Degarelix*) in our series also maintains the PSA control over the long term and reduces the risk of PSA progression. We acknowledge that patient serum testosterone levels were not measured in our study as this is not standard practice in the UK. We measure testosterone levels on when patients develop castrate resistant disease. This has been seen in parallel studies with *Firmagon*® (*Degarelix*) [7]. *Firmagon*® (*Degarelix*) was tolerated well by our patients. The commonest side effects included hot flushes, injection site pain and erythema, increased weight, nasopharyngitis and fatigue were seen in 27% of patients only.

A very interesting finding in our series was the significant reduction in bone pain on receiving the first injection of *Firmagon*® (*Degarelix*) in patients

presenting with extensive bone metastasis secondary to prostate cancer. A total of 13 patients had presented with bone pain at presentation and 3 patients (23%) had a complete resolution in bone pain within 3 days of receiving *Firmagon*® (*Degarelix*) and continue to be pain free at mean follow up of 12 months. This has not been reported previously. The mechanism of how *Firmagon*® (*Degarelix*) causes a significant exact reduction in bone pain in patients with metastatic disease remains to be evaluated.

We aim to re-audit this data in 12 months to evaluate PSA response and failure rates.

CONCLUSION

Our data from our audit highlights that *Firmagon*® (*Degarelix*) is a well tolerated drug with no evidence of renal toxicity and liver toxicity in our series. A total of 23% of patients who had presented with bone pain confirmed a reduction in symptoms. There was no incidence of tumour flare in our series. Longer follow and larger patient numbers are required to validate this further.

ACKNOWLEDGEMENTS

Editorial support for this paper has been provided by Hayward Medical Communications using an educational grant from Ferring Pharmaceuticals.

REFERENCES

[1] Cancer Research UK. Prostate cancer - UK incidence statistics. http://info.cancerresearchuk.org/cancerstats/types/prostate/incidence/ (last accessed 25 May 2012).

[2] National Institute for Health and Clinical Excellence. Prostate cancer: diagnosis and treatment. Clinical guideline CG58. http://publications.nice.org.uk/prostate-cancer-cg58 (last accessed 25 May 2012).

[3] Bagi CM. Targeting of therapeutic agents to bone to treat metastatic cancer. Adv Drug Deliv Rev 2005; 57(7): 995-10.

[4] Galasko CS. Skeletal Metastases. Clin Orthop Rel Res 1986; 210: 18-30. http://dx.doi.org/10.1016/j.addr.2004.12.014

[5] National Institute for Health and Clinical Excellence. Metastatic spinal cord compression: Diagnosis and management of adults at risk of and with metastatic spinal cord compression. Clinical guideline CG75. http://publications.nice.org.uk/metastatic-spinal-cord-compression-cg75

[6] Damber JE, Tammela TL, Iversen P, Abrahamsson PA, Boccon-Gibod L, Olesen TK, *et al*. The effect of baseline testosterone on the efficacy of degarelix and leuprolide: further insights from a 12-month, comparative, phase III study in prostate cancer patients. Urology 2012; 80(1): 174-80. http://dx.doi.org/10.1016/j.urology.2012.01.092

[7] Crawford ED, Tombal B, Miller K, Boccon-Gibod L, Schröder F, Shore N. A Phase III Extension Trial With a 1-Arm Crossover From Leuprolide to Degarelix: Comparison of Gonadotropin-Releasing Hormone Agonist and Antagonist Effect on Prostate Cancer. J Urol 2011; 186(3): 889-97. http://dx.doi.org/10.1016/j.juro.2011.04.083

Received on 10-01-2013 Accepted on 31-01-2013 Published on 14-02-2013

DOI: http://dx.doi.org/10.6000/1929-2279.2013.02.01.4