FSH SUPPLEMENTATION INCREASES THE GROWTH OF PC-3 HUMAN PROSTATE CANCER CELL XENOGRAFT IN GONADOTROPIN-SUPPRESSED NUDE MICE

Olayiwola O Oduwole[1], Ariel Poliandri[2], Phil Rawson[1], Nafis Rahman[3], Wolfgang Koechling[4] and Ilpo Huhtaniemi[1,3]

[1]Imperial College London, UK. [2]Queen Mary University of London, UK. [3]University of Turku, Finland. [4]Ferring Pharmaceuticals Denmark

INTRODUCTION:

Gonadotropin-releasing hormone (GnRH) analogues are now the standard hormonal treatment for prostate cancer[1]. A fundamental difference between GnRH agonist and antagonist treatment is the permanent suppression of both LH and FSH by antagonist (e.g. Degarelix), while a rebound in FSH is associated with agonist (e.g. Leuprolide) treatment (Figs. 1A and B)[2,3]. The benefits of antagonist include the immediate onset of action and profound long-term suppression of FSH, suggested to be an independent growth factor in prostate cancer.

Fig. 1A

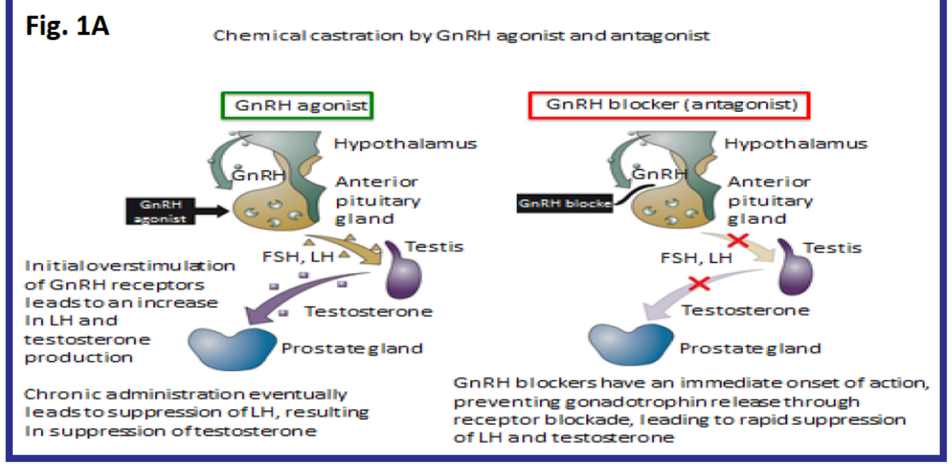
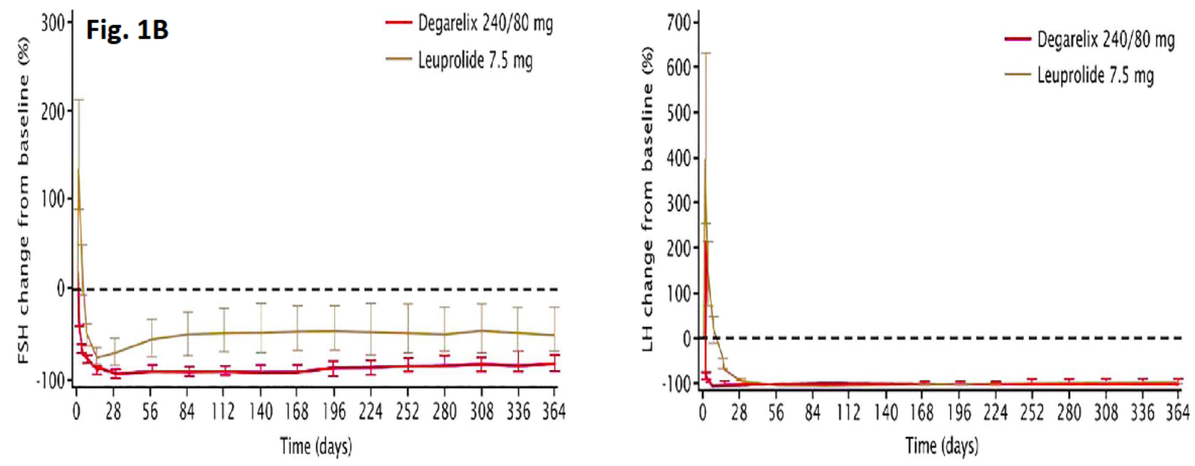


Fig. 1B



AIMS:

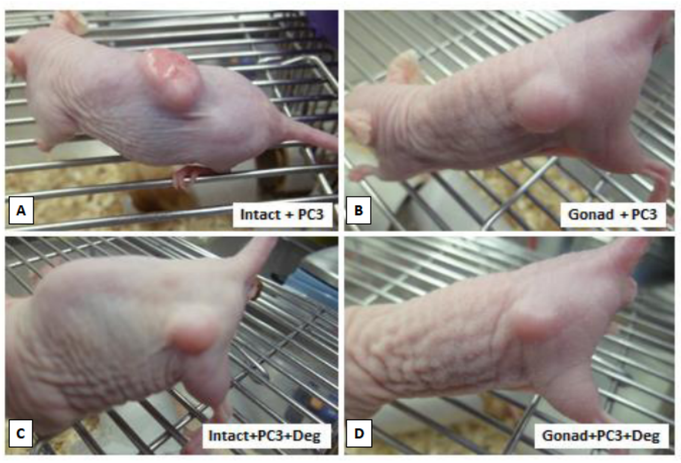
To assess the potential beneficial effects of permanent FSH suppression in the hormone ablation treatment of prostate cancer, we studied the effect of GnRH antagonist, degarelix, in the absence and presence of FSH supplementation on the growth of prostate cancer cell xenografts in athymic nude male intact and gonadectomised mice.

METHODS:

Nude male Intact mice (IM; N=20) and gonadectomised mice (GM; N=20) were inoculated with $2x10^6$ PC-3 human prostatic cancer cells. Half of the mice (N=10/group) received degarelix at a dose of 10 mg/kg body weight subcutaneously in a slow-release formula. In another experiment (N=10/group), degarelix treatment was supplemented with recombinant human FSH at 10 IU/kg/day using i.p. ALZET osmotic minipumps. Tumour growth was monitored over a 4-week period by external inspection and calliper measurement.

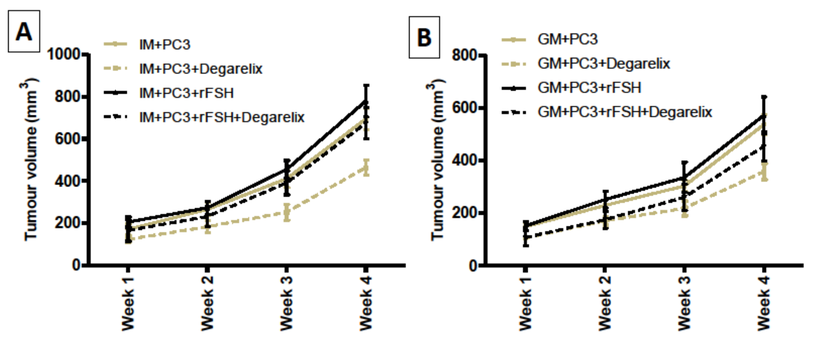
RESULTS:

1. Degarelix suppressed growth of PC-3 cells in IM and GM male nude mice



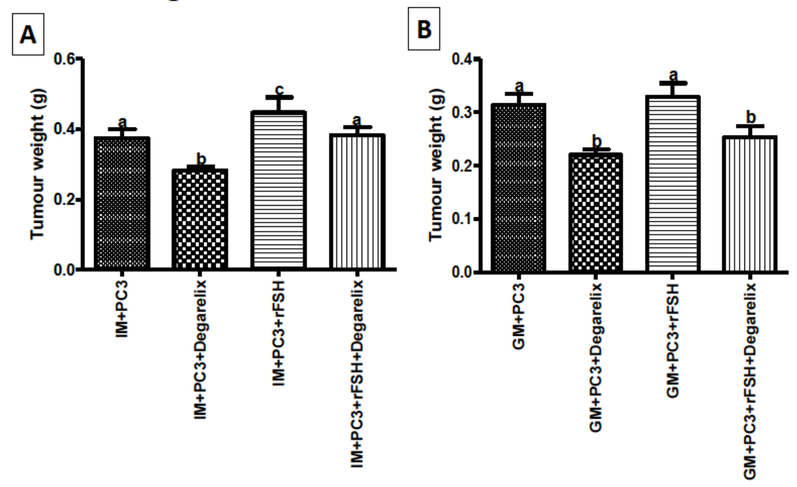
IM and GM nude mice harbouring PC-3 cells xenografts. (A) and (B) controls without treatment. (C) and (D) treatment with degarelix for 4 weeks.

2. Inhibition of PC-3 xenografts growth by degarelix



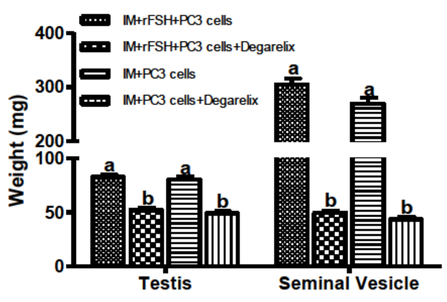
Assessment of tumour volumes over 4 weeks' treatment period in (A) Intact and (B) Gonadectomised mice (N=10/group). Degarelix treatment reduced tumour growth in similar manner, by 33% and 35%, respectively, in IM and GM as compared to non-treated controls ($p<0.0001$). The observed suppression of PC-3 xenograft growth by degarelix was inhibited by concomitant FSH treatment. Data are expressed as Mean ± SEM in all figures.

3. FSH treatment increased tumour size in IM with and without degarelix treatment



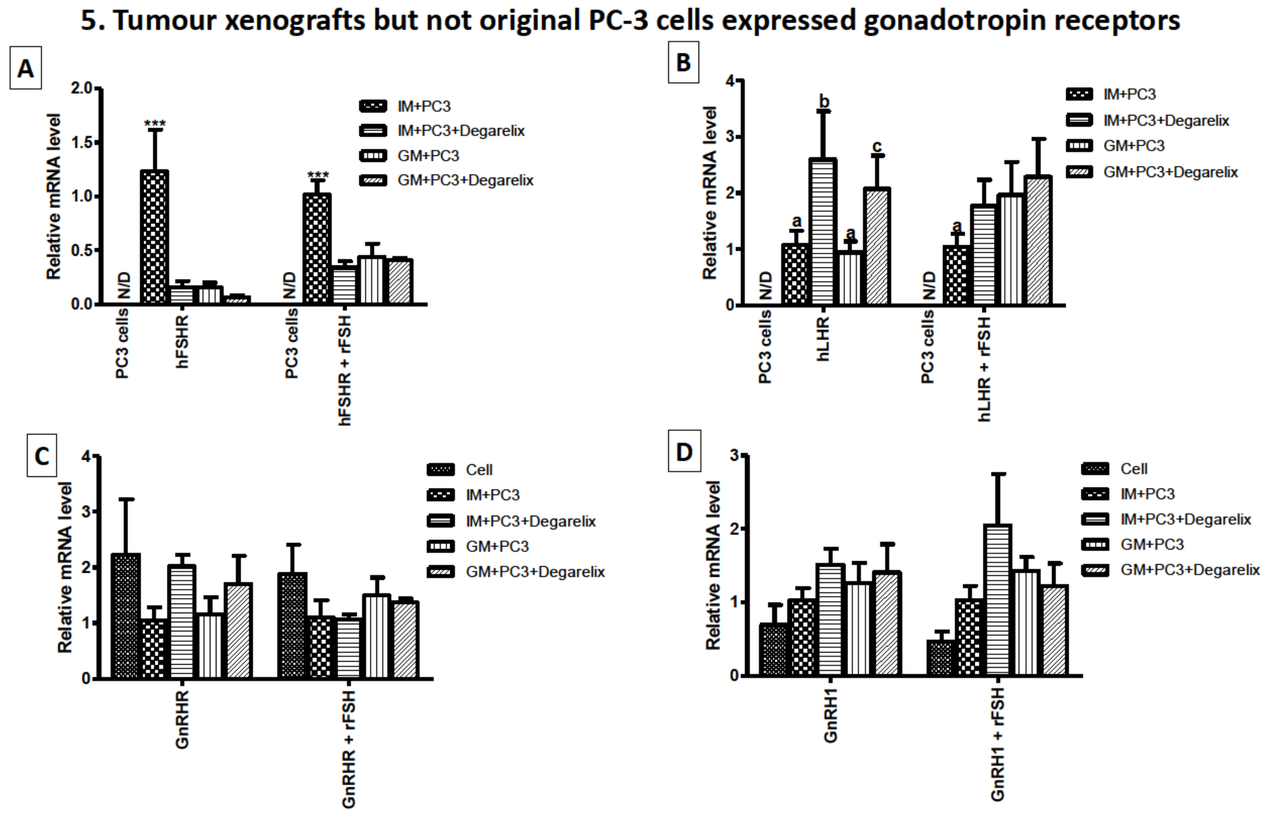
Effect of degarelix and/or human rFSH treatment on final tumour weights. (A) IM and (B) GM. Groups with different superscript letters are significantly different ($p<0.05$).

4. Degarelix decreased reproductive organ weights of Intact Mice



Testes and seminal vesicles weights of controls and degarelix treated mice. Different superscript letters indicates significant differences.

5. Tumour xenografts but not original PC-3 cells expressed gonadotropin receptors



qRT-PCR of tumour mRNA was performed to obtain relative mRNA levels of (A) FSH receptor (R), (B) LHR, (C) GNRH and (D) GNRH-R (N = 3/group). Non-inoculated PC-3 cells used as controls. The cells did not express either FSHR or LHR.

CONCLUSIONS

1. GnRH antagonist (degarelix) treatment clearly suppresses PC-3 xenograft growth.
2. FSH treatment increases tumour weights in both control and degarelix treated mice.
3. Cultured PC-3 cells do not express FSHR and LHR, but both receptors are expressed in tumours.
4. Similar findings in both groups of mice indicates that testicular function is not involved in growth of the androgen receptor-negative PC-3 cells.
5. The findings suggest that the suppression of both gonadotropins by GnRH antagonist treatment may offer an advantage over GnRH agonist (only LH is permanently suppressed) in the treatment of prostatic cancer.

References:

1. Shore N. D. et al. Prostate Cancer Prostatic Dis. 2013;16:7-15
2. Huhtaniemi I et al. J Androl 1987;8:355-62
3. Klotz L et al. BJU Int 2008;102:1531-8

Acknowledgements:

This work was supported by an unlimited grant from Ferring Pharmaceuticals

Imperial College London
IRDB, Faculty of Medicine