# Switching from a gonadotropin-releasing hormone (GnRH) agonist to a GnRH antagonist in prostate cancer patients: A systematic review and meta-analysis

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Cite as: *Can Urol Assoc J* 2020;14(2):36-41. http://dx.doi.org/10.5489/cuaj.5996

Published online July 23, 2019

See related commentary on page 42

## Abstract

**Introduction:** We sought to address whether there are clinical responses when patients who are failing gonadotropin-releasing hormone (GnRH) agonist therapy are switched to degarelix. Androgen-deprivation therapy remains the backbone of treatment for disseminated prostate cancer and may be achieved with orchiectomy, GnRH agonists, or degarelix, a GnRH antagonist.

**Methods:** We conducted a systematic review and meta-analysis with a search of the BIOSIS Previews, Embase, International Pharmaceutical Abstracts, MEDLINE, and Google Scholar databases using key terms. Quantitative meta-analysis was performed to provide a pooled estimate of prostate specific antigen (PSA) response at three months.

**Results:** Thirteen studies were identified, eight of which were included in the qualitative and quantitative analyses. Patient characteristics were broadly similar between the studies. Out of 155 patients across all included studies, 20 had stable PSA after the switch (12.9%), 14 had a 10–30% decrease in PSA (9.0%), three had a 30–50% decrease (1.9%), and 13 had a more than 50% decrease (8.4%). Random effects meta-analysis of these data demonstrated a pooled response rate of 27.75% (95% confidence interval 18.9–36.5%; $I^2$=7.9%). Changes in testosterone levels following the switch could not be quantitatively assessed due to lack of sufficient data.

**Conclusions:** Our results suggest that a switch to GnRH antagonist following progression on a GnRH agonist may result in a stable or decreased PSA at three months in about 30% of patients. This information should be considered among the potential options to discuss with patients with a rising PSA on GnRH agonist therapy.

## Introduction

The backbone of treatment for patients with newly diagnosed metastatic hormone-sensitive prostate cancer is androgen-deprivation therapy (ADT). Bilateral orchiectomy remains an economical option, but for psychological and other reasons, medical therapy is often preferred. Both gonadotropin-releasing hormone (GnRH) agonists and antagonists are used for ADT, with GnRH agonists being most widely used as first-line treatment. Although effective, patients eventually develop resistance to GnRH agonists, including the development of castration-resistant prostate cancer (CRPC).

Upon disease progression to CRPC, more potent therapies, such as abiraterone plus prednisone, enzalutamide, and docetaxel are available. However, these engender more side effects and much higher costs. GnRH antagonists, such as degarelix, have been shown to be equivalent in efficacy to the GnRH agonist leuprolide.[1] In addition to rapid testosterone suppression and lower follicle-stimulating hormone (FSH) levels, some data suggest better treatment response in terms of overall survival (OS)[2] and prostate-specific antigen (PSA) progression-free survival (PFS) with degarelix.[3] However, evidence regarding whether, upon resistance to GnRH agonist, a switch to GnRH antagonists could represent a second-line treatment in ADT for patients prior to starting potent CRPC treatment agents is thus far limited to case reports and case series.

Current clinical guidelines do not recognize the possibility of switching to GnRH antagonists as treatment after PSA progression on a GnRH agonist, although a switch may be considered when testosterone levels are incompletely suppressed.[4,5] The use of a GnRH agonist to antagonist switch at time to PSA progression has several potential advantages. It may delay the introduction of more potent side effects of first-line CRPC agents. Similarly, it has potential to decrease treatment costs by delaying the introduction of these costlier agents. However, the efficacy of this switch

from GnRH agonist to antagonist for patients progressing on ADT is yet unproven.

The objective of our study was to perform a systematic review and meta-analysis evaluating the efficacy of switching from a GnRH agonist to a GnRH antagonist. Our results present a pooled estimate of the PSA response to a GnRH agonist to antagonist switch from all reported studies and will facilitate better patient counselling and shared decision-making with regard to this treatment option.

## Methods

### Research question

We defined our central research question as the following: Do prostate cancer patients treated with GnRH agonist who have clinical, biochemical, or radiological progression on ADT respond to a switch to degarelix, a GnRH antagonist?

### Types of studies

We include in our analysis all patients on ADT for metastatic or recurrent prostate cancer. Progression of disease on GnRH therapy was defined as a rising PSA or appearance of new metastases on imaging despite standard, regular GnRH agonist dosing. We focus on degarelix, as it is the only currently available GnRH antagonist for prostate cancer patients, except in Germany where abarelix is available. Both prospective and retrospective observational studies were included, as well as case reports. Both published papers and abstracts, where sufficient detail existed to confirm patient characteristics and results, were included. Studies with less than three months' followup were excluded.

### Types of participants and exposure

Patients included had prostate cancer with or without distant metastases for which ADT was deemed indicated by the treating physician. Dosing of the GnRH agonist was according to the agent prescribed and information on testosterone levels was collected when reported. The definition of a rising PSA on GnRH was not strict for inclusion in our analysis, but generally expected to encompass recommendations from the PCWG3 guidelines.[6] A minimum followup of at least three months following a switch to degarelix was required. Dosing of degarelix was typically 240 mg initially, followed by monthly maintenance doses of 80 mg; however, the loading dose was not required for study inclusion. Studies were included irrespective of the serum PSA or testosterone at the switch, the duration of prior GnRH agonist treatment, GnRH agonist formulation, or the number of prior treatment options.

### Outcome measures

The primary outcome was the PSA response rate. For the quantitative meta-analysis, a response was defined as stable or decreasing PSA at three months following the switch from a GnRH agonist to degarelix. For the qualitative analysis, we also examined the degree of PSA response where stability is defined as ≤10% variation and decreasing PSA is either >10%, >30%, or >50% reduction. We further planned to assess changes reported in castrate testosterone levels as a secondary outcome.

### Literature review and search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used in reporting this systematic review and meta-analysis.[7] To identify reports to address our research question, a search of the BIOSIS Previews, Embase, International Pharmaceutical Abstracts, MEDLINE, and Google Scholar databases was performed. Terms used included "gonadotropin-releasing hormone agonist," "gonadotropin-releasing hormone antagonist," with related terms and individual drug names, prostate cancer, switch, and related terms. For each relevant article identified, references were hand-searched, as well as all related papers linked on the Pubmed portal.

Selection of studies was performed by P.T. Titles, abstracts and, where necessary, full-text review was used to determine if each study met inclusion and exclusion criteria. The final list of studies selected was agreed upon by P.T. and N.F. The data extraction of study characteristics and outcome measures was performed by K.S.A., with independent verification by other authors.

### Statistical analysis

Based on the identified literature following systematic review, quantitative meta-analysis was performed to provide a pooled estimate of the proportion of patients with any response three months following a switch from a GnRH agonist to degarelix. Due to clinical heterogeneity among the included studies, we used random effects models using the procedure of Neyeloff, Fuchs, and Moreira.[8] Data are presented as the proportion of responders at three months with 95% confidence interval (CI). We quantified heterogeneity using $I^2$ values.[9] To assess for publication bias, we planned to use funnel plots for all outcomes with 10 or more included studies.

## Results

Following our literature review, 13 studies were identified and after review, eight were included in the qualitative and

quantitative analyses, representing a total of 155 patients (Supp. Fig. 1). Studies that used GnRH antagonists other than degarelix, such as abarelix (n=2), or that switched therapies other than upon PSA progression (n=2), were excluded. A case report that had data only for one month following the switch was also excluded. In total, five prospective studies, two retrospective studies, and one case report were included.

Patient characteristics were broadly similar between the studies included in this meta-analysis. The groups studied comprised mainly older patients with advanced or metastatic prostate cancer from North America, Europe, or Japan. Most of the patients had a Gleason score above 6 and some had undergone prior local therapy in the form of either radical prostatectomy or radiation therapy. Patients who had undergone chemotherapy before the switch were included in one study.[10] Some studies comprised only or included patients treated with complete androgen blockade (ADT plus an anti-androgen),[11-15] while others included patients with ADT alone before the switch.[16,17] However, all published studies described excluding the possibility of anti-androgen withdrawal syndrome. Patients were mostly treated with either leuprolide or goserelin for at least 12 months before PSA progression and at least 93% of patients (144/155) had castrate-level testosterone (<0.5 ng/mL) before the switch to degarelix. Baseline patient characteristics of the included studies are summarized in Tables 1 and 2.

All studies used PSA response as the main outcome of clinical assessment reported following a switch to degarelix. Based on reported results and qualitative assessment of individual patient data, out of 155 patients across all included studies, 20 had stable PSA after the switch (12.9%), 14 had a 10–30% decrease in PSA (9.0%), three had a 30–50% decrease (1.9%), and 13 had a more than 50% decrease (8.4%). A summary of PSA responses in the selected studies is presented in Table 3. From this data, the range of any PSA response at three months after the switch was 14–100%. Random effects meta-analysis of these data demonstrated a pooled response rate of 27.75 (95% CI 18.9–36.5%; $I^2$=7.9%) (Fig. 1; Supp. Table 1).

Some studies determined that overall, there was no statistically significant difference between PSA levels before and after the switch.[10,12] These studies also found no correlation between initial PSA levels and response to the switch. Furthermore, out of 24 patients with PSA response in the studies that reported followup data beyond the evaluation three months after the switch, 16 had no PSA progression during followup (mean 9.5 months [range 5–20]), seven had PSA progression (4.83 months [range 4–7]), and two switched therapies or withdrew from the trial.[11,14-16]

Changes in testosterone levels following the switch to degarelix could not be quantitatively assessed due to lack of sufficient individual data for analysis. When this detail was available, most patients across the included studies showed no significant difference in testosterone levels and maintained castrate levels of testosterone after the switch. On the other hand, several studies found that FSH level decreased further in many patients after the switch, although decreases were not necessarily associated with a PSA response.[10,11,14]

## Discussion

Our systematic review and meta-analysis suggest that the switch to degarelix following failure of GnRH agonist therapy results in a PSA response at three months in almost

**Table 1. Study and patient characteristics for the GnRH agonist to GnRH antagonist switch studies included in the meta-analysis**

| Study | Type of study | Year | Country | Number of patients | Clinical stage | Gleason score at diagnosis |
|---|---|---|---|---|---|---|
| Borsellino et al[17] | Prospective observational study | 2014 | Italy | 20 | N1 or M1 (n=20) | NR |
| Casey et al[16] | Prospective observational study | 2012 | Canada | 40 | NR | NR |
| Ezaki et al[10] | Retrospective observational study | 2015 | Japan | 18 | N0/M0 (n=9)<br>N1 or M1 (n=9) | ≤6 (n=3)<br>>6 (n=15) |
| Fukui et al[11] | Prospective observational study | 2016 | Japan | 14 | N0/M0 (n=7)<br>N1 or M1 (n=7) | ≤6 (n=2)<br>>6 (n=9) |
| Masson-Lecomte et al[12] | Retrospective observational study | 2013 | France | 17 | N0/M0 (n=4)<br>N1 or M1 (n=13) | Mean ± SD, 8±1 |
| Miller et al[14] | Prospective observational study | 2015 | Germany | 24 (Cohort I)<br>12 (Cohort II) | Cohort I : M0 (n=17), M1 (n=7)<br>Cohort II : M0 (n=7), M1 (n=5) | Cohort I: ≤6 (n=5) >6 (n=19)<br>Cohort II: ≤6 (n=5), >6 (n=7) |
| Raddin et al[15] | Case report | 2011 | U.S. | 2 | Case 1 : M1<br>Case 2 : N1M0 | Case 1: 9<br>Case 2: 7 |
| Soga et al[13] | Prospective observational study | 2015 | Japan | 8 | N0/M0 (n=2)<br>N1 or M1 (n=6) | ≤6 (n=1)<br>>6 (n=7) |

NR: not reported; SD: standard deviation.

**Table 2. Baseline patient characteristics at the time of the switch from a GnRH agonist to GnRH antagonist for included studies in the meta-analysis**

| Study | Age at the switch | PSA level at the switch (ng/mL) | Testosterone level at the switch (ng/mL) | Duration on agonist before switch (months) |
|---|---|---|---|---|
| Borsellino et al[17] | Median (range), 77.5 (65–86) | NR | <0.5 (n=7)<br>0.2<T<0.5 (n=13) | NR |
| Casey et al[16] | Median (range), 81 (63–93) | Mean (range), 17.7 (1.3–141) | Mean (range),<br>0.288 (0.029–3.58) | NR |
| Ezaki et al[10] | Median (range), 74 (61–91) | Median (range), 7.9 (0.37–1709) | Median (range),<br>0.17 (<0.08–0.81) | Median (range),<br>35.5 (9–177) |
| Fukui et al[11] | Mean ± SD, 81.4±4.3 | Mean ± SD, 28.6±35.0 | <0.03 | Mean ± SD,<br>79.6±63.9 |
| Masson-Lecomte et al[12] | Mean ± SD, 73±9 (at diagnosis) | Mean ± SD, 34.33±50.32 | Mean ± SD,<br>0.21±0.13 | Mean ± SD,<br>42±37 |
| Miller et al[14] | Cohort I: Median (range), 73.5 (52–85)<br>Cohort II: Median (range), 75 (72–88) | Cohort I: Median (range), 10.4 (2.1–201.8)<br>Cohort II: Median (range), 9.13 (0.587–669) | Cohort I: Median (range), 0.085 (0.015–1.00)<br>Cohort II: Median (range), 0.075 (0.05–1.44) | ≥12 |
| Raddin et al[15] | Case 1: 64<br>Case 2: 45 | Case 1: 0.5<br>Case 2: 58 | Case 1: 2.08<br>Case 2: 0.43 | Case 1: 15<br>Case 2: 4 |
| Soga et al[13] | Mean ± SD,<br>72.7±4.5<br>(64–80) | NR | 0.2≤T<0.5 | NR |

NR: not reported; PSA: prostate-specific antigen; SD: standard deviation.

30% of patients with predominantly advanced or resistant prostate cancer. With varied reports and relatively few identified studies, this provides a useful estimate for clinicians to consider and discuss this option with patients who are progressing on ADT. To date, this represents the most comprehensive analysis of this topic and remains highly pertinent, as layering and sequencing of treatments for CRPC is rapidly evolving.

Prior to the current era of potent AR antagonists, manoeuvres for patients progressing on ADT have previously been evaluated. Escalation of bicalutamide dose to 150 mg resulted in a PSA response at 12 months of 22% in a phase 2 Canadian study.[18] Moreover, the option of anti-androgen withdrawal may still be considered in patients who are taking concomitant bicalutamide. However, newer agents demonstrate superior treatment responses in non-metastatic patients. In the TERRAIN study, the median time to PSA progression was 19.4 months with enzalutamide vs. 5.8 months with bicalutamide,[19] with even more impressive differences between apalutamide or enzalutamide and placebo in the SPARTAN[20] and PROSPER[21] studies, respectively. The use of a GnRH agonist to antagonist switch permits sequential layering of ADT with these newer agents. Moreover, for patients and healthcare systems around the world with limited ability to pay for newer agents, this therapeutic option could also have economic value.

Two mechanisms potentially contributing to the PSA response with degarelix after failure on a GnRH agonist include a more profound decrease in testosterone and a decrease in serum FSH levels.[22] Prior studies suggest achieving and maintaining castrate-level testosterone with GnRH agonists is associated with longer duration of response to

**Table 3. Summary of prostate-specific antigen (PSA) responses among included studies**

| Study | Sample size | Any PSA response | PSA response >10% decrease | PSA response >30% decrease | PSA response >50% decrease |
|---|---|---|---|---|---|
| Borsellino et al[17] | 20 | 10 | 8 | 0 | 0 |
| Casey et al[16] | 40 | 12 | 5 | 3 | 3 |
| Ezaki et al[10] | 18 | 7 | 5 | 5 | 3 |
| Fukui et al[11] | 14 | 2 | 1 | 0 | 0 |
| Masson-Lecomte et al[12] | 17 | 4 | 3 | 2 | 1 |
| Miller et al[14] | 36 | 8 | 4 | 2 | 2 |
| Raddin et al[15] | 2 | 2 | 2 | 2 | 2 |
| Soga et al[13] | 8 | 5 | 2 | 2 | 2 |
| **Overall** | **155** | **50** | **30** | **16** | **13** |

A PSA response was defined as a change in PSA from the baseline value at the time of switch from GnRH agonist to degarelix that is either stable (≤10% variation) or decreasing.

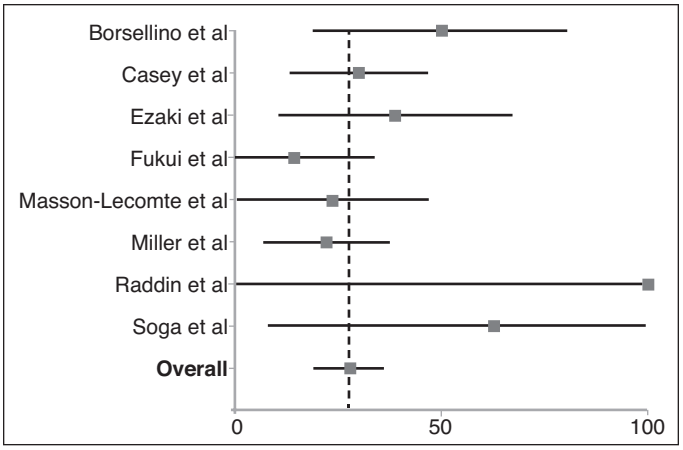


***Fig. 1.*** Proportion (%) of patients with any prostate-specific antigen (PSA) response among included studies and a pooled PSA response rate by random effects meta-analysis.

ADT.[23] However, our systematic review and meta-analysis did not support significant differences in testosterone levels after the switch. Moreover, a prior randomized study of degarelix subsequent to one year of leuprolide did not show decreases in serum testosterone.[3] In the same study and others, FSH levels have been shown to be further reduced with GnRH antagonists after orchiectomy[24] or GnRH agonist therapy.[25-27] The significance of FSH in prostate cancer is still under investigation, with one study indicating the FSH receptor is overexpressed in prostate cancer metastases[28] and another suggesting a link to the development of CRPC.[29] In this meta-analysis, studies by Miller et al[14] and Ezaki et al[10] demonstrated significantly decreased FSH levels after the switch to degarelix, while Fukui et al did not.[11] FSH reductions were also observed in patients with no PSA response.[10,11,14] Therefore, the contribution of reduced FSH signalling in achieving a PSA response is possible but remains to be further explored.

Our study has limitations that need to be considered. Despite a broad search of both abstracts and published papers, the number of studies identified was low. Given the nature of the literature available on this subject, there is a high potential for publication bias. Moreover, the assessed timepoint in the reported studies remains relatively short, with most being around three months with few long-term followups. Additionally, it is unclear whether PSA responses at three months represent a meaningful endpoint for patient outcomes. Accordingly, prior studies of anti-androgen withdrawal found PSA responses at 3–6 months, but not measurable differences in long-term outcomes.[30] Given the results available in the identified studies on changes in testosterone levels after the switch, this secondary outcome could not be included in the analysis to provide a useful estimate for clinicians. Lastly, the small sample size, as well as the lack of control groups and randomized, controlled trials within this meta-analysis are limitations that emphasize the need for more studies to better define the utility of GnRH antagonists after agonist failure.

## Conclusions

Treatment decisions for prostate cancer patients on ADT need to be individualized to each patient and physician context. Our systematic review and meta-analysis suggest that a switch to GnRH antagonist following progression on a GnRH agonist may result in a stable or decreased PSA at three months in almost 30% of patients. This information should be among the potential options to consider and discuss with patients with a rising PSA on GnRH agonist therapy.

**Competing interests:** Dr. Fleshner has been a consultant or advisory board member for Abbvie, Amgen, Astellas, Bayer, Ferring, Hybridyne Health, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Bavarian Nordic, Ferring, Janssen, Medivation, Nucleix, Progenics, Sanofi, and Spectracure AB. Dr. Toren has been an advisory board member for and received honoraria from Abbvie, Asetllas, Ferring, and Sanofi; has received research funding from Innocrin and Janssen; and has participated in clinical trials supported by AstraZeneca, Bayer, Janssen, Merck, MedImmune, Progenics, and Roche. The remaining authors report no competing personal or financial interests related to this work

**Funding:** Funding for statistical analyses was provided by Ferring Pharmaceuticals. Dr. Toren is supported by a clinician-scientist award from Fonds de Recherche du Québec – Santé (#32774).

**Acknowledgements:** The authors would like to thank Sergio Della Nora (Medical Director – Urology, Ferring Pharmaceuticals) for having reviewed the manuscript.

This paper has been peer-reviewed

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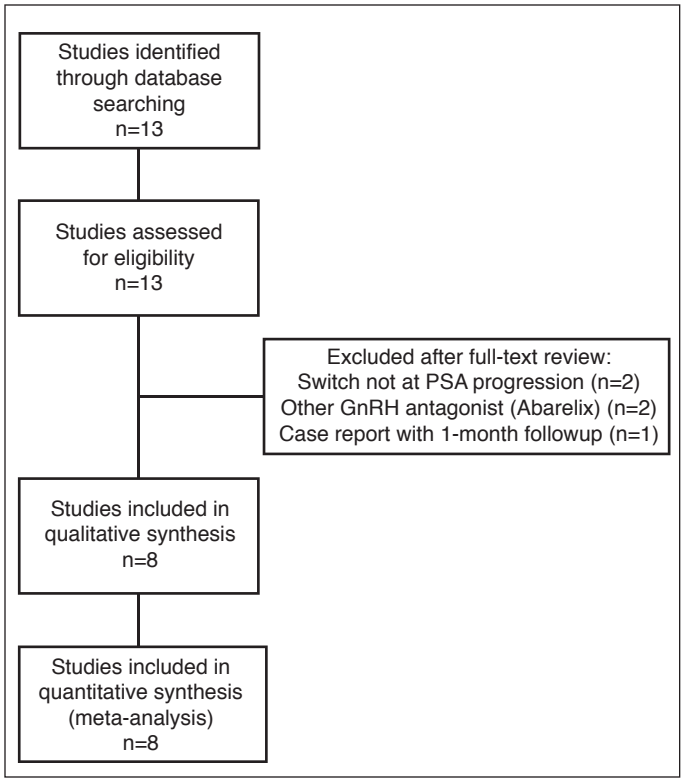


***Supplementary Fig. 1.*** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram outlining the literature search and the included and excluded studies. PSA: prostate-specific antigen. GnRH: gonadotropin-releasing hormone.

**Supplementary Table 1. Proportion of patients with any prostate-specific antigen (PSA) response among included studies and a pooled PSA response rate by random effects meta-analysis and a $I^2$ value for assessment of heterogeneity**

| Study | Sample size | Outcome (events) | Proportion (95% CI) | Heterogeneity ($I^2$) |
|---|---|---|---|---|
| Borsellino et al[17] | 20 | 10 | 50 (19–81) | |
| Casey et al[16] | 40 | 12 | 30 (13–47) | |
| Ezaki et al[10] | 18 | 7 | 39 (10–68) | |
| Fukui et al[11] | 14 | 2 | 14 (0–34) | |
| Masson-Lecomte et al[12] | 17 | 4 | 24 (0–47) | |
| Miller et al[14] | 36 | 8 | 22 (7–38) | |
| Raddin et al[15] | 2 | 2 | 100 (-38–239) | |
| Soga et al[13] | 8 | 5 | 63 (8–117) | |
| **Overall** | **155** | **50** | **27.7 (18.9–36.5)** | **7.90%** |

CI: confidence interval.