

Switching Patients With Prostate Cancer from GnRH Antagonist to Long-acting LHRH Agonist for Androgen Deprivation: Reducing Hospital Visits During the Coronavirus Pandemic

MOTOHIRO FUJIWARA, TAKESHI YUASA, YOSHINOBU KOMAI, RYO FUJIWARA, TOMOHIKO OGUCHI, NOBORU NUMAO, SHINYA YAMAMOTO and JUNJI YONESE

Department of Urology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Abstract. *Aim: To reduce the frequency of the need for hospital visits for patients with prostate cancer (PCa) taking androgen-deprivation therapy during the SARS-CoV-2 (COVID-19) pandemic, we switched them from gonadotropin-releasing hormone (GnRH) antagonist to a long-acting luteinizing hormone-releasing hormone (LH-RH) agonist. Here, we confirmed the efficacy and safety profile of this switching. Patients and Methods: We analyzed the medical records of 32 patients with PCa who received ADT and switched from GnRH antagonist to a long-acting LH-RH agonist during the COVID-19 pandemic, evaluating hematological and serological variables, including serum testosterone and prostate-specific antigen. Results: Before and after the switching from GnRH antagonist to LH-RH agonist, the median serum testosterone levels were 0.22 and 0.18 ng/ml, respectively, and the median serum prostate-specific antigen levels were 0.18 and 0.11 ng/ml, respectively. No changes in the rates of flare-ups of conditions or adverse events were observed. Conclusion: Switching from GnRH antagonist to a long-acting LH-RH agonist appears to be a reasonable option that does not diminish efficacy or exacerbate adverse events.*

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Correspondence to: Motohiro Fujiwara, MD, Department of Urology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Ariake, Tokyo 135-8550, Japan. Tel: +81 358035295, e-mail: motohiro.fujiwara@gmail.com

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The novel coronavirus disease 2019 (COVID-19) pandemic is changing Japanese medical society. In order to minimize the risk of infection among both patients and medical staff, telemedicine is now recommended. Our Institution has accordingly changed its general medical practices by beginning to offer consultations and prescriptions by telephone. We have also sought to enable more virtual and telephone interaction with our patients with prostate cancer during their treatment.

Androgen deprivation therapy (ADT) is the mainstream treatment paradigm for metastatic prostate cancer (1). The fundamental aim of this strategy, maintaining serum testosterone at the castration level (<0.5 ng/ml), can be achieved with or without blockade agents for androgen receptor (1). Some blockade agents, such as bicalutamide, flutamide, enzalutamide, apalutamide, and abiraterone acetate, can be prescribed by telephone. The Japanese medical system allows physicians to send prescriptions for these agents to the patient's nearest pharmacy without requiring the patient to visit the hospital. Other agents, such as the luteinizing hormone-releasing hormone (LH-RH) agonists, leuprorelin acetate and goserelin acetate, and the gonadotropin-releasing hormone (GnRH) antagonist degarelix, must be injected and therefore cannot be sent directly to the patients because the Japanese medical system does not allow patients to inject themselves with these medications.

At present, degarelix is the only GnRH antagonist available in Japan. Although degarelix blocks GnRH receptors in the pituitary gland, resulting in a rapid decrease in the production of testosterone, the effects of degarelix on androgen deprivation last for only 1 month (2, 3). LH-RH antagonists, in contrast, are available in 1-, 3-, and 6-month depot formulations (4-6). Several prospective and retrospective studies have demonstrated that patients can also be safely switched from GnRH antagonist therapy to LH-RH agonist therapy without

Table I. Patient characteristics at the time of switching from gonadotrophin-releasing hormone antagonist to luteinizing hormone-releasing hormone agonist (n=32).

Characteristic		Value
Age, years	Median (IQR)	73 (68-77)
ECOG PS, n (%)	≥2	7 (21.9%)
Gleason score, n (%)	≥8	28 (87.5%)
Prostate-specific antigen, ng/ml	Median (IQR)	0.18 (0.12-0.28)
Testosterone, ng/ml	Median (IQR)	0.22 (0.03-0.93)
Concurrent therapy, n (%)	Yes	25 (78.1%)
	None (ADT monotherapy)	7 (21.9%)
	Bicalutamide	10 (31.2%)
	Flutamide	2 (6.3%)
	Abiraterone acetate	6 (18.7%)
	Enzalutamide	7 (21.9%)
Prior radical prostatectomy, n (%)	Yes	0 (0%)
Prior radiation therapy for prostate, n (%)	Yes	4 (12.5%)
Metastasis, n (%)	Lymph node	21 (65.6%)
	Bone	22 (68.8%)
	Visceral	4 (12.5%)
	Yes	8 (25.0%)

IQR: Interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: prostate-specific antigen, ADT: androgen deprivation therapy.

any adverse clinical or oncological effects (7-10). In order to reduce the frequency of required hospital visits for our patients during the COVID-19 pandemic, we switched them from the GnRH antagonist degarelix to long-acting LH-RH agonists. Here, we report the efficacy and safety profile of this emergent switch in a retrospective pilot study.

Patients and Methods

Patients and treatments. At the initial outbreak of the COVID-19 pandemic, we began offering prescription consultations and sending prescriptions by telephone without blood examinations. Patients were invited to reduce the frequency of their required hospital visits by switching from 80 mg degarelix to a long-acting LH-RH agonist. Here, we reviewed the medical records of 32 Japanese patients who received ADT for prostate cancer at our Institution and who switched from 80 mg degarelix to a long-acting LH-RH agonist at the outset of the pandemic between April and June 2020. To measure patients' hematological and serological variables, including serum tumor markers, prostate-specific antigen (PSA) was usually assessed at least every 1 to 3 months. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (11). This retrospective study was approved by the Institutional Review Board of the Cancer Institute Hospital, Japanese Foundation for Cancer Research (2020-1141).

Statistical analysis. The Wilcoxon signed-rank test was used for comparisons of testosterone and PSA. All statistics are reported as the mean±standard deviation unless otherwise indicated, and *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using JMP software version 12.1 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. Among the patients with prostate cancer who were treated at our Institution during the study period, this study examined 32 who switched from 80 mg degarelix to a long-acting LH-RH in order to reduce the risk of infection with SARS-CoV-2 by minimizing the frequency of hospital visits. Of these 32 patients, 30 (93.8%) switched to 22.5 mg leuprolide acetate, while the remaining two (6.2%) switched to 11.25 mg leuprolide acetate. Patient characteristics and demographic data at the time of this switch are shown in Table I. All 32 patients had previously undergone ADT with a GnRH antagonist and switched to an LH-RH agonist. Moreover, androgen receptor-targeting agents such as bicalutamide, flutamide, enzalutamide, and abiraterone acetate were administered to 25 (78.1%) of these patients. One fifth of all patients demonstrated poor Eastern Cooperative Oncology Group performance status (≥2) (Table I). In addition, at the initial diagnosis with prostate cancer, median serum testosterone and PSA levels were 3.83 ng/ml [interquartile range (IQR)=1.84-4.90 ng/ml] and 135.5 ng/ml (IQR=17.4-620.8 ng/ml), respectively.

Changes in serum testosterone and PSA level upon switching from Gn-RH antagonist to LH-RH agonist. Before the switch from the GnRH antagonist to the LH-RH agonist, the median serum testosterone level was 0.22 ng/ml (IQR=0.12-0.28 ng/ml); after the switch to the long-acting agonist, it was 0.18 ng/ml (IQR=0.10-0.36 ng/ml). this difference was not significant (*p*=0.122, Figure 1A). If castration-level serum

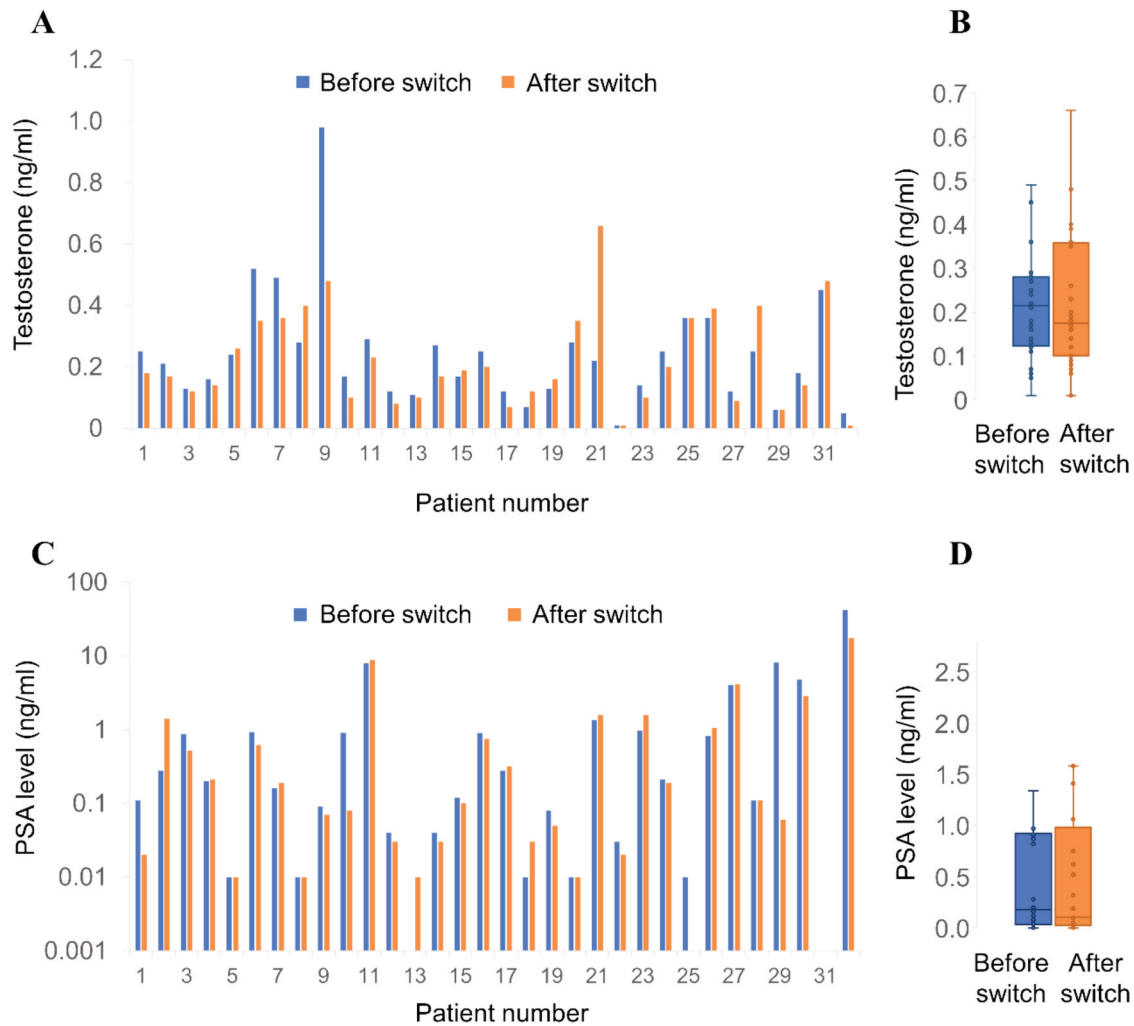


Figure 1. Comparison of serum levels of testosterone (A) and prostate-specific antigen (PSA) (B) before and after switching from 80 mg degarelix to long-acting leuprolerin. Left panels: The serum levels of testosterone and PSA of all 32 patients before and after the switch. Right panels: Box plots of serum of testosterone and PSA levels before and after the switch.

testosterone is defined as ≤ 0.5 ng/ml, one patient (no. 9) had exceeded this level before the switch but achieved it after the switch, while one other patient (no. 21) had achieved castration-level serum testosterone before the switch but exceeded it after the switch. All other patients' serum testosterone levels remained below that threshold both before and after the switch. Thus, the percentage of individuals with testosterone suppression (≤ 0.5 ng/ml) both before and after the switch were 96.9% (31/32). In addition, before the switch from GnRH antagonist to LH-RH agonist, the median serum PSA level was 0.18 ng/ml (IQR=0.03-0.93 ng/ml); three or six months after the switch, it was 0.11 ng/ml (IQR=0.02-0.98 ng/ml). This difference was likewise not significant ($p=0.435$, Figure 1B). In this pilot study, no patient experienced a testosterone surge or a symptomatic prostate

cancer flare-up. Furthermore, to date, none of these patients has contracted COVID-19.

Safety profile of the switch from Gn-RH antagonist to LH-RH agonist. Adverse events such as hot flashes, loss of libido, and fatigue were minimal among all patients. No changes in or flare-ups of any adverse events were linked to the switch to leuprolide. Moreover, all patients reported that they preferred leuprolide to degarelix because of the reduced incidence of injection site reaction.

Discussion

In this retrospective pilot study, we demonstrated the safety profile of switching Japanese patients with prostate cancer

from a GnRH antagonist to a long-acting LH-RH agonist without any impairment of drug efficacy in the context of the COVID-19 pandemic. Most patients (96.9%) achieved a castration-level of serum testosterone, as in previous reports on these drugs (7-10). The 2020 onset of the COVID-19 pandemic required rapid and unprecedented changes to Japanese medical society. Our cancer screening center was temporarily closed; since it reopened, in order to reduce the risk of transmission, the body temperature of all outpatients is measured in front of the hospital before they enter. Any patient with a high body temperature must consult with an Infectious Disease Department and undergo a health check, which sometimes includes a thoracic computed tomographic scan and a coronavirus polymerase chain reaction test. Our Department of Urology has also changed its typical methods by beginning to offer consultations and prescription services by telephone. In addition, in order to reduce the number of hospital visits necessary, patients with prostate cancer were offered the option to switch from a GnRH antagonist to a long-acting LH-RH agonist.

At our Hospital, degarelix is only available in a 1-month depot formulation. The 3-month depot formulation is not used due to an unacceptably high rate of injection site reactions (12). In addition, the efficacy and safety profile of switching from a 1-month depot to a 3-month depot of degarelix have not been confirmed. Therefore, the Japanese medical system does not allow this switch. Because degarelix produces a rapid reduction in serum testosterone without flare-ups, most patients with metastatic prostate cancer at our hospital currently start ADT with degarelix (2, 3).

Regarding the switch from this GnRH to a long-acting LH-RH agonist, several prospective and retrospective studies have previously been reported because many patients prefer the longer-acting formulation as it reduces the number of hospital visits (7-10). Zuckerman *et al.* have reported a prospective, single-arm, open-label trial for the evaluation of a potential testosterone surge during the transition from degarelix to leuprolide (8). In this study, although four out of 45 patients (8.9%) experienced a testosterone surge with a mean peak serum testosterone of 80.7 ng/dl, the level in all of these patients returned to castration level within 7 days of the switch and no patients developed clinical symptoms (8). Miyazaki *et al.* also conducted a prospective study that investigated the efficacy and safety profile of this switch among patients with treatment-naïve prostate cancer (n=40) and who were initially treated with degarelix, then switched to leuprolide within 3 months. Clinical symptoms were not exacerbated either before or after the switch in any patient. Neither significant elevation of PSA level nor exacerbated clinical symptoms were observed in any patient (9). In addition, Asakawa *et al.* compared the survival periods between patients who switched from degarelix to an LH-RH agonist (changed group) and patients who continued with

degarelix treatment (continued group) (10). The overall 5-year survival was statistically superior in the changed group (96.6%) than in the continued group (74.1%) ($p=0.006$) (10). Based on these prospective and retrospective studies, we decided that it would be advantageous to switch our patients from the GnRH antagonist to long-acting LH-RH therapy in response to the COVID-19 pandemic. The present study shows that GnRH antagonist therapy can be safely changed to an LH-RH agonist without any adverse clinical or oncological effects. Therefore, we propose this switch to be a useful measure that the prostate cancer community can take during the COVID-19 pandemic.

The major limitations of our study are that its design was retrospective in nature and that the study cohort was small in size. However, due to the ongoing COVID-19 pandemic, no large, multi-institutional, prospective or retrospective urological study is currently possible in Japan.

In conclusion, based on the data presented in this retrospective pilot study, switching from degarelix to longer-acting leuprolide appears to be a reasonable therapeutic option as it is not linked to any loss of efficacy or the exacerbation of any adverse event. This switch is a useful strategy by which hospitals can reduce the chance of COVID-19 transmission among their patients and staff while also delivering necessary cancer therapy.

Conflicts of Interest

T. Yuasa received remuneration for a lecture from Astellas (Tokyo, Japan). The other Authors declare that they have no conflicts of interest that might be relevant to the contents of this article.

Authors' Contributions

MF and TY contributed to the conception and design of the study; MF contributed to the analysis and interpretation of the data, carried out the statistical analysis, and drafted the article; all Authors contributed to the acquisition of data, critical revision of the article, and approved the final submitted version.

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