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Questionable oncologic benefits of degarelix

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Abstract

Introduction: Luteinizing hormone releasing hormone (LhRh) antagonist degarelix has been approved by the Food and Drug Administration (FDA) for the treatment of advanced prostate cancer in 2008. However, the studies that followed such initial approval have several limitations.

Objective: To make a critical review of those publications.

Methods: Literature search on degarelix.

Results: The studies supporting the use of degarelix are criticized on the basis of selection bias in regards to the heterogeneous populations described, ad hoc analyses with low statistical merit, and the presentation of selected data that would appear to be favorable to the evaluated medication. In addition, those studies still have not shown that any of the data that they point out have any association with clinical benefit.

Conclusion: The flawed methodology of these publications makes the evidence to support the use of degarelix rather weak.

Keywords: LhRh Antagonist; Prostate cancer; Advanced; Hormones

Luteinizing hormone–releasing hormone antagonists like degarelix has potential inherent advantages like avoiding testosterone flare and has been approved by the Food and Drug Administration for the treatment of advanced prostate cancer in 2008 based on a Phase III study showing that degarelix was at least as effective as leuprolide in sustaining castrate levels of testosterone and had a statistically significant faster reduction of testosterone [1].

In such clinical pivotal trial, the primary endpoint was to estimate the cumulative probability of achieving testosterone levels ≤ 0.5 ng/ml at any monthly measurement from day 28 to 364. The authors randomized patients to 3 groups —group 1, received degarelix initial dose of 240 mg and maintenance of 80 mg s.c. per month ($n = 210$); group 2, received degarelix initial dose of 240 mg and maintenance of 160 mg. s.c. per month ($n = 206$); group 3, received leuprolide 7.5 mg i.m monthly ($n = 204$).

At day 3 and 14 of treatment, 96% and 99% of degarelix patients achieved castrate levels of testosterone, compared with 0% and 18% receiving leuprolide, respectively. However, such difference disappeared by day 21 and remained the same throughout a 1-year treatment period among groups. The authors concluded that degarelix was not inferior to leuprolide at maintaining low testosterone levels over a 1-year treatment period [1].

Serum prostate-specific antigen (PSA) levels were also monitored as a secondary endpoint. Serum PSA levels had a faster decrease within the first month of treatment in patients treated with degarelix compared with those receiving leuprolide *alone*; however, such difference was not observed when compared with the subgroup of 22 patients on leuprolide who received concomitant antiflare treatment with an antiandrogen [1]. These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied. In addition, no evidence has shown that the rapidity of PSA decline is related to a clinical benefit.

This initial publication was followed by other 3 studies that utilized the same randomized group of patients to evaluate other secondary endpoints. These subsequent studies have several additional flaws that are herein described.

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After 2 years, a second pivotal study evaluated one of several secondary endpoints of the first study in a separate publication utilizing the same study population [2]. The authors sought to compare the activity of degarelix and leuprolide regarding PSA recurrence-free survival.

A main limitation of this second study analysis was that the population was not suitable to evaluate those secondary objectives. Overall, 31% of the patients had localized disease, 29% had locally advanced disease, 20% had metastatic disease, and 19% had rising PSA after radical prostatectomy or radiotherapy (this group was originally called "not classifiable" in the Table 2 of the first pivotal study [1]). In other words, 80% of the study population had not demonstrated clinical indication of hormone therapy. More so, to whom of those clinical stages would his conclusions be applicable?

The authors of the second pivotal study found that up to 1 year, the risk of PSA progression-free survival (PFS) was significantly lower with degarelix 240/80 mg vs. leuprolide ($P = 0.0495$, log-rank) [2]. However, they only reported and compared the outcomes of groups 1 and 3. There is no information or comparison of clinical outcomes in group 2, except for what can be inferred from the Table where the overall incidence and probability of PSA recurrence or death at 1 year was described [2]. At 1 year, such rate was 10.1% in group 1, 15.3% in group 2, and 17.4% in group 3. Despite having randomized 3 groups, the authors only showed Kaplan-Meier curves for groups 1 and 3, but not for group 2 (degarelix 160 mg) [2].

The PSA recurrence /death rate for both degarelix groups (groups 1 and 2) together was 12.7% at 1 year. When all degarelix patients are included (both groups 1 and 2), the PSA/death event incidence difference between degarelix and leuprolide decreases from 7.3% to 4.7%, i.e., a 36% loss in difference between the 2 treatments.

The second pivotal study concluded that at 1 year, PSA PFS was superior in the degarelix arm than the leuprolide arm. This might have been the case, but only selected data were presented as the results of only half of the degarelix patients was reported. In addition, few absolute numbers of events drove the conclusions of that analysis.

After 1 year, a third pivotal study [3] compared PSA PFS of degarelix treatment and the effects of switching from leuprolide to degarelix in an ongoing extension study with a median 27.5-month follow-up. Patients who completed the prior study (CS21) were offered the option of entering the open label, multicenter extension trial. Patients who initially received degarelix 80 mg (group 1) continued with the same monthly maintenance dose. Those who previously received leuprolide 7.5 mg were re-randomized (1:1) to a degarelix 240 mg starting dose, followed by monthly doses of 80 or 160 mg. Upon receiving regulatory approval of degarelix 240/80 mg on December 24, 2008, patients re-randomized to the 160-mg dose were switched to the approved 80-mg dose.

At 27.5 months' median follow-up, hazard rate of PSA PFS significantly decreased in leuprolide patients switched to degarelix compared with before the switch (0.20 vs. 0.08; $P = 0.003$). The authors found a significant PSA PFS hazard change, from 0.20 events/year in the first year to 0.09 following the switch in leuprolide patients ($P = 0.006$) [3].

Again, a potential patient selection bias is identified in the study population. Only 134 of 204 patients receiving leuprolide accepted crossing over to degarelix. Of these 134, 62 discontinued degarelix switch because of adverse events, thus 72 of 204 (35%) of group 3 patients finally continued in the study. Only 74 of the 210 patients belonging to group 1 continued in the study (35%) [3].

In addition, authors found that PSA PFS in patients with PSA $>$ 20 ng/ml at baseline had a significantly lower hazard rate after switch to degarelix ($P = 0.031$) assuming that PSA was the only driving force of disease severity, rather than Gleason score, stage, etc. It is unclear what proportion of patients with PSA $>$ 20 ng/ml had localized, locally advanced, metastatic disease or rising PSA after radical prostatectomy or radiotherapy [3].

Similarly to what happened in the second pivotal study [2], findings in the third pivotal study could have been clearly influenced by patient selection bias, and may have been wholly unrelated to treatment effect. Conclusions were based in a low number of events and no effect on survival was demonstrated. Of note, there was no information of the outcome of the 206 patients receiving degarelix 160 mg. s.c. per month (group 2) [3].

In 2014, a fourth pivotal study [4] utilized the same study population (with the same aforementioned biases) to "demonstrate the safety and efficacy of up to 5 years of degarelix treatment and the effects of crossing over from leuprolide to degarelix." Unfortunately, only 48% of the patients who continued on degarelix 240/80 mg and 40% of those who crossed over from leuprolide to degarelix completed the study [4], i.e., less than a third of the originally randomized patients in the first pivotal study [1].

The authors [4] concluded that "over the 5-year period, degarelix resulted in improved PSA PFS compared with leuprolide"; however, the authors failed to show the Kaplan-Meier curves for those patients who continued on leuprolide over the same time period. In other words, they assume that degarelix has better efficacy than leuprolide over 5 years without having a leuprolide arm followed over the same time period.

Interestingly, the authors still failed to show the oncologic outcomes of group 2 (degarelix initial dose of 240 mg and maintenance of 160 mg). Notwithstanding, they did show the incidence of treatment-related adverse events of group 2 in the Table of such article to demonstrate similar toxicity profile to the other 2 groups, meaning that group 2 actually exists [4,5]. In other words, the authors showed their adverse event profile but still failed to show their oncologic outcome [4].

Other authors [5] declared certain cardiovascular safety of degarelix in men without prior cardiovascular disease. More recently [6], an e-poster was presented at the 2015 SIU annual meeting in Melbourne showing less