Utility of LHRH antagonists for advanced prostate cancer

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Introduction: *Androgen deprivation therapy (ADT) is the lynchpin of treatment for advanced prostate cancer. Prescribing physicians and patients have a choice between orchiectomy, luteinizing hormone releasing hormone (LHRH) agonists, combined androgen deprivation (CAD) or LHRH antagonists.*

Materials and methods: *Literature relating to the use of LHRH antagonists in the management of prostate cancer was reviewed.*

Results: *Abarelix was the first-in-class LHRH pure antagonist that was Food and Drug Administration (FDA) approved in 2003. Due to a variety of concerns including hypersensitivity reactions it was withdrawn from the United States (U.S.) market in 2005. The only currently commercially available LHRH antagonist in the U.S. is degarelix available as a once-a-month depot injection. The potential clinical advantage of degarelix compared to the LHRH agonists is the very rapid and sustained testosterone suppression with no identifiable physiological or clinical testosterone surge or flare. The main disadvantage of degarelix compared to the LHRH agonists is the monthly dosing and the inconvenience for some patients and practices. Recent studies tout improved disease control for degarelix compared to monthly leuprolide acetate; however, these results remain controversial.*

Conclusions: *The rapid T-suppression achieved with degarelix may provide a clinical benefit for various groups of men with advanced or locally advanced disease.*

Key Words: degarelix, LHRH, abarelix, antagonists, prostate cancer, hormonal therapy, androgen deprivation

Introduction

For most of the last 25 years, hormone therapy (HT) or androgen deprivation therapy (ADT) for treatment of advanced prostate cancer has been based on luteinizing hormone releasing hormone (LHRH) agonists, such as leuprolide acetate or goserelin acetate.[1] LHRH agonists traditionally have been considered equivalent to bilateral orchiectomy in terms of reported testosterone suppression. Since the late 1980's another ADT strategy is combination of the LHRH agonist with an oral non-steroidal antiandrogen. Called "combined androgen blockade" (CAB) or "maximal androgen blockade" (MAB) the oral agents used include bicalutamide, flutamide, or nilutamide.[2] This combined treatment has remained controversial since its inception with some clinicians endorsing it's use and others concluding that the modest survival benefit does not outweigh the potential for increased side-effects from using two hormonal medications rather than one.

The challenge with LHRH agonists, even when administered as CAB in combination with an antiandrogen, is the possibility of periodic testosterone surges, flares and micro-surges. Gonadotropin releasing hormone (GnRH) receptor antagonism with agents such as abarelix (no longer commercially available) or degarelix represents a class of treatment that acts via immediate and competitive blockade of pituitary GnRH receptors, directly blocking release of both LH and follicle stimulating hormone (FSH).[3-6] The LHRH agonists work primarily by the competitive blockade of LH while degarelix can be classified as a GnRH antagonist since it blocks both LH and FSH. However it is recognized that the primary clinical application in prostate cancer is the LHRH antagonism. With no LH available to stimulate production of testosterone, the result is rapid testosterone suppression without an initial stimulation of the hypothalamic–pituitary–gonadal axis and the testosterone surge associated with LHRH agonists,

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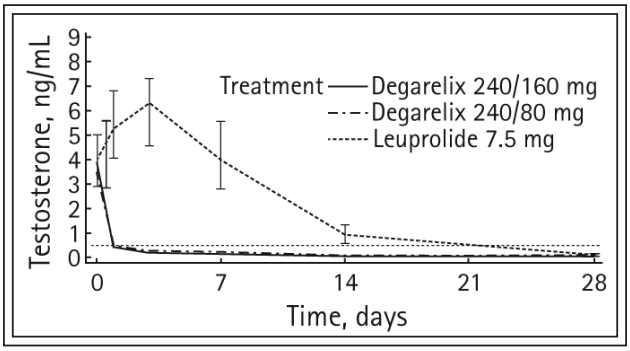

Figure 1. Comparison of serum testosterone levels during first 28 days of degarelix versus leuprolide in the Klotz et al pivotal phase III clinical trial which formed the basis for FDA approval of degarelix. Note the testosterone surge in the leuprolide patients (dotted line) compared to the rapid testosterone suppression in the degarelix treated patients. This is the key clinical data supporting degarelix use in clinical practice.[5] Reprinted with permission.

Figure 1. This mode of therapy avoids any need for concomitant antiandrogen flare protection although some clinicians prefer to continue to use oral antiandrogens even with degarelix for chronic adrenal androgen blockade.

Abarelix

Abarelix was the first-in-class LHRH pure antagonist that was Food and Drug Administration (FDA) approved in December 2003 to treat advanced prostate cancer.[3] While very effective at inducing a very rapid lowering of serum T, it was found to cause a hypersensitivity reaction in a very small percentage of patients and received a "Black Box Warning" from the FDA in late 2004. Shortly thereafter in early 2005, it was discontinued from the United States (U.S.) market. The remainder of this chapter will refer to degarelix since it is the only agent in the class that is currently FDA-approved and commercially available.

FDA approval of degarelix

A second-in-class pure LHRH antagonist, degarelix, was FDA-approved in December of 2008.[5] Now with over 5 years of clinical use, degarelix has not been associated with any serious adverse events and has steadily gained some market share as a parenteral ADT agent. More recent follow up of the degarelix pivotal phase III trial in which the agent was compared to monthly leuprolide suggests that it may be more effective than leuprolide for patients with metastatic disease at study entry.[7-9]

Degarelix (Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(L-hydrorootyl)-D-4Aph(carbamoyl)-Leu-Ilys-Pro-D-Ala-NH_2) is a synthetic, linear decapeptide amide analogue of endogenous GnRH. This compound is produced by insertion of seven exogenous amino acids, five of which are D-isomer amino acids. Degarelix binds to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone, and importantly this binding is reversible.

The initial dose-finding studies with degarelix suggested that 240 mg appeared to be the optimal starter dose, as this regimen resulted in castrate testosterone levels in > 96% of patients within 3 days. This led to a 1 year, multicenter, randomized, open-label, parallel-group, phase III trial (CS21) designed to demonstrate the statistical non-inferiority of degarelix versus the LHRH receptor agonist leuprolide.[5] This trial enrolled 610 patients with all stages of histologically confirmed prostate cancer and eligible for ADT. The study randomized patients to a starter dose of 240 mg sc degarelix followed by monthly maintenance doses of either 80 mg (240/80 group, n = 207) or 160 mg (240/160 group, n = 202) or to monthly leuprolide depot 7.5 mg im (n = 201). For the patients in the LHRH receptor agonist group, CAB with an antiandrogen could be added at the investigators' discretion.

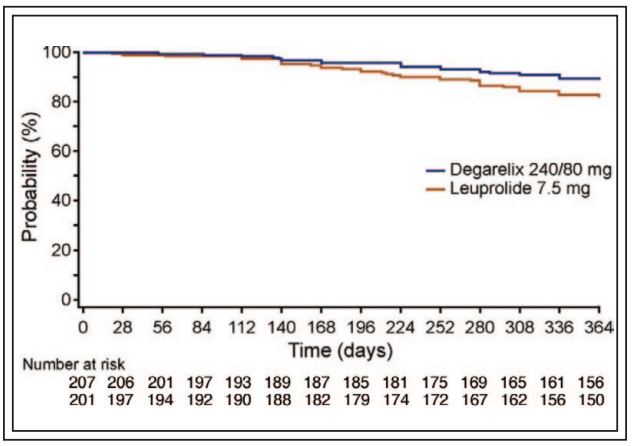

Figure 2. In follow up of the Klotz et al phase III RCT comparing degarelix versus monthly leuprolide, the disease-free survival in the patients with metastatic disease was statistically improved for degarelix-treated men compared to leuprolide-treated man at 1 year follow up. This data is in the peer reviewed literature (Tombal et al) however, the findings remain controversial. It is intriguing but must be considered hypothesis generating and is not considered valid level I evidence.[8] Reprinted with permission.

In the degarelix groups, median LH and FSH levels decreased rapidly and remained suppressed until the end of the study, whereas as expected LH and FSH levels showed an initial increase for patients in the leuprolide group, and FSH levels did not fall to the same extent as they did in the degarelix arms. In parallel with the testosterone results, the data for prostate-specific antigen (PSA) reduction showed a statistical difference at 7, 14, and 28 days, with significantly greater suppression than in the leuprolide group, and this finding correlated with a significantly lower risk of PSA failure or death. However by 1 year overall survival did not differ significantly between the degarelix 240/80 mg group and the leuprolide group (probability of death at 1 year, 2.6% versus 4.9%, respectively, NS). On the basis of these findings, the U.S. FDA approved degarelix injection on December 24, 2008 as a treatment of patients with advanced prostate cancer.

When the trial was extended beyond 1 year, the higher percentage of patients on degarelix versus leuprolide having a PSA of < 4 persisted out to about 73 weeks, Figure 2. It is important to note, however, that the patients on leuprolide were allowed to switch to degarelix after 52 weeks, with the result that between weeks 52 and 73, the curve for progression-free survival in patients on leuprolide converged with that for patients on degarelix. Therefore, by the end of the follow up period the progression-free survival results were essentially equivalent in the two arms, Figure 3.

This prostate-specific antigen (PSA) progression-free survival comparison remains very controversial especially in light that the primary endpoint of T non-

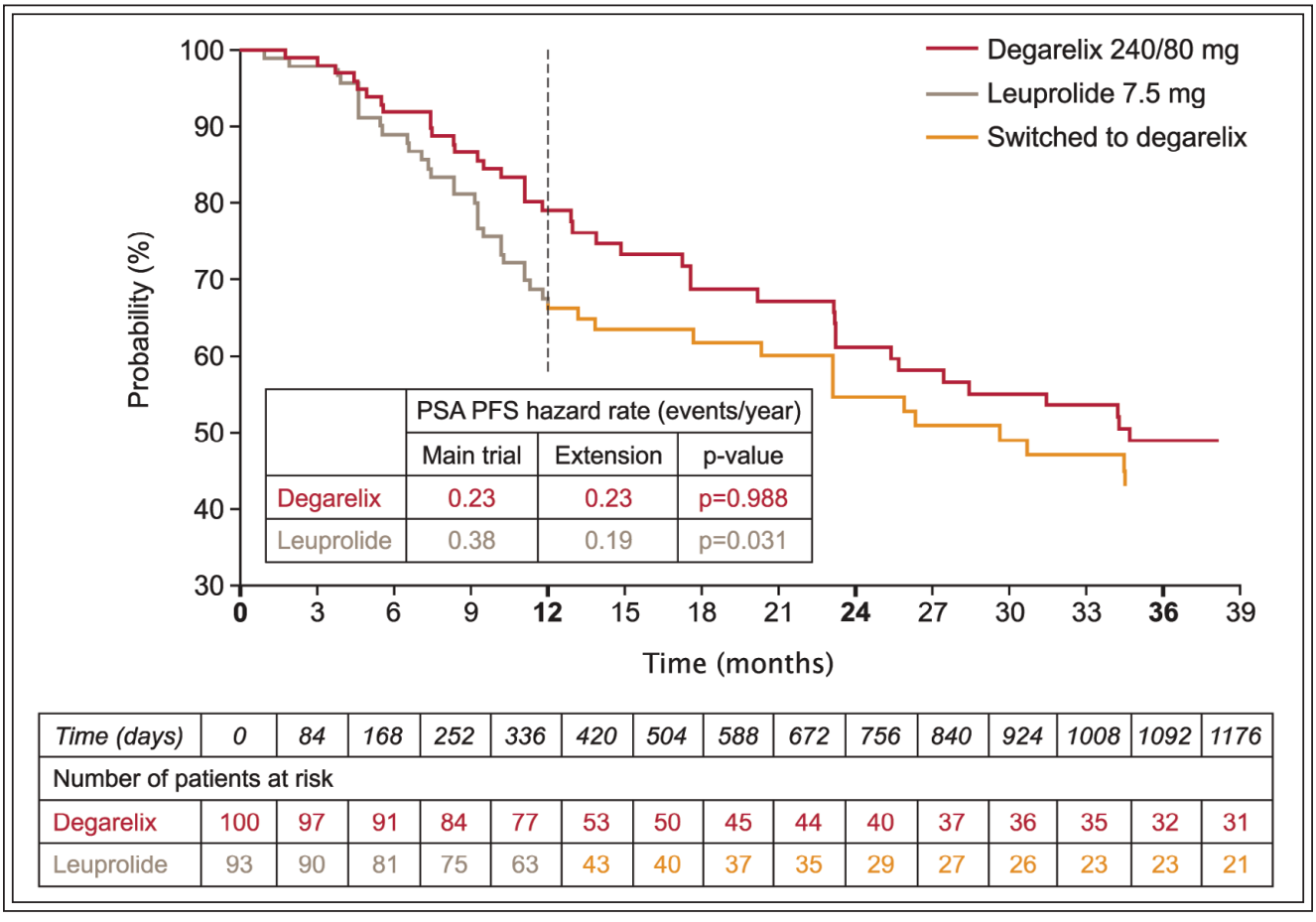

Figure 3. In the long term follow up extension study of the pivotal Klotz et al phase III RCT, the patients in the leuprolide arm could be switched to degarelix at the 1 year point (marked by the vertical dotted line). This switch from leuprolide to degarelix resulted in the survival curves converging at approximately 3 year follow up. Crawford et al suggest in the peer reviewed publication of this data that this implies that degarelix may be more effective than leuprolide. While intriguing and hypothesis-generating, this was not a pre-planned analysis and it remains speculative if degarelix is truly more effective than a comparable LH-RH agonist based on this data.[7] Reprinted with permission.

inferiority was met and in fact testosterone suppression beyond the first 28 days was similar between all three groups. A number of proposed theories to possibly explain the difference is worthy of mention such as initial rapid PSA suppression, lack of mini-flares of T with each injection, and better FSH suppression with degarelix. There are ongoing trials in Europe and North America with respect to the possible utility of degarelix in intermittent ADT. These trials may also shed more light on PSA suppression, micro surges and FSH suppression.

A final difference comparing LHRH agonists and degarelix has recently emerged- cardiovascular event rates. In the pooled global trials of degarelix recently presented by Albertsen et al, there was a substantially lower cardiovascular event rate in patients treated by degarelix.[10] This phenomenon is likely to cause significant controversy but also worthy of mention given the large patient population (pooled global trials) from which the data is obtained. Similar the findings of improved PSA control, such a finding is difficult to explain on the surface given that in general, cardiac events are felt to be exacerbated by the lowering of testosterone and in the case of degarelix, this happens at an initially faster but nonetheless there appears to a 50% decrease in cardiac events.

Clinical uses of degarelix

In theory if testosterone is lowered to castrate levels more rapidly, a patient might achieve clinical benefit more rapidly. There are certain clinical situations where degarelix is preferred or even mandated over LHRH agonists. In patients who present with metastatic prostate cancer and impending spinal cord compression, ureteral obstruction due to adenopathy or severe bone pain, the use of degarelix is of obvious utility as it avoids clinical testosterone surge or flare. In fact, LHRH agonists are specifically contraindicated in these clinical situations and either immediate orchiectomy, oral ketoconazole or degarelix would be mandated. Most patients do not desire orchiectomy and oral ketoconazole may not be properly absorbed in this acute setting making degarelix the preferred agent.

Beyond the above ideal use of degarelix, there are other clinical scenarios where clinicians might prefer degarelix over the traditional agonists. Since there is no testosterone flare/surge, some physicians prefer to start all patients on degarelix and then to switch the patient to a longer acting LHRH agonist after 2-12 months. Garnick et al showed that this practice was safe for abarelix and many clinicians extrapolate this finding to switching with degarelix.[6,11] This clinical switching is done due to the main clinical disadvantage of degarelix: the drug is currently only available as a 1 month depot injection. It is likely that if degarelix or another future GnRH pure antagonist was available in a longer acting depot (such as 3 to 6 month depot), the switching would become unnecessary.

The long term follow up of the original Klotz et al clinical trial suggest that degarelix may be more effective than monthly leuprolide acetate.[7-9] However, the cancer control outcome comparisons of degarelix versus leuprolide were not pre-specified as primary endpoints in the original Klotz et al pivotal trial so it is unclear if degarelix truly offers a survival benefit compared to LHRH agonists. If a clinician in practice feels that degarelix is more effective than LHRH agonists, then it opens clinical use to any/all patients who are placed on traditional ADT, such as high risk biochemical recurrence, newly diagnosed men with M1 disease, and in neoadjuvant/adjuvant settings. I believe it is reasonable to educate men about the option for long term degarelix noting the possible efficacy advantage versus the convenience disadvantage. In my experience, some men may want to avail themselves of the possible improved disease control and not be concerned about the monthly visits for injections. Other men choose convenience and desire longer acting depot agonists and forgo the possible efficacy difference.

In the specific setting of neoadjuvant hormonal therapy (NHT) use prior to the start of radiation, we know that degarelix provides more rapid PSA reduction over the first 56 days of use compared to monthly leuprolide in the Klotz et al clinical trial. If we believe that PSA is a general surrogate for cancer activity and prostate size, some clinicians may prefer degarelix over an agonist in this early phase. Furthermore, there is some evidence that PSA nadir while on NHT before the start of external beam radiotherapy (EBRT), predicts disease-free outcome. This would imply that using an agent with rapidity, such as degarelix, will have a better chance of lowering the PSA more robustly before radiation and might result in better long-term disease control. While speculative, there is little downside of considering degarelix for the first few months of NHT. Furthermore, in a case of intermediate risk disease where the total duration of NHT is going to be 4-6 months, there is minimal patient and physician office inconvenience of using a monthly depot for this relatively brief duration.

In addition, more rapid downsizing facilitated by the more rapidly acting degarelix might facilitate more rapid surgical scheduling in selected men with large glands prior to brachytherapy. Likewise, in the radical prostatectomy patient, there may be clinical situations where NHT is used for technical reasons. For example, NHT may also be used for prostate size considerations

or in the case of clinic T3/T4 disease where the clinician is trying to shrink the gland to facilitate a technically less-demanding operative experience. In these cases, some surgeons use degarelix in the hopes of a more rapid response.

In the setting of intermittent hormonal therapy (IHT), it is unclear if degarelix offers any advantage to the traditional LHRH agonists. There is no level I evidence to support degarelix in this setting. However, some clinicians feel the rapidity of onset may be of advantage for the first (and possibly subsequent) "on" cycles. While there have been many nuances to IHT use, most of the phase III trials have used a 6-9 month initial "on" cycle of ADT therapy. The basis for this initial duration of therapy was the time to PSA nadir on ADT. For the typical patient with M1 disease, it will take approximately 7 months to reach PSA nadir and the clinicians who designed the IHT trials felt that nadir PSA should be achieved before starting the "off" cycle. It is theoretically possible that the more rapid testosterone and PSA decline with degarelix would be an advantage to using degarelix. Furthermore, some clinicians feel that return of testosterone levels during the "off" cycle may be more rapid with degarelix compared to leuprolide and favor its use. Again, there is no level I evidence for degarelix over LHRH agonists in IHT and the concepts described are speculative.

Cost considerations

In most clinical settings, degarelix is comparably priced to commercially available branded LHRH agonists. As a result, if a prescribing physician believes there is a clinical benefit of degarelix over LHRH agonists, there would be no or little cost/price disincentive to use this agent. Two recent pharma-economic analyses have demonstrated cost effectiveness.[12,13] However, the office overhead costs, personal costs, patient travel and lost work costs of patients being seen monthly must also be considered. In my practice setting of a hospital-based clinic tertiary cancer center, many monthly patient visits for degarelix are "nurse-only" visits which does not generally impact physician workflow. However, in the first few months of administration, especially for men with more advanced disease and/or other comorbidities, the visits for degarelix also entail a provider visit which may be with a physician or an advanced practice provider.

Conclusions

Degarelix is a second-in-class pure GnRH antagonist that physiologically produces a very rapid reversible surge-free testosterone blockade. Available in the U.S. since December of 2008, it is a monthly depot androgen deprivation agent FDA-approved to treat men with advanced prostate cancer. The pivotal phase III clinical trial comparison to monthly leuprolide acetate showed equivalency in maintaining serum testosterone levels below 50 ng/dL (traditional castrate level). However, degarelix effect was much more rapid than leuprolide with over 95% of men achieving castrate testosterone within 72 hours and an overall benefit of testosterone lowering over the first 28 days of use. Longer term follow up studies of the pivotal trial patients suggest that degarelix may be more effective than leuprolide, but these data remain controversial. Various clinical situations were discussed where degarelix might be considered over agonist use. The main disadvantage of degarelix is the sole monthly depot dosing. Clinicians generally have to discuss efficacy and convenience issues with their patients when making a decision on androgen deprivation therapy.

Disclosure

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