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Firmagon: Re-designing Medical Castration?

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Since the innovative work of Charles Huggins, androgen deprivation therapy (ADT) is the main systemic therapy for advanced prostate cancer (PCa). Initially achieved by surgical castration or estrogens, ADT is today most often obtained by Luteinizing Hormone Releasing Hormone agonist (LHRHa). LHRHa compete with natural LHRH in binding to the pituitary receptor and suppressing the production of the luteinizing hormone (LH) and, subsequently, the secretions of testosterone (T) by the testes. Because they are agonists, initial exposure to LHRHa first causes an increase in LH and T before desensitizing the receptor so that the onset of ADT is delayed by about 3 to 6 weeks. Patients with advancing symptomatic PCa may experience transient worsening of symptoms and in dramatic but rare cases potentially lethal complications.

Degarelix is a LHRH-receptor antagonist (blocker) that immediately blocks the LHRH receptor in the pituitary, resulting therefore in a fast and sustained suppression of LH without initial stimulation [1]. The efficacy and safety of degarelix has been tested against leuprolide in a 1-year phase III trial [2]. A total of 610 patients with PCa (any stage; median age 72 years; median PSA 19.0 ng/mL) was randomized into 3 arms: degarelix one subcutaneous 240 mg starting dose followed by monthly maintenance doses of 80 mg or 160 mg for a total of 12 months, or intramuscular monthly leuprolide 7.5 mg. The primary endpoint of the trial, defined by FDA and EMEA, was suppression of testosterone to ≤ 0.5 ng/mL at all monthly measurements from day 28 to day 364, thus defining the treatment response. This was achieved by 97.2 %, 98.3 %, and 96.4 % of patients in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively (ITT population). At 3 days after starting treatment, testosterone levels were ≤ 0.5 ng/mL in 96.1 % and 95.5 % of patients in the degarelix 240/80 mg and 240/160 mg groups, respectively, and in none in the leuprolide group. No transient testosterone surge was seen in the degarelix arm, in contrast to leuprolide. The median PSA levels at 14 and 28 days were significantly lower in the degarelix groups than in the leuprolide group ($p < 0.001$). The hormonal side-effect profiles of the 3 treatment groups were similar to previously reported effects for androgen-deprivation therapy. The s.c. degarelix injection was associated with a higher rate of injection site reactions than with the i.m. leuprolide injection (40 % vs < 1 %; $p < 0.001$, respectively). There were no systemic allergic reactions seen with degarelix. Based on this study, the dose of 240/80 mg was chosen and then registered by FDA and EMEA.

More interestingly, and less expected, pre-planned sub-analysis showed degarelix to be significantly superior to leuprolide in decreasing the rate of PSA and alkaline phosphatase failure, especially in patient with the most advanced cancers. The first analysis focused on PSA progression-free survival (2 consecutive increases in PSA of 50 % compared with nadir and ≥ 5 ng/ml on 2 consecutive measurements at least 2 wk apart or death) [3]. Patients receiving degarelix showed a significantly lower risk of PSA progression or death compared with leuprolide ($p = 0.05$). PSA recurrences occurred mainly in patients with advanced disease and exclusively in those with baseline PSA > 20 ng/ml. Patients with PSA > 20 ng/ml had a significantly longer time to PSA recurrence with degarelix ($p = 0.04$). The second analysis has been focused on alkaline phosphatase (S-ALP) [4]. Baseline S-ALP levels were higher in metastatic patients. In metastatic disease, after initial peaks in both groups, S-ALP levels were suppressed below baseline with degarelix but were maintained around baseline with leuprolide. The late rise in S-ALP seen with leuprolide was not apparent with degarelix. The pattern of S-ALP response was similar in patients with a baseline PSA level of ≥ 50 ng/mL. Between-treatment differences in patients with metastatic disease and those with a PSA level of ≥ 50 ng/mL were significant at day 364 ($p = 0.014$ and 0.007, respectively).

Patients with metastatic disease or those with PSA levels of ≥ 50 ng/mL at baseline had greater reductions in S-ALP levels with degarelix than with leuprolide. Patients in the degarelix group maintained S-ALP suppression throughout the study, in contrast to those in the leuprolide group.

These data were confirmed in a study extension (CS21a) in which patients receiving degarelix were allowed to crossover to degarelix [5]. This pinpoints at an additional benefit of LHRH antagonists, beyond the initial flare suppression.

Literature:

1. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 2008; 102: 1531–8.

2. Van Poppel H, Tombal B, de la Rosette JJ, et al. Degarelix: a novel gonadotropin-releasing hormone (GnRH) receptor blocker-results from a 1-yr, multicentre, randomised, phase 2 dosage-finding study in the treatment of prostate cancer. Eur Urol 2008; 54: 805–13.

3. Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol 2010; 57: 836–42.

4. Schroder FH, Tombal B, Miller K, et al. Changes in alkaline phosphatase levels in patients with prostate cancer receiving degarelix or leuprolide: results from a 12-month, comparative, phase III study. BJU Int 2010; 106: 182–7.

5. Crawford ED, Sartor O, Chu F, et al. A 12-month clinical study of LA-2585 (45.0 mg): a new 6-month subcutaneous delivery system for leuprolide acetate for the treatment of prostate cancer. J Urol 2006; 175: 533–6.

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