coding SNPs highly associated with the disease. Whilst at first this may appear to be disappointing, many positive findings can be elicited. First, these data suggest that a familial bladder cancer gene does not exist. Second, the modest risk attributed to the SNP suggests that environmental factors are far more important than genetic factors for bladder cancer (changing behaviour could reduce burden). Third, one can identify homozygous individuals at whom to target health promotion. Finally, these findings potentially point to new methods of genetic susceptibility. Studies in breast, colon, and prostate cancer (referenced in Ghoussaini et al [3]) have all identified SNPs within the 8q24 region that predispose to their respective cancers. Why these tumours all share this region, in which there are few genes, is unclear. Could this region mark a distant genetic event or represent part of the machinery of an unknown molecular control mechanism?

Conflicts of interest: The author has nothing to disclose.

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DOI: 10.1016/j.eururo.2009.03.038

Re: The Efficacy and Safety of Degarelix: A 12-Month, Comparative, Randomized, Open-Label, Parallel-Group Phase III Study in Patients with Prostate Cancer

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BJU Int 2008;102:1531–8

Experts' summary:

This study is the first published phase 3 trial on degarelix, a gonadotropin-releasing hormone (GnRH) antagonist for the treatment of advanced prostate cancer. Between February 2006 and October 2007, a total of 620 patients with prostate cancer of various stages were randomized to receive degarelix 240 mg subcutaneously (SC) followed by 80 mg SC every 4 wk (arm A) or degarelix 240 mg SC followed by 160 mg SC every 4 wk (arm B) or leuprolide 7.5 mg by intramuscular injection (IM) every 4 wk (arm C) for a total study period of 1 yr.

The primary end point (ie, testosterone suppression to a predefined castrate level of $\leq$0.5 ng/ml from day 28 to day 364) of this noninferiority open-label trial was reached in 96–98% of patients without a difference between the study groups. Results for a total of 14 different secondary end points also showed comparable results with a few exceptions. As expected, testosterone and prostate-specific antigen (PSA) in arms A and B declined earlier compared with arm C. At day 3, the predefined castration level was reached in 96.1% and 95.5% of patients in arms A and B, respectively, while patients in arm C demonstrated a testosterone elevation of 65% from baseline. At days 14 and 28, PSA levels had respectively declined by 64% and 85% in arm A, by 65% and 83% in arm B, and by 18% and 63% in arm C. While most adverse events were comparable among the study groups, 40% of patients receiving degarelix experienced pain at the injection site compared with $<$1% in the leuprolide group. Additionally, 4% of patients experienced chills following the application of degarelix compared with zero in the leuprolide arm.

Experts' comments:

For a long time, GnRH antagonists demonstrated insufficient water solubility and induction of allergic reactions [1]. Indeed, the first approved GnRH antagonist, abarelix, was associated with systemic allergic reactions in 1–3% of patients. Degarelix does not seem to be associated with this problem.

Degarelix ran through various phase 1 and 2 trials, and dose finding was a major goal of these trials [2]. Now, the ideal dose seems to be known and noninferiority to leuprolide could be demonstrated in the discussed trial. Despite so many end points in this trial, progression-free survival, cancer-specific survival, and overall survival were not addressed.

In theory, rapid suppression of testosterone and a fast PSA decline is clearly positive, but its impact on the outcome may be rather small in practice.

About 40% of patients experienced pain at the SC injection site of degarelix compared with <1% at the IM injection site of leuprolide. Why is the application of degarelix that painful? One explanation could be that the injected volume is rather high. In fact, 3×2 ml are injected to apply the initial dose of 240 mg degarelix. Is the pain associated with the injection of degarelix really clinically relevant? Well, you may ask your patient!

In December 2008, degarelix was approved for the treatment of advanced prostate cancer by the US Food and Drug Administration and its approval by the European Medicines Agency has been recommended. Degarelix is given at a dose of 240 mg SC followed by 160 mg SC every month. It is a clear disadvantage that degarelix is currently not available as a 3-mo formulation.

If efficacy and side effects of GnRH antagonists would be comparable to GnRH agonists, then the price of the drugs is an even more relevant criterion; however, the price of degarelix and its relation to the cost of other drugs are currently unknown.

Finally, hormonal therapy of patients with prostate cancer is currently questioned due to its limited impact on cancer-specific and overall survival in certain clinical scenarios and its associated side effects. In the absence of prospective data, the American Urological Association has not recommended the use of hormonal therapy as a primary approach in patients with localized prostate cancer [3]. In a population-based cohort study of 19 271 patients >65 yr old, it was recently demonstrated that cancer-specific survival in patients receiving hormonal therapy ($n = 7{,}867$) was 80.1% compared with 82.6% (hazard ratio (HR): 1.17; 95% confidence interval (CI): 1.03–1.33) in patients receiving conservative therapy ($n = 11\ 045$), defined as not receiving operative therapy, radiotherapy, or hormonal therapy within 180 d from diagnosis [4]. In terms of side effects, there is growing evidence that hormonal therapy is associated with an increased risk of cardiovascular disease and diabetes [5]. In an observational study of a population-based cohort of 73 196 patients with prostate cancer who were >65 yr old, the use of a GnRH agonist (in 36.3% of all patients) was associated with an increased risk of incident diabetes (adjusted HR: 1.44; $p < 0.001$), coronary heart disease (adjusted HR: 1.16; $p < 0.001$), myocardial infarction (adjusted HR: 1.11; $p < 0.03$), and sudden cardiac death (adjusted HR: 1.16; $p < 0.003$).

With respect to the latter discussion, the potential advantages of degarelix seem to be limited.

Conflicts of interest: The authors have nothing to disclose.

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DOI: 10.1016/j.eururo.2009.03.039