Analysis of testosterone suppression in men receiving histrelin, a novel GnRH agonist for the treatment of prostate cancer

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Background: *Androgen deprivation therapy (ADT) is the standard care in men with advanced prostate cancer. Continuous testosterone suppression is essential to treatment efficacy. Recently a 1 year depot compound histrelin, (VANTAS; Orion Pharmaceuticals, Finland; Endo Pharmaceuticals, USA), a gonadotropin-releasing hormone (GnRH) analog, was approved for hormone therapy of prostate cancer. In the present study the therapeutic efficacy of this compound was investigated, in addition to its impact on testosterone values and velocity as well as PSA.*

Method: *One hundred thirty-one patients with histologically confirmed prostate cancer and normal testosterone levels were prospectively evaluated over 1 year. Androgen deprivation therapy was performed using a once yearly implant of the GnRH agonist histrelin. Testosterone and PSA levels, and histrelin serum profile were measured prospectively every month for 1 year. In addition, patients were stratified according to their PSA results and D'Amico risk profile.*

Results: *Testosterone suppression (testosterone ≤ 50 ng/dL) was measured in all patients between weeks 4 and 52; 88% of patients had a continuous testosterone level under 20 ng/dL. The PSA level in the total population decreased significantly within the first 2 weeks compared with baseline, and after 52 weeks the median PSA level of the total population was 0.2 ng/mL. PSA responses were grouped into three typical therapeutic outcomes and correlated with the clinical risk distribution, and levels were lowered in all three risk groups.*

Conclusion: *The GnRH agonist histrelin successfully suppressed testosterone over the entire study period. This effect was measured across a number of different clinical definitions of PSA response and clinical risk. The GnRH agonist therefore offers an effective therapy option in hormone treatment of prostate cancer.*

Key Words: prostate cancer, hormone therapy, histrelin, testosterone, prostate-specific antigen

Introduction

Hormone therapy is the most common treatment regimen for advanced or metastatic prostate cancer. Other indications for systemic androgen deprivation are second-line therapy in systemic relapse after curative treatment, and neoadjuvant therapy in high risk cancer. Antiandrogens, GnRH antagonists, and GnRH analogs are additionally available for hormone therapy.

Androgen deprivation therapy (ADT) takes on a particular significance and importance among other therapeutic treatments, since not only is a high risk event involved in the medical decision to perform ADT, but the decision is often made when curative therapy is no longer possible. Considering the palliative character of ADT and possibility of treatment-induced adverse effects, other treatment strategies are regularly pursued. This is to ensure optimal therapeutic benefit while simultaneously maintaining the best possible patient quality of life.

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Within the field of GnRH agonists, the therapy regimen includes intermittent androgen blockade[1,2] and PSA progression-guided androgen deprivation. These strategies are particularly important to patients in relation to the management of adverse events during treatment, and as antihormonal therapy must be classified as a long term treatment among the other treatments of prostate cancer.

Initial exposure to GnRH treatment produces a flare response in the first 7 to 10 days of treatment, with a surge in the pituitary release of LH and subsequent testosterone secretion. Continued exposure however then produces desensitization and down-regulation of receptors, leading to LH and testosterone suppression.[3,4] Such treatment has been shown to produce metastatic lesion regression and relief of symptoms such as bone pain in about 85% of patients with advanced disease.[5]

To ensure better patient compliance and maximize quality of life throughout treatment, pharmaceutical development of GnRH agonists is continually developing toward longer application intervals.[6] Modifications resulted in longer half-lives and higher receptor affinity for the active ingredients, and enabled extended active ingredient release in the current pharmaceutical formulations.

Histrelin, (VANTAS; Orion Pharmaceuticals, Finland; Endo Pharmaceuticals, USA), presents a novel therapy of prostate cancer. Unlike other GnRH agonists that have a maximum duration of application of 6 months, histrelin can be administered continuously over a period of 12 months, with the goal of achieving consistently low levels of active ingredient and testosterone throughout the treatment period. This study investigates whether histrelin can produce effective suppression of testosterone levels within a heterogeneous patient population, over a treatment period of 12 months.

Patients and method

One hundred thirty-one patients with various stages of histologically confirmed prostate cancer were included in this study. Before beginning therapy, all patients had normal testosterone levels. Patients received either primary treatment with hormone therapy (n = 72) or were receiving hormone therapy after failure of curative therapy and a PSA relapse (n = 59). Patients who underwent bilateral orchidectomy or receiving hormonal agents, including androgen receptor blockade, androgen ablative therapy or systemic corticosteroid therapy in the last year, were excluded from this study. The data on which this study is based was obtained from the Schlegel et al 2006 approval study for the histrelin implant. Seven patients from the Schlegel et al approval study were not included in our study because these patients rejected the implant. The descriptive data for the patient population is shown in Table 1.

All patients received a histrelin implant with a therapeutic efficacy of 12 months. The histrelin implant was inserted using a trocar and cannula system into the inner aspect of the nondominant upper arm with the patient under local anesthesia. The histrelin implant releases its active ingredient through controlled diffusion, which results in the maintenance of uniform active ingredient levels.[7-9]

In the assessment of the total population patients were divided into subgroups according to the following criteria:

Subgroup 1: Lower PSA levels across the entire follow up period – once a nadir was achieved, no later increase occurred.

Subgroup 2: Stable PSA pattern once a nadir was achieved, with fluctuations that showed no clear trend toward increase or decrease.

Subgroup 3: Consecutive increases in PSA level from a specific time point within the follow up period or no response to the hormone therapy.

TABLE 1. **Total patient population**

Patient population	**Mean + SD**	**Median**
Age (yrs)	74.9 + 7.3	75.0
PSA (ng/mL)	73.3 + 211.9	8.5
Testosterone (ng/mL)	412.4 + 124.4	404.0
		N (%)
T-stage		
	T1	12 (9.2)
	T2	22 (16.8)
	T3	58 (44.3)
	T4	16 (12.2)
	Tx	23 (17.6)
Previous therapy		
	Radiation	37 (28.2)
	Prostatectomy	33 (25.2)
Metastases		
	Bone	22 (16.8)
	Lymph nodes	10 (7.6)
Time following diagnosis (yrs)		
	0-2	57 (43.5)
	3-5	28 (21.4)
	6-10	38 (29.0)
	> 10	8 (6.1)

We additionally classified the patient population into risk groups according to D`Amico.[10]

The end point of this analysis was to achieve castration levels (testosterone ≤ 50 ng/dL) in all three subgroups, as well as a decrease in testosterone level to less than 20 ng/dL in all patients. These end points were selected as a decrease below 50 ng/dL on a standard test is seen as the upper limit for effective testosterone suppression. We additionally analyzed how often a value under 20 ng/dL was achieved, as this cut-off level is recommended in current analyses with more sensitive measuring methods.[11-13] A further end point was to achieve a significant decrease in the PSA level after 8 weeks in all subgroups, which remained stable throughout the study period.

Quality of life during treatment was assessed via different validated questionnaires for prostate cancer patients (Fact-G, FACT-P Total, Trial Outcome Index Score), with questions drawn from a total of five areas of life to be answered by the patient.

Statistical method

Quantitative variables were described using the mean and standard deviation, in addition to the median and were checked with the Kolmogorov-Smirnov test for normal distribution if another statistical analysis was performed. Nominal and ordinal scaled variables were represented using absolute and percentage frequency. The descriptive and graphical presentation was performed for the three subgroups and the total population.

A significant deviation from the normal distribution was found in all three subgroups in respect to the distribution of PSA values. The non-parametric Friedman test was then used to make a comparison of the first seven PSA measurements for each group. Post hoc pair comparisons were performed using the Schaich-Hamerle method.

Two-sided testing and a significance level of 5% were always applied. The statistical analysis was performed with PASW 17 (SPSS Inc., Chicago, IL) and BiAS for Windows, Version 9 (Epsilon Verlag, Frankfurt).

Results

Effective testosterone suppression was measured in all patients. The serum testosterone levels of the total population, Figure 1, and of all three subgroups, Figure 2, remained under 50 ng/dL consistently from weeks 4 to 52. The testosterone median and mean levels showed very little intra- or inter-subgroup variability among the three subgroups. All patients (100%) in all three subgroups had a testosterone level below

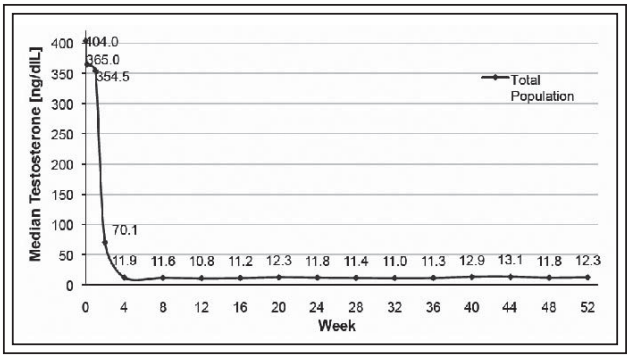

Figure 1. Serum testosterone level of all patients over 12 months.

castration level (testosterone ≤ 50 ng/dL) from weeks 4-52. Overall, 88% of the total population additionally achieved a testosterone level ≤ 20 ng/dL throughout the same period, and the range of patients within the three subgroups with testosterone levels ≤ 20 ng/dL during this same period was 85.7%-89.4%, Figure 3. Slight irregularities were detected in regard to the percentage of patients with testosterone levels above 20 ng/dL in subgroup 2 and subgroup 3 at 8 and 40 weeks, respectively, unfortunately these were not explained by other data and remain outliers.

The distribution of patients into subgroups was based on 52 week PSA outcomes. This resulted in 100 (89) patients being assigned to subgroup 1, 13 (10) patients to subgroup 2, and 18 (14) patients to subgroup 3. The number of patients in parentheses shows the

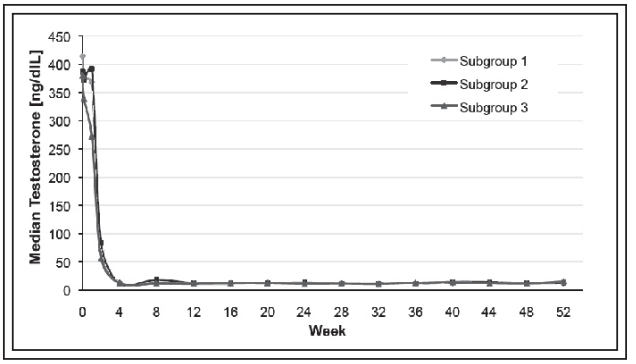

Figure 2. Serum testosterone level over 12 months including the three subgroups.
Subgroup 1. Lower PSA levels across entire follow up period.
Subgroup 2. Stable PSA pattern once a nadir was achieved, with fluctuations that showed no clear trend to increase or decrease.
Subgroup 3. Consecutive increase in PSA within the follow up period or no response to hormone therapy.

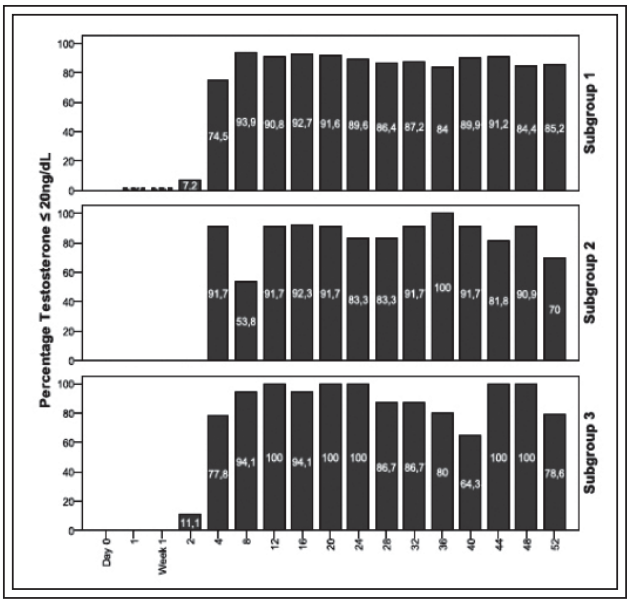

Figure 3. Percentage of patients with serum testosterone ≤ 20 ng/dL at respective time points of measurements in each subgroup. Mean percentage of week 4-52: Subgroup 1: 87.8%, subgroup 2: 85.7%, subgroup 3: 89.4%

minimum number of assessable patients per group and measurement point, since data were not obtained for all patients at each measurement point.

The PSA level in the total population showed a steady downward trend over time, with a median level of 0.2 ng/mL at the end of the 52 week follow up period, Figure 4. A 90% reduction in PSA levels was achieved within 8 weeks (median level) or 16 weeks (mean level).

Different PSA outcomes were measured in the subgroups, Figure 5. In subgroup 1, a decrease in PSA level to below 1 ng/mL was recorded within 8 weeks (median level) or 20 weeks (mean level). Although the PSA level did not fall below this limit for subgroups 2

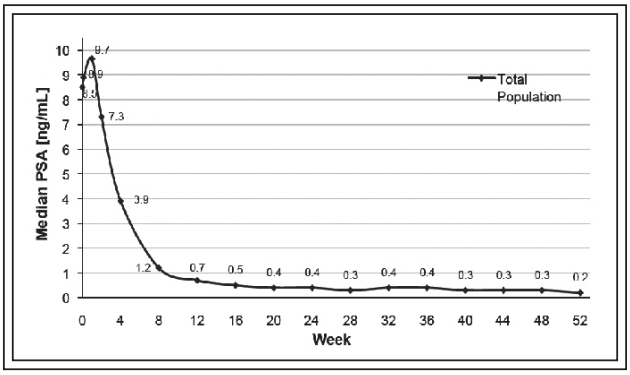

Figure 4. Prostate-specific antigen level of all patients over 12 months.

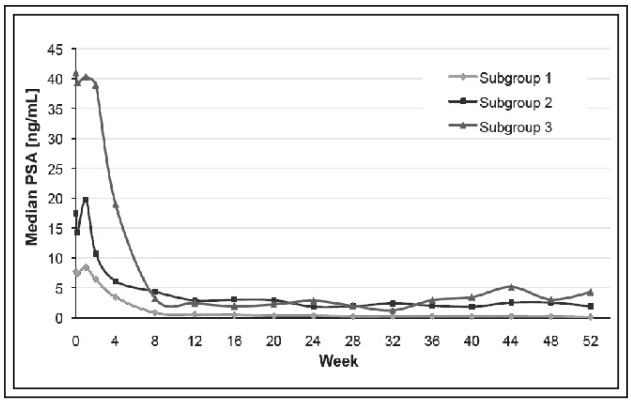

Figure 5. PSA level of each subgroup over 12 months.

and 3, in subgroup 2 a stable PSA course was observed. Overall, the largest deviations between median and mean levels were found in subgroup 3. In subgroup 1 a significant reduction in PSA level was observed, compared to overall baseline level after 2 weeks ($p = 0.044$) and after 8 weeks in both subgroup 2 ($p = 0.019$) and subgroup 3 ($p = 0.04$). A statistically significant decrease in the PSA level was detected within 2 weeks ($p = 0.015$) in the total population.

To establish a correlation between PSA outcome and patient clinical status, the patients were classified according to the D'Amico risk criteria at enrollment, Table 2. A total of three patients from group 1 were not evaluated because of a lack of classification criteria. The majority (66.4%) of all patients were assigned to the high-risk group. Review of the distribution of subgroups within the risk distribution revealed that 100% of patients in the low-risk group, and all but two patients in the moderate-risk group were to be found in subgroup 1. Patients in the high risk group were distributed over all three subgroups, but the majority was assigned to subgroup 1.

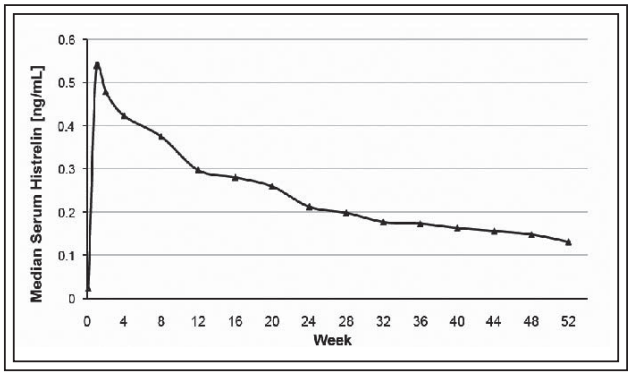

Figure 6. Histrelin serum level of all patients over 12 months.

TABLE 2. **Risk table including subgroups according to D'Amico**

N (%)	Low risk	Intermediate risk	High risk
Subgroup 1	23 (100.0%)	18 (90.0%)	56 (65.9%)
Subgroup 2	0 (0.0%)	0 (0.0%)	13 (15.3%)
Subgroup 3	0 (0.0%)	2 (10.0%)	16 (18.8%)
Total population	23 (100.0%)	20 (100.0%)	85 (100.0%)

The histrelin serum levels were recorded in a subpopulation of 61 (40) patients composed of patients from all three subgroups, Figure 6. Slowly decreasing serum levels were observed over the follow up period; after 6 months histrelin serum levels of 0.21 ng/mL were recorded, and after 12 months the levels were 0.13 ng/mL.

The most common adverse events reported were hot flashes, arthralgia, reactions at the implant site, and fatigue. The severity of hot flashes was reported to be mild in 60% of patients, moderate in 38%, and severe in 2%. Reactions at the implant site occurred in 14.5% of patients and were classified as mild for the most part (79%); all others were classified as moderate and were due to the not yet standardized methods of implantation.

Serious adverse events occurred throughout the study period in 30 patients, and 7 of these events resulted in death. None of the serious adverse events or deaths was considered to be associated with the study medication.

Quality of life was evaluated using a number of questionnaires (Fact-G, FACT-P Total, Trial Outcome Index Score). The analysis showed only a slight trend toward a reduction in the quality of life over the follow up period of 12 months. The score for social/family well-being (e.g. satisfaction with sex life) remained stable, and the score for emotional well-being (e.g. no anxiety about aggravation of the disease) actually showed an improvement.

Discussion

The degree of testosterone suppression is currently a highly debated topic. It is considered to be a critical factor for therapy outcomes in regard to the efficacy of antihormonal treatments for prostate cancer as inadequate testosterone suppression can lead to disease progression.[14,15]

Ideally the testosterone level in systemic antihormonal therapy should match the testosterone level resulting from surgical castration, which is usually 15 ng/dL-20 ng/dL. Most patients achieve a testosterone level of less than 20 ng/dL within a month after the start of GnRH treatment, but a somewhat substantial proportion of the patients later exceed this limit and have higher levels of testosterone at some point throughout the course of therapy.

Numerous publications address the question of "therapy failure" in testosterone suppression with GnRH therapy. Patients who did not achieve castration levels of 20 ng/dL are described, attributing this "therapy failure" to testosterone breakthroughs or follow up applications of GnRH agonists ("acute-on-chronic phenomenon").[16] Other studies have indicated that in 13% of patients receiving GnRH therapy the testosterone level was not completely suppressed, but stayed between 20 ng/dL and 50 ng/dL.[17]

Morote et al[10] recently published data identifying an 11% failure rate in achieving castration levels of 50 ng/dL or lower. A further analysis of survival and clinical correlation showed that patients with testosterone levels of 32 ng/dL or higher had significantly worse outcomes then those with testosterone levels of 32 ng/dL or lower.[11] Thus, lowering testosterone levels below the "standard" 50 ng/dL is essential and results in better oncological outcomes.

In this study, effective testosterone suppression was achieved for the total patient population over the entire follow up period using the histrelin implant. A decrease in the testosterone level below the castration level (testosterone ≤ 50 ng/dL) was observed for all patients (100%) from weeks 4 to 52, and in addition the testosterone levels fell below 20 ng/dL in 88% of the patients (mean) in the total population over the same period.

The consistent testosterone suppression observed in this study is the basis for the analysis of PSA outcomes in the patient population. Due to the continuous release of the active ingredient from the hydrogel depot, the histrelin implant is able to create consistently low testosterone levels without fluctuations or testosterone breakthroughs. In addition, the onset of mini-flares within a long therapy interval is prevented through the 12-month duration of application without intermediate dosing of any kind.

The recovery of testosterone levels after discontinuation of ADT is another important factor to consider when evaluating treatment options. Rapid recovery of testosterone levels in an intermittent therapy regimen seems to be an important factor in the improvement of patient quality of life during pauses after reaching the PSA nadir. Previous GnRH agonists were often accompanied by an efficacy related overhang after the intended time of application, leading to long term suppressed testosterone levels after the end of the intended duration of application. The histrelin implant, on the other hand, has shown to allow recovery of testosterone levels within a short time after removal.

Following a mean implant application time of 33 months, a 2-25 fold increase in LH (luteinizing hormone) level was recorded within 28 days after removal of the implants, followed by an increase in testosterone levels. This means that most patients recovered to levels above the castration level 42 days following implant removal.[18]

Within 8 weeks the PSA level of the total population was reduced to 1.2 ng/mL with downward trends continuing over 52 weeks, until a nadir of 0.2 ng/mL was achieved at the end of the follow up period. The analysis of the PSA response revealed typical therapy outcomes within the subgroups. A secure response (PSA < 1ng/mL) was achieved in the numerically largest subgroup (subgroup 1) with 100 patients. The upper limit of 1 ng/mL was never exceeded throughout the entire follow up period; in week 52 a nadir of 0.1 ng/mL was recorded. The widest distribution in PSA levels was found in subgroup 3, which highlights the heterogeneity of this subgroup. This is also evident from the clinical data, as 50% of patients in subgroup 3 were already in metastatic T4 stages. If the median and mean PSA levels of the 3 subgroups are compared, substantially greater differences emerge than if the testosterone levels of the subgroups are compared.

The clinical risk distribution of the patient population showed extensive agreement with the clinical outcomes. A very good response to therapy was found in all patients in the low-risk group (probability 100%). For patients in the intermediate risk group, the probability was 90%, and for patients in the high-risk group 66%, Table 2.

The observations regarding quality of life closely resemble those reported in other studies where patients received treatment with GnRH agonists.[19,20] The expanded Fact-P questionnaire[4] includes 40 specific questions for prostate cancer patients with five scoring options for each question, while the commonly used WHO/ ECOG (Eastern Cooperative Oncology Group) performance scale[13] includes five general classification questions for cancer patients.

Despite the evident benefits of good controllability and secure testosterone reduction over 1 year, the comparably difficult placing of the histrelin implant compared to depot injections is worth noting. Since it is a non-degradable depot histrelin has to be implanted subcutaneously during a short procedure under local anesthesia.

Future studies are needed to additionally examine and verify the clinical relevance of the minimized risks of testosterone breakthroughs or miniflares in the 12-month duration of application of the implant. Studies are currently in completion in the USA, and should shed light on the clinical significance of the 12-month application.

Conclusions for clinical practice

This study shows that histrelin, a novel GnRH analog, can offer uniform active ingredient levels without fluctuations over a full year are enabled through a controlled diffusion process. Placement of the subcutaneous histrelin implants is required once yearly.

In the present study, the histrelin implant produced a uniform and significant testosterone suppression in all patients. In all patients the castration limit of 50 ng/dL was achieved, while 88% of the patients achieved even a limit of 20 ng/dL or less, irrespective of the PSA subgroup. In the total population PSA levels decreased continuously over the entire study period and achieved a median nadir of 0.2 ng/mL. □

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