Efficacy and tolerability of 1- and 3-month leuprorelin acetate depot formulations (Eligard®/Depo-Eligard®) for advanced prostate cancer in daily practice: a Belgian prospective non-interventional study

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Submitted: 7 June 2013
Accepted: 25 July 2013

Arch Med Sci 2014; 10, 3: 477–483
DOI: 10.5114/aoms.2014.43743

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Abstract

Introduction: The 1-, 3- and 6- month biodegradable polymer matrix depot formulations of leuprorelin acetate (Eligard®/Depo-Eligard®, Astellas Pharma Inc/BV) were shown to reduce testosterone and prostate-specific antigen levels and to be well tolerated in patients with advanced prostate cancer in several clinical trials. This study aimed at evaluating the efficacy, safety and tolerability of the 1- and 3-month leuprorelin acetate depot formulations in daily clinical practice.

Material and methods: A prospective, open-label, non-interventional, phase IV study (MANTA) was conducted in 243 Belgian prostate cancer patients who had been prescribed the 1-month (7.5 mg) or 3-month (22.5 mg) leuprorelin acetate depot formulation. Patients were followed for at least 3 months.

Results: Median serum prostate-specific antigen levels were reduced by 95% from 12.0 ng/ml at baseline to 0.60 ng/ml after a median follow-up time of 132 days, while median testosterone levels were reduced by 94% from 360 ng/dl to 20 ng/dl. Partial or complete treatment response was observed in 83% of patients at the final visit (according to the physician's assessment). Ninety-two patients (37.86%) experienced treatment-emergent adverse events, with injection site-related reactions, hot flushes and tumor flare being the most common ones. Overall safety and tolerability of the leuprorelin acetate depot formulation were rated as good or excellent by 90% of physicians.

Conclusions: These data are consistent with efficacy and tolerability results from clinical trials. They confirm that the 1- and 3-month leuprorelin acetate depot formulations are well tolerated and reliably lower serum prostate-specific antigen and testosterone levels in routine clinical practice.

Key words: leuprolide, physician's practice patterns, prospective studies, prostatic neoplasms, treatment outcome.

Introduction

Prostate cancer (PCa) is the most common cause of cancer in the Belgian male population, accounting for about 30% of new cancer cases per year (estimated incidence in 2008: 9,990 new PCa cases per year) [1]. The disease is responsible for 1,570 deaths per year (2008) in Belgium, thereby ranking 3rd in the list of causes of cancer death in men, after lung cancer and colon/rectum cancer [1].

Androgens are essential for growth and perpetuation of PCa cells. Therefore, androgen deprivation therapy (ADT) aims at suppressing androgen activity, either by lowering androgen secretion from the testes (surgical or medical castration) or by inhibiting the binding of androgens to their androgen receptors in prostate cells (using antiandrogens). The ADT is indicated as treatment for patients with (locally) advanced or metastatic PCa [2]. It is also increasingly used in patients with high-risk localized PCa or in patients with prostate-specific antigen (PSA) relapse after local therapy, either as monotherapy or as adjuvant therapy to radiation therapy (RT) or radical prostatectomy (RP) [2].

Medical castration by injection of long-acting luteinizing-hormone-releasing hormone (LHRH) agonists, such as leuprorelin acetate (LA), is currently the most commonly used form of ADT [2]. The LHRH agonists are synthetic analogues of LHRH. They bind to pituitary LHRH receptors, thereby inducing release of luteinizing hormone (LH), which in turn stimulates testosterone production by the testes. This initial rise in testosterone production – also known as the 'flare-up phenomenon' or 'testosterone surge' – is only transient (1st week of therapy). Indeed, chronic exposure to LHRH agonists elicits a negative feedback mechanism and results in downregulation of LHRH receptors, leading to suppression of LH release and decreased testosterone production. Consequently, most patients achieve testosterone 'castration levels' (< 50 ng/dl) within 2 to 4 weeks after treatment start [2]. This medical castration method is preferred over surgical castration by most patients because it is equally effective, while the physical and psychological discomfort associated with orchiectomy can be avoided. Moreover, medical castration is reversible and can be administered intermittently, unlike surgical castration [2].

Whereas LHRH agonist treatment originally required daily subcutaneous injections, depot formulations have now become available. Eligard®/Depo-Eligard® (Astellas Pharma Inc/BV) is an LA depot formulation that uses the Atrigel® delivery system, i.e. a biodegradable polymer matrix that allows sustained release of the drug following subcutaneous administration. Eligard®/Depo-Eligard® is available in Europe in 1-, 3- and 6-month depot injections. The 1-month (7.5 mg) and 3-month (22.5 mg) formulations have been available in Belgium since 2005 [3, 4], while the 6-month (45 mg) formulation was introduced to the Belgian market in 2008 [5].

In clinical trials, these 3 LA depot formulations have been shown to produce and maintain therapeutic suppression of serum testosterone and PSA levels and to be well tolerated [6–8]. However, data on the use of the LA depot formulation in daily clinical practice are limited, with only 2 non-interventional studies being published to date [9, 10]. Hence, this non-interventional study – named MANTA (**M**onitoring tolerance, safety and acceptance of (Depo-)Elig**A**rd® in a **N**on-in**T**erventional tri-**A**l) - aimed at collecting additional data on the efficacy and tolerability of the 1- and 3-month LA depot formulations in daily clinical practice in Belgium.

Material and methods

Study design and patients

This prospective, open-label, non-interventional, phase IV study (MANTA) was conducted in 53 Belgian centers between December 2006 and February 2008. Patients with PCa who had been prescribed the 1-month (7.5 mg) or 3-month (22.5 mg) LA depot formulation (Eligard®/Depo-Eligard®, Astellas Pharma Inc/BV) in accordance with the terms of marketing authorization were followed for at least 3 months. Data were collected at baseline (visit 1), during an intermediate visit (visit 2; timing at the physician's discretion) and during a final visit (visit 3; ≥ 3 months after treatment start). Diagnosis of PCa and length of treatment period with LHRH agonist were at the discretion of the treating physician.

Study endpoints

As the primary objective of this study was to evaluate the safety and tolerability of the 1- and 3-month LA depot formulation in daily clinical practice, primary safety variables were occurrence of treatment-emergent adverse events (TEAE) throughout the entire observational period and physician's assessment of overall safety and tolerability. The secondary endpoints were efficacy parameters such as testosterone and PSA levels (if available), physician's assessment of objective disease response and overall efficacy, and patient's assessment of overall efficacy, treatment benefit (acceptance) and cancer-related pain.

Statistical analysis

Statistical analysis was performed by Prof. Dr. L. Kaufman (Veeda Clinical Research, Belgium) using SAS software, Version 9.2. All documented variables were analyzed descriptively. Continuous variables were summarized using descriptive statistics (number of patients, mean, standard deviation, median, interquartile range (Q25–Q75), minimum and maximum). Categorical variables were described using frequencies and percentages.

The following analysis sets were considered: (i) the safety (SAF) set, consisting of all patients enrolled in the study for whom there was evidence they used study medication and for whom any follow-up information was available; (ii) the intention-to-treat (ITT) set, consisting of all patients enrolled in the study and for whom any follow-up efficacy information was available.

Ethics

This study was conducted in accordance with the Declaration of Helsinki, the European Union Clinical Trials Directive 2001/20/EC, ICH GCP guidelines, and local laws and regulations. It was approved by an Independent Ethical Committee. Written informed consent was obtained from all patients.

Results

Patient baseline characteristics

In total, 247 patients were enrolled in the study by 46 treating urologists (i.e. 46 centers were active and included at least 1 patient, while 7 centers were non-active). Of these, 4 patients were excluded from the SAF set because there was not any follow-up information available, including 1 patient who never used the study medication. In addition, 19 patients were excluded from the ITT set because they did not have any follow-up efficacy data. As such, the SAF and ITT set comprised 243 and 224 patients, respectively.

Patient baseline characteristics are given in Table I. Median age was 76 years and median time since diagnosis was 0.21 years. Most patients had (locally) advanced PCa (stage T3–T4). About two thirds of patients had received prior therapy for PCa. For 43% (n = 96) of them, this prior therapy was ADT, i.e. orchiectomy (2%), LHRH-analogue treatment (16%), antiandrogen treatment (50%) or complete androgen blockade (32%), either as

Table I. Baseline patient characteristics (intention-to-treat set; N = 224)

Characteristic	**Median**		**Q25–Q75**	
Age [years]	76.4		70.1–81.1	
Time since first diagnosis [years][†]	0.21		0.1–3.6	
Age at first diagnosis [years]	74.33		67.6–78.9	
Gleason score (n = 202)	7		6–8	
TNM classification	**Number**		**Percent**	
T-category:				
T1	20		8.9	
T2	40		17.9	
T3	118		52.7	
T4	25		11.2	
Missing	21		9.4	
N-category:				
N0	116		51.8	
N1	31		13.8	
Missing	77		34.4	
M-category:				
M0	138		61.6	
M1	35		15.6	
Missing	51		22.8	
Prior therapy (since PCa diagnosis)	**Monotherapy**		**Combination therapy**	
	Number	**Percent[‡]**	**Number**	**Percent[‡]**
None	74	33		
TURP	19	8.5	33	14.7
Radical prostatectomy	13	5.8	23	10.3
Radiotherapy	7	3.1	33	14.7
Orchiectomy	0	0	3	1.3
Antiandrogen	26	11.6	54	24.1
LHRH analogue	6	2.7	40	17.9
Estramustine	0	0	3	1.3
Other			7	3.1

[†]*Seven patients were diagnosed a few days after the baseline visit.* [‡]*Percentages refer to total patient number (n = 224) and do not add up to 100%, as 79 patients had multiple previous therapies. LHRH – luteinizing-hormone-releasing hormone, TURP – transurethral resection of the prostate*

Table II. Time between study visits and number of patients included in safety (SAF) and intention-to-treat (ITT) set for each visit

Visit	Median time since prior visit (Q25–Q75)	SAF	ITT
1st LA depot injection	–	–	–
Visit 1 (baseline)	0 weeks (–14–0)	243	224
Visit 2 (intermediate)	91 days (42–105)	153	153
Visit 3 (final)	91 days (56–98)	241	222

LA – leuprorelin acetate (Eligard®/Depo-Eligard®, Astellas Pharma Inc/BV)

Table III. Study medication (intention-to-treat set; *n* = 207)

Characteristic	Number	Percent
LA monotherapy	110	53.1
LA + antiandrogen (flare-up)	60	29.0
LA + antiandrogen (continuous)	23	11.1
LA + antiandrogen (flare-up + continuous)	1	0.5
LA + antiandrogen (flare-up) + radiotherapy	5	2.4
LA + radiotherapy	7	3.4
LA + other	1	0.5

LA – leuprorelin acetate (Eligard®/Depo-Eligard®, Astellas Pharma Inc/BV)

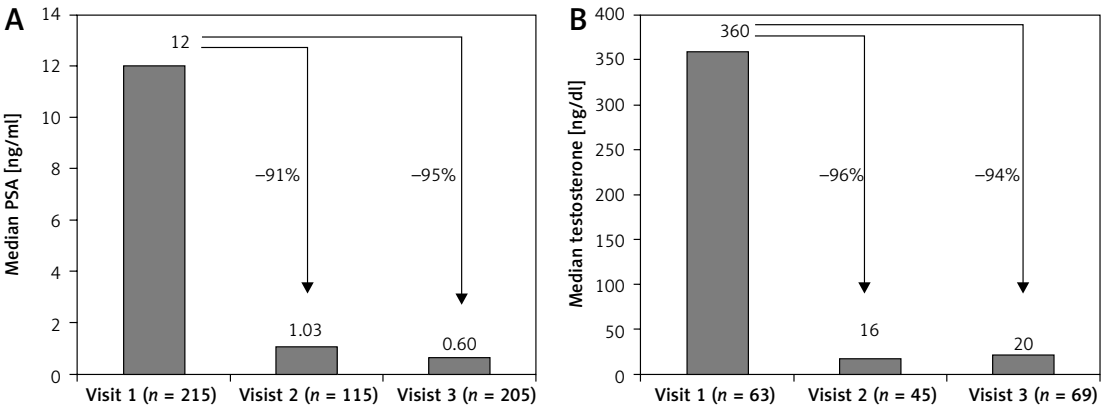
monotherapy (45%) or in combination with local treatment (RP, RT, transurethral resection of the prostate (TURP)) (55%).

Treatment with leuprorelin acetate depot formulation

The number of patients included in the SAF and ITT set for each visit and median time between study visits are given in Table II. Median time between the baseline visit and the last visit was 132 days (92–197 days). All patients in the ITT set received an injection with the 1- (*n* = 46) or 3-month (*n* = 175) LA depot formulation during the baseline visit (dose unknown for 3 patients). For about half of the patients (53.1%), this LHRH agonist was their only PCa therapy during the observational period, while 43% of patients received additional antiandrogens (flare-up or continuous) (Table III). Only 5.8% of patients were treated with the combination of RT and ADT. At study termination, 95.3% of patients still continued treatment with the LA depot formulation.

Efficacy of leuprorelin acetate depot formulation

Median serum PSA levels were reduced by 95% from 12.00 ng/ml at baseline to 0.60 ng/ml at the 3rd visit (Figure 1 A). Measurement of testosterone levels was only done in about one third of patients with PSA measurements. In these patients, median testosterone level was reduced by 94% from 360 ng/dl at baseline to 20 ng/dl at the 3rd visit (Figure 1 B). Efficacy was similar for both LA de-



PSA	Q25	Q75
Visit 1	5.4	22.0
Visit 2	0.3	5.0
Visit 3	0.1	3.0

Testosterone	Q25	Q75
Visit 1	130	460
Visit 2	10	40
Visit 3	10	30

Figure 1. Median serum PSA (**A**) and testosterone (**B**) concentrations during treatment with the 1- or 3-month leuprolide acetate depot formulation (Eligard®/Depo-Eligard®, Astellas Pharma Inc/BV). Median time between each visit was 91 days

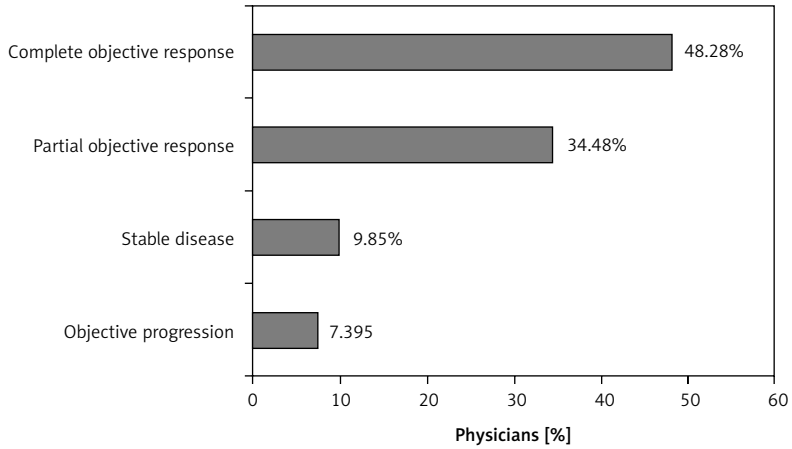


Figure 2. Physicians' assessment of patient's objective disease response at the final visit (n = 203)

pot formulations, with a 96% reduction of median testosterone levels for the 1-month formulation (from 400 ng/dl to 17 ng/dl) and a 93% reduction for the 3-month formulation (from 305 ng/dl to 20 ng/dl).

When physicians were asked to assess objective disease response, 83% indicated that the patient had responded partially or completely to treatment with the LHRH agonist at the final visit, while another 10% indicated that PCa was stabilized (Figure 2).

Tolerability of leuprorelin acetate depot formulation

In total, 92 patients (37.86%) experienced TEAE. Only 4 (1.65%) of them were serious TEAE (1 death due to PCa, 1 death due to intestinal obstruction, 1 syncope requiring hospitalization, 1 prostatic obstruction requiring hospitalization), and none of these serious TEAE were related to the study drug. Of the 9 patients (4.02%) who prematurely discontinued treatment, only 2 (0.82%) discontinued due to TEAE, while 5 patients discontinued due to a lack of efficacy (not further specified). Non-serious TEAE reported by at least 2% of patients were injection site-related pain (45 patients; 18.52%) and injection site-related hematoma (15 patients; 6.17%), vascular disorders such as hot flushes (21 patients; 8.64%) and flushing (6 patients; 2.47%), and tumor flare (12 patients; 4.94%). Overall, safety and tolerability of the LA depot formulation at the final visit was rated as good or excellent by 90% of physicians (Figure 3).

Discussion

To our knowledge, this Belgian non-interventional MANTA study is the first study evaluating the efficacy and tolerability of the 1- and 3-month LA depot formulation in daily clinical practice. Indeed, only 2 non-interventional studies with the 3- and/or 6-month LA depot formulations have been published to date [9, 10]. Only one of them actually used objective parameters, such as serum PSA and testosterone levels, to evaluate the efficacy of the 6-month LA depot formulation in a population of German PCa patients [9]. In this study, median total serum PSA and testosterone levels had decreased by 94% (from 11.6 ng/ml to

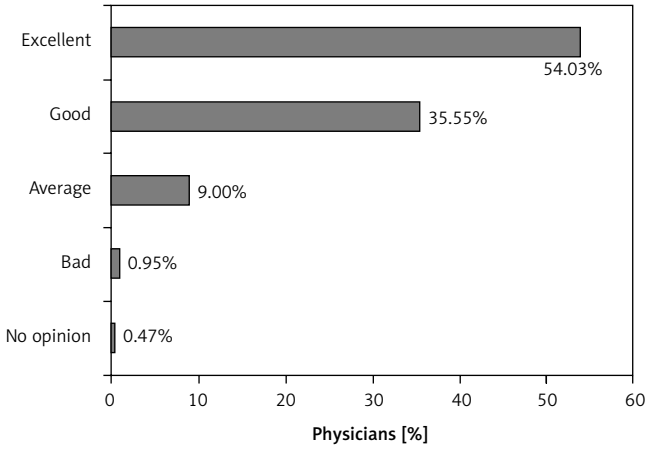


Figure 3. Physicians' assessment of overall safety and tolerability at the final visit (n = 211)

0.7 ng/ml) and 89% (from 89 ng/dl to 10 ng/dl) 6 months after injection of the LHRH agonist. The results of the current study are comparable, showing a 95% reduction in median PSA levels (from 12.0 ng/ml to 0.6 ng/ml) and a 94% reduction in median testosterone levels (from 360 ng/dl to 20 ng/dl) about 4 months (median time between baseline and last visit) after the first injection with the 1- or 3-month LA depot formulation. Thus, in daily clinical practice, the 1- and 3-month LA depot formulations can effectively lower serum PSA and testosterone levels.

As such, the results of this MANTA study are an external validation of the clinical trial results [6, 7], showing that the 1- and 3-month LA depot formulations can reliably suppress serum PSA and testosterone levels. However, in contrast to the clinical trials, the MANTA study includes a heterogeneous group of patients, more accurately reflecting daily clinical practice. Moreover, it does not only include patients on LHRH agonist monotherapy – as in the clinical trials – but also includes patients being treated with additional antiandrogens (> 40% of patients). In addition, it reflects the real-life conditions for administration of the LA depot formulation. Given these differences between the highly controlled study environment of the clinical trials and the real-life situation of this observational trial, it is not surprising that PSA and testosterone levels varied more in the current study, both at baseline and during follow-up visits. Nevertheless, testosterone levels were still reduced below the 50 ng/dl threshold in the majority of patients, as in the clinical trials. Moreover, 83% of physicians indicated that the patient had partially or completely responded to treatment at the final visit, resulting in improvement or stabilization of the patient's condition in > 90% of patients. These results indicate that the efficacy results of the clinical trials for the 1- and 3-month LA depot formulation [6, 7] also apply to a broad patient population encountered in daily clinical practice.

Interestingly, in daily clinical practice – where monitoring of testosterone levels was not mandatory, as in clinical trials – testosterone levels were only measured in about one third of patients with PSA measurements. This finding was an unexpected finding, as both serum PSA and testosterone values are recommended in the European Association of Urology (EAU) guidelines as follow-up parameters for patients on ADT [2]. Indeed, evaluation of testosterone levels several times after initiation of LHRH agonist therapy (at least after 1 and 6 months) can serve several purposes [2, 11]: it can be used (i) to identify patients who fail to achieve testosterone castration levels [12, 13], (ii) to determine the optimal time for LHRH agonist redosing, and (iii) to monitor the potential development of castration-resistant PCa, as several studies have shown that lower serum testosterone levels achieved during ADT are associated with slower progression to castration resistance [14, 15] and a lower risk of dying from PCa [16]. Patients with a parallel increase in PSA and testosterone levels during ADT might benefit from an additional injection of the same or another LHRH analogue (or from surgical orchiectomy), while patients with rising PSA levels despite testosterone levels below the castration level have probably become castration resistant and require a different approach [2, 11]. Both in the current observational study and in the German non-interventional study [9], it was noted that, in routine clinical practice, there is a lack of compliance with these EAU guidelines regarding testosterone monitoring. This might indicate that physicians are not fully aware of the added value of measuring testosterone levels besides PSA for follow-up of patients on ADT and that they do not completely realize the importance of lowering testosterone as much as possible and avoiding testosterone breakthrough.

With regard to safety and tolerability, fewer patients experienced TEAE in daily clinical practice than in the clinical trials with the 1- and 3-month LA depot formulation [6, 7]. The frequency of injection-site-related complaints – typical for subcutaneous injectable products – in this real-life MANTA study was comparable to what was observed in the clinical trials [6, 7]. However, in the current study, physicians were asked specifically to describe all complaints related to injection of the LA depot formulation (pain, hematoma, tumor flare, etc.), but they were not asked to indicate the severity grade of these complaints. As some, but not all, complaints were reported as TEAE, it was decided – for the sake of consistency – to consider all injection-site-related complaints as TEAE. Thus, without this specific question regarding injection-site-related complaints, the reported frequency of such TEAE would probably have been comparable to the frequency that was described for the 6-month LA formulation in the daily clinical practice setting (3.2% of patients) [9]. We therefore reason that very few of the injection-site-related complaints reported in this MANTA study actually provoked clinical concern, which is underlined by the fact that 90% of physicians rated the overall safety and tolerability of the 1- or 3-month LA depot formulation as good or excellent.

In conclusion, this Belgian non-interventional study externally validates the efficacy and tolerability results from the clinical trials, demonstrating that the 1- and 3-month LA depot formulations are well tolerated in daily clinical practice and that

they can reliably lower serum PSA and testosterone levels.

Acknowledgments

The authors are grateful to Ismar Healthcare NV for assistance in writing of the manuscript. This study was funded by Astellas Pharma BV, Belgium. We also want to thank the following physicians for their contribution to this study: A. Abi-Aad, K. Ackaert, F. Ameye, C. Assenmacher, I. Billiet, G. Boeckx, H. Claes, A. Corbusier, P. Cortvriend, B. Dardenne, P. De Groote, L. Denis, J. Desirotte, F. Devos, L. Dewilde, L. Hoekx, A. Leonard, L. Louis, K. Maes, D. Maes, JH Maquet, G. Martens, P. Martens, P. Mattelaer, W. Oosterlinck, T. Pontus, M. Pouya, O. Reul, C. Schulman, M. Stragier, J. Stragier, L. Timmermans, P. Van Brien, P. Van Erps, J. Van Nueten, H. Van Poppel, H. Vandendriesche, M. Vandendris, T. Wildschutz and P. Willemen.

Conflicts of interest

Johan Braeckman received consultancy fees and research grants from Astellas Pharma BV, Belgium. Dirk Michielsen received speakers' fees from Pfizer.

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