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EXPERT OPINION

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Extended release, 6-month formulations of leuprolide acetate for the treatment of advanced prostate cancer: achieving testosterone levels below 20 ng/dl

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Introduction: Luteinizing hormone-releasing hormone agonists such as leuprolide acetate (LA) are the most frequently utilized treatment of advanced prostate cancer as the regimen for achieving androgen deprivation therapy (ADT). The efficacy of LA is determined by extent of testosterone (T) suppression in prostate cancer patients. Although, the historical castrate T suppression target has been defined as < 50 ng/dl, this level may not be as low as required to deliver equivalent suppression as achieved by surgical castration. Recent studies have demonstrated that a T level as low as 20 ng/dl may produce improved clinical outcomes.

Areas covered: LA is available in long-acting formulations that deliver active drug over the course of 1–6 months from a single-dose administration. The technologies utilized to provide sustained drug delivery differ: one mode of administration uses microspheres, which encapsulate the drug and are injected as a suspension intramuscularly; another mode of administration uses a liquid polymer that creates a single, solid depot after injection subcutaneously. This article will review the safety and efficacy of both 6-month LA formulations, as well as their impact in prostate cancer treatment.

Expert opinion: As the understanding of optimal T castrate level evolves and may be refined pending new data from contemporaneous trials, achievement and maintenance of T levels well below 50 ng/dl may be important in evaluating potential differences in ADT regimens.

Keywords: biodegradable polymer, depot, leuprolide acetate, leuprorelin, microspheres, prostate cancer

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1. Introduction

Prostate cancer is second only to skin cancer as the most common type of cancer among men in the US [1]. Testosterone (T) is a known promoter of prostate cancer cell growth. Thus, a cornerstone element of advanced prostate cancer treatment is androgen deprivation therapy (ADT), which aims to reduce serum T levels to those achieved with surgical castration. Although ADT is not curative in most patients, and there is almost always progression to castrate-resistant prostate cancer (CRPC), ADT may alleviate symptoms of metastatic disease as well as prolong overall survival [2]. The initial method of achievement of ADT was surgical bilateral orchiectomy. Surgical castration has been, for the most part, replaced with the use of drugs that suppress the secretion of androgens and inhibit the action of circulating androgens. The most common form of ADT utilized worldwide is the use of



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Box 1. Drug summary.

Drug name (generic)	Leuprolide acetate
Phase (for indication under discussion)	Ph IV, marketed drug
Indication (specific to discussion)	Prostate cancer
Pharmacology description/mechanism of action	Luteinizing hormone-releasing hormone agonist
Route of administration	Subcutaneous or intramuscular injection
Chemical formula	5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolineamide acetate (salt)
Pivotal trial(s)	See Table 3

synthetic peptides that mimic natural luteinizing hormone-releasing hormone (LH-RH) [3]. The aim of this review is to describe and discuss the available long-acting therapies, the levels of T suppression achieved by different methods of long-acting release, and potential impact on clinical outcomes in light of recent advancements in the field.

2. Body of review

2.1 Overview of the market

2.1.1 LH-RH agonists

LH-RH agonists have a high affinity for the gonadotropin releasing hormone (GnRH) receptor and benefit from longer half-lives than natural LH-RH. Whereas endogenous LH-RH has a half-life of approximately 2 – 6 min [4,5], synthetic analogs of LH-RH have extended half-lives of approximately 3 h. Chronic exposure to LH-RH agonists results in prolonged GnRH signaling, which leads to downregulation of receptors for LH-RH, ultimately suppressing T production in the testes [6]. These LH-RH agonists have been shown to be more effective than anti-androgen monotherapy and are recognized as the standard-of-care treatment for locally advanced and advanced prostate cancer [7,8]. Key safety and efficacy features of the most commonly used LH-RH agonists as well as the only currently available LH-RH antagonist, degarelix, are summarized in Table 1. After injection of LH-RH agonists, serum T transiently increases, but continuous administration of a LH-RH agonist leads to decreased androgen production, generally within a few weeks. This transient increase does not occur with the LH-RH antagonist. The goal of ADT therapy with LH-RH agonists is to achieve T suppression to castration level and to maintain this level throughout the course of therapy [9].

2.1.2 Optimal serum T level in ADT

Evaluation of efficacy of ADT for patients with prostate cancer may be assessed through testing of serum T. For over 40 years, a T level of < 50 ng/dl defined the target level for

castration, but this level was based on the lower sensitivity of T assays available at the time (i.e., double isotope derivative dilution technique) [10]. Advancements in hormone assays such as chemiluminescent assay technology now allow detection of T levels as low as 0.1 ng/ml [11]. Based on this improved detection of lower levels of circulating androgens, it has been reported that the T level equivalent to surgical castration may be much lower than originally defined. New recommendations have been forthcoming for the management of prostate cancer patients undergoing ADT, such as the European Association of Urology redefining castration level as T below 20 ng/dl. A literature search of clinical trial papers evaluating T levels during ADT and patient outcomes were conducted to capture recent information that may contribute towards new treatment standards.

In 2000, Oefelein *et al.* evaluated T levels attained with bilateral orchiectomy using chemiluminescent technology [10]. Their results (n = 35) showed that post-castration T levels above 20 ng/dl were infrequent [10], and the mean value of T after surgical castration was 15 ng/dl. These results were corroborated in a study by van der Sluis *et al.*, which showed that surgically castrated men (n = 34) had a median T level of 9.2 ng/dl with 97% of these men having levels < 20 ng/dl [12].

Furthermore, recent literature has suggested that achieving lower levels of serum T during ADT in the androgen-sensitive population resulted in improved clinical outcomes. The relationship between T level and mortality was evaluated in a retrospective analysis of 129 consecutive patients who were newly diagnosed with bone-only metastatic disease and treated with goserelin acetate, an LH-RH agonist [13]. Results showed that mean T levels at 6 months were 40 ng/dl, and higher T levels were associated with increased risk of death by 1.33 times (p < 0.05). A study by Dason *et al.* supports a T threshold of 32 ng/dl [2]. In this prospective cohort study, 32 patients undergoing ADT were stratified into groups based on mean T levels (those with mean levels > 50 ng/dl were excluded). The results showed that patients with T levels < 32 ng/dl had significantly increased time to CRPC compared to those with levels of 32 – 50 ng/dl. In 2013, Bertaglia *et al.* conducted a larger, prospective study in 153 patients with advanced prostate cancer, 54 with metastatic disease, and 99 with biochemical failure [14]. A multivariate Cox proportional hazards model showed that T levels < 20 ng/dl were associated with a significantly lower risk of death (p = 0.020) and a trend towards a lower risk of disease progression (p = 0.12) compared with T > 20 ng/dl. Similarly, Perachino *et al.* demonstrated through a multivariate Cox model in 129 patient study, a statistically significant and clinically meaningful correlation between the risk of death and 6-month serum T levels. The 6-month serum T level hazard ratio (HR) for risk of death in metastatic bone-only prostate cancer patients treated with ADT was 1.33 (95% CI 1.05 – 1.68; p < 0.05). They concluded that the lowest possible serum T level achievable should be the goal for any LH-RH agonist treatment [13].

Table 1. Key characteristics of currently available LH-RH agonists.

Attributes	Subcutaneous leuprolide acetate	Intramuscular leuprolide acetate	Triptorelin	Goserelin	Degarelix*
<i>Efficacy</i> [5,20,30-35,44-52]					
Patients (%) with T ≤ 50 ng/dl at study end	99 – 100	93 [‡] – 100	93 – 96 [§]	65 – 91	97 – 98 [¶]
Patients (%) with T ≤ 20 ng/dl at study end	88 – 98	66 [#]	25 ^{**}	55 ^{††}	Not available
Onset of T suppression ≤ 50 ng/dl (days)	21	28	29	21	3
Total clinical trial patients (N)	438	348	434	402	409
T ≤ 50 ng/dl breakthroughs (%)	0 – 3	2.2 – 5.4	3.8 – 6.7 ^{§§}	9.4 ^{¶¶}	1 – 1.9 [53]
<i>Safety</i>					
Adverse effects in ≥ 15% of patients in any study [5,20,45-47,54]	Hot flashes, fatigue	Hot flashes, general pain, GI disorders, testicular atrophy, joint disorder	Hot flashes	Hot flashes, sexual dysfunction, decreased erections	Hot flashes
<i>Storage/Administration</i> [5,20,45-47]					
Needle gauges	18 (45 mg), 20 (7.5 mg), 22.5 mg, 30 mg)	23 (all doses)	21 (all doses)	16 (3.6 mg), 14 (10.8 mg)	27 (all doses)
Injection type	Subcutaneous	Intramuscular	Intramuscular	Subcutaneous	Subcutaneous
Available dosing intervals (months)	1, 3, 4, 6	1, 3, 4, 6	1, 3, 6	1, 3	1
Injection volume per dosage (ml)	0.25 – 0.5	1.0 – 1.5	2.0	2.0	6.0
Injection site range	Any SC region	Buttock, thigh, deltoid	Buttock only	Abdomen only	Abdomen only
<i>Other</i>					
Year of FDA approval [54]	2002 (7.5 mg), 2002 (22.5 mg), 2003 (30 mg), 2004 (45 mg)	1989 (7.5 mg), 1995 (22.5 mg), 1997 (30 mg), 2011 (45 mg)	2000 (3.75 mg), 2001 (11.25 mg), 2010 (22.5 mg)	1989 (3.6 mg), 1996 (10.8 mg)	2008

*LH-RH antagonist; [‡]Kaplan-Meier (K-M) estimate within group from week 4 – 48 for minimum only; [§]K-M estimates from day 57- end of study; [¶]K-M estimates within group from day 28 – 364; [#]Data available for 1-month formulation only [32]; ^{**}Data available for 3-month formulation only [55]; ^{††}Data available for 1-month formulation only [48]; ^{§§}Extrapolated from K-M estimates days 57-end of study; ^{¶¶}Data available for 3-month formulation only. LH-RH: Luteinizing hormone-releasing hormone.

Klotz *et al.* recently presented data demonstrating that nadir serum T < 20 ng/dl correlates with improved duration of response to ADT and concluded that patients undergoing ADT should have their T and prostate specific antigen levels monitored regularly [15]. The study also found significant differences in cancer specific survival (p = 0.01) among continuous androgen deprivation patients (n = 626) with nadir T < 20, between 20 – 50, and ≥ 50 ng/dl. Patients with nadir T ≥ 50 ng/dl had significantly higher risk of dying of disease (HR: 2.93, 95% CI 0.7 – 12.3) compared to patients with nadir T 20 – 50 (HR: 2.08, 95% CI, 1.28 – 3.38) and < 20 ng/dl (HR: 1). Furthermore, the median T during the first year on continuous ADT also correlated with time

to androgen-independent progression and cancer-specific survival. Overall survival was not assessed in this study due to limitations in duration of follow-up [15]. It is important to keep in mind that in studies evaluating the relationship between serum T levels during ADT and clinical outcome, there are possible covariates associated with higher T levels that could also have contributed to an inability to reach the lowest nadir serum T levels, as well as poorer outcomes.

During the course of ADT, an increase in serum T above the castration level is considered a breakthrough escape or miniflare and should be avoided [7]. Multivariate analyses from Morote *et al.* support a lower T threshold for both the initial target level and those seen throughout maintenance of

Table 2. Summary of characteristics of liquid to biodegradable solid implant and microsphere depot technologies.

Characteristic	Liquid to biodegradable solid implant (used in SQ-LA) [26]	Microspheres (used in IM-LA) [23,26]
Needle size	Standard (size 3/8 – 5/8 inch) [56]	Standard (size 1½ inch) [56]
Maximum time from reconstitution to injection	30 min	2 h
Drug release	From a single, solid implant	From ~ 10,000 small microspheres
Clinical experience	Extensive record of safety and efficacy	Extensive record of safety and efficacy
Potentially removable	Yes	No
Delivery	Subcutaneous (in the case of SQ-LA)	Intramuscular (in the case of IM-LA)
6-month LH-RH agonist depot approval (year)	2004 [57]	2011 [58]

LH-RH: Luteinizing hormone-releasing hormone; LA: Leuprolide acetate; IM-LA: LA injected intramuscularly; SQ-LA: Solid depot of LA.

Table 3. Summary of pivotal clinical trials with SQ-LA and IM-LA.

Author (year)	LA dose(s)	Dosing frequency	Study design	No.	Duration of study
<i>SQ-LA</i>					
Perez-Marreno et al. (2002) [44]	7.5 mg	1 month	Open label	120	24 weeks
Chu et al. (2002) [33]	22.5 mg	3 months	Open label	117	24 weeks
Sartor et al. (2003) [35]	30.0 mg	4 months	Open label	90	32 weeks
Crawford et al. (2006) [34]	45.0 mg	6 months	Open label	111	48 weeks
<i>IM-LA</i>					
Sharifi et al. (2002) [59]	7.5 mg, 22.5 mg	1 month, 3 months	Open label	71	12 weeks, 52 weeks
Sharifi et al. (1996) [51]	22.5 mg	3 months	Open label	94	24 weeks
Sharifi et al. (1998) [52]	30.0 mg	4 months	Open label	49	32 weeks
Spitz et al. (2012) [31]	45.0 mg	6 months	Open label	151	48 weeks

LA: Leuprolide acetate; IM-LA: LA injected intramuscularly; SQ-LA: Solid depot of LA.

ADT. The study evaluated 73 patients with non-metastatic prostate cancer treated with depot LH-RH agonist for 3 months [16] and found that 43.6, 31.5, and 24.7% of patients achieved T levels of < 20, 20 – 50, and > 50 ng/dl, respectively. Survival data showed that patients who experienced T breakthrough events above 32 ng/dl had a mean survival free of androgen-independent progression of 88 (95% CI 55 – 121) months, compared to 137 (95% CI 104 – 170) months in those without breakthroughs ($p < 0.03$).

This recent literature, including a recent review article [17], suggests that the historic T target for ADT of ≤ 50 ng/dl is too high, given that surgical castration results in T levels < 20 ng/dl, and significant improvements in clinical outcomes for patients meeting lower serum T thresholds have been demonstrated. Although some data suggest < 32 ng/dl is a potential target [2,16], other studies indicate that a lower level of < 20 ng/dl should be the goal [15]. In light of these new data, in 2014 the European Association of Urology revisited the definition of castration in their guidelines on the treatment of prostate cancer and updated the target level for T to < 20 ng/dl. Although other guidelines have not yet been updated, given the increasing evidence from recent, large studies, there appears to be renewed interest in the subject and movement towards redefining the standards.

2.2 Introduction to the compound

2.2.1 Leuprolide acetate formulations

Although the optimal T target for ADT is still under discussion, the need for long-acting drugs able to effectively suppress circulating T remains well established. Due to the relatively short half-life of LH-RH analogs, early LH-RH agonist therapy required daily subcutaneous injections [18]. As maintenance of castration level T is required for successful ADT, daily therapy was costly and cumbersome. However, long-acting depot LH-RH agonist formulations have been developed that entrap or encapsulate the active drug, allowing for continuous, sustained release of drug to maintain therapeutic levels over the course of therapy – typically, 1 – 6 months [8].

Leuprolide acetate (LA) (Box 1) is the most widely prescribed LH-RH agonist due to favorable tolerability and has been used for > 20 years in the treatment of prostate cancer in various formulations and regimens [18,19]. A variety of formulations of LA depots have been developed, allowing for single injections that last for 1-month, 3-month, 4-month, or 6-month intervals [5,20]. These depot formulations of LA provide an improved pharmacokinetic (PK) profile compared to non-encapsulated LA, and are associated with more predictable efficacy, and ultimately, improved patient outcomes [21]. The current technologies used to create LA depot

formulations are polymer microspheres and biodegradable polymer delivery systems that are injected as a viscous liquid that form a single, solid depot *in situ*.

2.3 Chemistry

2.3.1 Microspheres

Microspheres, a commonly used drug delivery system, encapsulate a given drug and degrade *in situ* after injection, releasing the drug over time into the circulation [22]. Different polymers are used in the manufacture of microspheres, and the type of polymer affects drug release rates [23]. LA for depot microsphere suspension is composed of LA encapsulated in polylactic-*co*-glycolic acid microspheres [24]. This formulation is available in 7.5 (1 month), 22.5 (3 month), 30 (4 month), and 45 mg (6 month) doses and is injected intramuscularly (IM-LA) [5]. Another LH-RH agonist, triptorelin acetate, uses a similar technology to create 1-, 3-, and 6-month formulations [25].

Poly(lactic-*co*-glycolic acid) is a bulk-eroding polymer, which is characterized by allowing water to permeate throughout the polymer matrix, degrading it over time [23]. Due to the complex and non-linear kinetics of microsphere drug release, it may be challenging for IM-LA to provide a fully controlled, sustained, and consistent release of LA throughout the dosing interval [23]. Factors affecting drug release rates include the microsphere fabrication method, type of polymer, the polymer molecular weight, the copolymer composition, the nature of excipients added to the microsphere formulation, and the microsphere size [23]. A summary of characteristics of the microsphere technology used in IM-LA is provided in Table 2.

Although microsphere technology is fairly mature, the manufacturing process remains complex [26]. Microspheres may also be incompatible with some drugs, particularly proteins, which may impact the utility of the technology for biologic drugs [23]. Another potential drawback of microsphere technology is that it is not removable which poses a potential safety issue for long-acting formulations; namely, if a patient has an adverse reaction to the drug, the long-acting drug must remain within the patient until it degrades over the course of weeks or months.

2.3.2 Biodegradable solid depot

This controlled-release technology is composed of biodegradable polymers dissolved in a biocompatible carrier [26]. The system utilizes a liquid polymer that should be combined with the active drug within 30 min before injection. After injection, the drug-polymer suspension solidifies following contact with aqueous body fluids and forms a solid implant, trapping the active ingredient within the polymer matrix. As the matrix biodegrades over time, the drug is delivered in a controlled, sustained manner [27]. LA formulated with this technology is presented in two separate syringes to be mixed prior to the injection, one with the active drug and one with the polymer mixture, for example, in the case of the 6-month formulation, it consists of LA mixed with a polymer

composed of 50% w/w 85/15 poly(DL-lactide-*co*-glycolide) and 50% w/w *N*-methyl-2-pyrrolidone [28]. It is injected subcutaneously using a short-length needle forming a solid depot of LA (SQ-LA) when exposed to subcutaneous tissue fluid. Correct preparation and subcutaneous injection technique is important for efficient drug delivery. SQ-LA is available in 7.5 (1 month), 22.5 (3 month), 30 (4 month), and 45 mg (6 month) doses [20]. A summary of characteristics of the technology used in SQ-LA is provided in Table 2.

The biodegradable polymer technology was originally developed in 1987, and there are now extensive patient-years of clinical experience, including use in periodontal disease, and acromegaly in addition to those in prostate cancer [26]. Of benefit to the patient, SQ-LA utilizes smaller injection needles and smaller drug volumes due to its subcutaneous administration, and it has less injection site discomfort compared with intramuscular delivery [21].

2.4 Pharmacodynamics, pharmacokinetics, and metabolism

During separate pivotal studies, PK/PD were evaluated for the 6-month formulations of SQ-LA and IM-LA ($n = 27$ and $n = 26$, respectively). For IM-LA, following a single injection, mean peak plasma concentration of 6.7 ng/ml was observed at 2 h and then declined to 0.07 ng/ml at 24 weeks [5]. The PK/PD observed during SQ-LA injections showed that mean serum LA concentrations rose to 82 and 102 ng/ml (C_{max}) at approximately 4.5 h following the initial and second injections, respectively. After the initial increase following each injection, mean serum concentrations remained relatively constant (0.2 – 2.0 ng/ml) [20].

To our knowledge, there have been no studies directly comparing the PK/PD of the two different 6-month LA formulations. However, there has been one head-to-head study of the 1-month formulations of IM-LA and SQ-LA. The PK/PD properties of the 7.5 mg doses of SQ-LA and IM-LA were compared in a head-to-head, single-center, randomized, Phase I study in healthy male subjects ($n = 32$; ages 18 – 55) [29]. Results of that study showed that the initial burst release of LA was higher with IM-LA than with SQ-LA (maximum concentration: 27.0 ± 4.9 vs 19.0 ± 8.0 ng/ml, respectively). As expected, upon administration of both products, the mean LA serum levels in patients showed a rapid increase, followed by continuous decrease over subsequent weeks. SQ-LA resulted in a longer duration of quantifiable mean LA in serum compared to IM-LA (42 – 56 vs 14 – 25 days). Administration of SQ-LA delivered levels of LA over time that resulted in an additional 14 days of T suppression for SQ-LA compared to IM-LA. This improved PK of SQ-LA may result in more stable T suppression over a longer period of time with fewer breakthroughs, although confirmatory studies are needed in prostate cancer patients to determine whether this difference would result in improved patient outcomes. Limitations of this study include the use of healthy subjects

Table 4. Testosterone levels and breakthroughs in pivotal clinical trial literature with SQ-LA and IM-LA: n/N (%).

Testosterone threshold	SQ-LA				IM-LA			
	1 mo [44]	3 mo [33]	4 mo [35]	6 mo [34]	1 mo [59]	3 mo [51]	4 mo [52]	6 mo [31]
≤ 50 ng/dl	118/118 (100%)	116/116 (100%)	88/90 (97.8%)	108/109 (99.1%)	Not reported	90/90 (100%)	45/45 (100%)	138/148 (93.4%)
≤ 20 ng/dl	115/118 (97.5%)	104/111 (93.7%)	81/90 (90.0%)	91/103 (88.3%)	Not reported	Not reported	Not reported	Not reported
Breakthrough	0/118 (0.0%)	1/116 (0.9%)	3/ 90 (3.3%)	1/103 (0.9%)	1/36 (2.8%)	2/90 (2.3%)	1/45 (2.2%)	8/148 (5.4%)

LA: Leuprolide acetate; IM-LA: LA injected intramuscularly; SQ-LA: Solid depot of LA; mo: Months.

rather than prostate cancer patients as well as the small size of this study.

2.5 Clinical efficacy

Both SQ-LA and IM-LA have been investigated in multiple clinical trials, using various doses and dosing frequencies (A summary of pivotal clinical trials is provided in Table 3). Of note, they have not been compared in a randomized clinical study in prostate cancer patients; therefore, direct comparison of results must be interpreted with caution. Although not fully reviewed as part of the scope of this paper, triptorelin acetate is a LH-RH agonist with a 6-month formulation and has also shown effective T suppression to the ≤ 50 ng/dl target (97.5% of patients; n = 120) [30]. A summary of the pivotal clinical efficacy experience with SQ-LA and IM-LA is provided in Table 4. Both formulations show excellent efficacy in lowering T levels to ≤ 50 ng/dl at most doses. Interestingly, all formulations by end of study resulted in > 97% of patients achieving T suppression below 50 ng/dl, with the exception of the 6-month dose of IM-LA in which 93% met the target efficacy end point [31]. T breakthroughs (defined in the pivotal trials as serum T ≥ 50 ng/dl) were generally infrequent with all doses of SQ-LA and IM-LA (Table 4). The only pivotal trial that had breakthroughs at a rate > 5% was the 45 mg (6-month) IM-LA trial, with breakthroughs reported in 5.4% (8/148) of patients [31].

Given the recent emphasis on lower castration target levels for T, it is of interest to determine whether current LA depot formulations can achieve the more rigorous target level for serum T of ≤ 20 ng/dl. These data are not reported in most of the IM-LA pivotal trials (Table 4). However, data available in one study that analyzed the proportion of patients with T levels ≤ 20 ng/dl showed that in subjects treated with 7.5 mg (1-month) IM-LA, 65.9% of subjects reached this level [32]. Recent analyses on the pivotal trials with SQ-LA showed that at end of study, 97.5, 93.7, 90.0, and 88.3%, for the 1-, 3-, 4-, 6-month formulations, respectively, were suppressed to T levels ≤ 20 ng/dl (Table 4) [21,33-35].

2.6 Safety and tolerability

LA was first approved by the US FDA in 1985 [36]. Given this 30-year history (including pre-approval clinical trials), the

overall safety profile of LA has been well established. The focus of this section will be on the 6-month doses of SQ-LA and IM-LA as they are among the most widely used formulations.

Crawford *et al.* investigated 45 mg SQ-LA in 111 patients with prostate cancer over the course of 48 weeks [34], and Spitz *et al.* investigated 45 mg IM-LA in 151 patients with prostate cancer over the course of 48 weeks [31]. The most common adverse events (AEs), including the intensity of those events, are summarized in Table 5. Overall, the safety profiles of the two formulations were similar, with the exception of severe AEs, which were more prevalent with IM-LA. The most common AEs in both formulations were hot flashes, injection site burning/pain, and fatigue. A higher proportion of subjects who received SQ-LA experienced moderate hot flashes (24.3%) than those who received IM-LA (15.2%). There was a single severe AE that was possibly treatment-related reported with SQ-LA (loss of libido), whereas there were two reported with IM-LA (colonic pseudo-obstruction and angina pectoris) [31,34].

2.7 Regulatory affairs

2.7.1 Should duration of action of LA drugs last longer than 6 months?

The newest approved depot formulations of LA are 45 mg which are dosed once every 6 months [31,34]; this is a significant advancement from the daily injections required for early LA agonist therapy [18]. The longer interval between dosing allows for fewer clinic visits as the drug is typically not administered at home, providing a more convenient and easy to follow regimen, thereby improving patient adherence and satisfaction [5,20]. Studies have shown that frequent dosing is associated with reduced treatment compliance [37,38], whereas long-acting formulations are associated with increased patient adherence to treatment [39,40].

In addition to increased patient satisfaction, another benefit of 6-month LA depot over shorter duration formulations was greater cost-effectiveness compared to both a 1-month and a 3-month LA depot [41]. A cost minimization analysis of SQ-LA across nine European countries found that the 6-month dose of SQ-LA was the least expensive treatment, with increased costs of the other doses related primarily to more

Table 5. Incidence and severity of treatment-emergent adverse events associated with 45 mg (6 month) doses of SQ-LA and IM-LA (> 10% of subjects).

Adverse event	SQ-LA (n = 111) [34]			Adverse event	IM-LA (n = 151) [31]		
	Mild	Moderate	Severe		Mild	Moderate	Severe
Hot flashes	33.3%	24.3%	0.0%	Hot flashes	38.4%	15.2%	4.6%
Arthralgia	9.0%	9.9%	4.5%	Injection site pain	14.6%	3.3%	0.0%
Fatigue	15.3%	4.5%	0.0%	Fatigue	9.9%	1.3%	0.7%
Limb pain	11.7%	8.1%	0.0%				
Injection site burning	16.2%	0.9%	0.0%				
Nasopharyngitis	9.0%	7.2%	0.0%				
Nausea	7.2%	7.2%	0.9%				
Dizziness	11.7%	3.6%	0.0%				
Edema peripheral	4.5%	5.4%	0.9%				

LA: Leuprolide acetate; IM-LA: LA injected intramuscularly; SQ-LA: Solid depot of LA.

frequent visits for injection and monitoring. Compared with the 6-month dose, the 3-month dose was 2.5 – 37.6% more expensive and the 1-month dose was 15.5 – 151.6% more expensive. The mean number of visits over 12 months was 2.1 – 2.3 visits for the 6-month dose, 4.4 – 4.8 visits for the 3-month dose, and 12 visits for the 1-month dose. Even if a patient follow-up schedule is more frequent, with longer drug formulations the focus of the visit can be disease or quality of life related rather than office time for injections.

In the effort to continually improve upon prostate cancer treatment regimens, there have been forays into developing LA formulations that last longer than 6 months. For example, Fowler *et al.* evaluated an implant that used osmotic pressure to deliver LA continuously over the course of 1 year [42]. In this study, 80 patients with prostate cancer received this implant and were evaluated for 1 year; patients then received another implant and were followed for an additional 2 months. T was suppressed to ≤ 50 ng/dl in all patients and no breakthroughs were reported. The safety profile was consistent with depot LA formulations; however, an implant did partially extrude in one patient due to inappropriate positioning [42].

The implant studied by Fowler *et al.* required a procedural insertion and removal [42], whereas current SQ-LA and IM-LA depots do not. Furthermore, the cost-effectiveness gains associated with a 6-month LA depot, compared with shorter duration depots, were primarily driven by decreased office visits [41]. It is unlikely that a once-yearly LA implant, compared with a 6-month depot, would substantially decrease the number of office visits among patients with advanced prostate cancer as standard follow-up timing during ADT is 6 months [18]; thus cost-effectiveness of these two formulations would likely be similar (assuming similar prorated drug costs).

3. Conclusion

The current debate over what should be the target level of T has not yet concluded. However, data suggest that achieving

and maintaining a lower serum T level (potential new target < 20 ng/dl) during ADT results in improved clinical outcomes in prostate cancer patients undergoing ADT. The two main technologies available for LH-RH agonist ADT are the depots, IM-LA and SQ-LA. All SQ-LA and IM-LA formulations have shown efficacy in suppressing T to below 50 ng/dl. However, there are few data on the effectiveness of IM-LA in suppressing T to ≤ 20 ng/dl, whereas SQ-LA has been shown to reliably suppress T to ≤ 20 ng/dl in $> 90\%$ of patients.

Furthermore, a head-to-head PK randomized comparison trial in healthy subjects showed that SQ-LA was associated with a slow, consistent release of LA over time, resulting in an additional 14 days of T suppression compared with IM-LA. Both IM-LA and SQ-LA are available in safe and effective formulations allowing for 6 months of treatment duration following a single injection, which is a significant advancement in prostate cancer treatment management.

4. Expert opinion

Key new findings in the field of LA treatment for ADT in men with locally advanced prostate cancer include increasing evidence that the target T threshold of < 50 ng/dl may be too high [17]. There is mounting interest in achieving and consistently maintaining the lowest possible serum T level during palliative prostate cancer treatment, as the latest findings correlate lower T levels with increased survival and longer time to androgen-insensitive progression. Hindering the adoption in clinical practice of a lower castrate T standard is a lack of consensus within the guidelines on the appropriate clinical target T level. This inconsistency has resulted in delays in updating treatment recommendations, a lack of standardization of therapy, and difficulty in determining optimal evidence-based practice. Furthermore, current research continues to struggle with the inevitability of progression towards CRPC after prolonged regimens of ADT. Another area of interest is whether switching from one LH-RH agonist to another following the

development of biochemical failure may enable prolonged, effective monotherapy. This strategy is common in European countries [43]; however, further studies and a better understanding of the underlying mechanism will be instrumental in identifying long-term solutions.

Further research on ADT and LA has the potential to enable identification of best practice to achieve medical castration in men with prostate cancer and to determine treatment modalities that prolong progression-free survival. The main objective is to reduce prostate cancer mortality and increase survival and quality of life in these men. In order to achieve this goal, larger studies with longer follow-up may be needed to confirm the clinical benefits of achieving T levels < 20 ng/dl. These studies would determine whether the available drug formulations result in sufficient suppression of T to < 20 ng/dl without escapes, whether any differences impact efficacy and patient outcomes, and ultimately will result in guideline modification and adoption. It is an interesting hypothesis that ADT therapies are not equivalent and/or interchangeable, and this has implications not only for monotherapy, but also for combination therapy, for example, when LHRH agonists are used in conjunction with newer agents for treatment of metastatic CRPC. One of the biggest challenges in achieving the goal of improved outcomes is the lack of awareness of the clinical implications of lowering T, as well as the lack of universal measurement of T in routine clinical practice. Further studies and continued education on this research area would certainly move the field in the right direction and likely have immediate positive impact on prostate cancer patients.

In the future, increased interest in ADT therapies that provide long-lasting, consistent, and stable T suppression will continue. Patients who are placed on ADT should remain on a T-suppressing regimen for the rest of their lives. As new studies are conducted and new information becomes

available, the optimization of tools in the current armamentarium and the incorporation of these tools in combination with other treatments, for example, radiotherapy and chemotherapy, may enable improved survival and the quality of life in patients diagnosed with prostate cancer.

Of particular interest in this area of prostate cancer research is the elucidation of the factors driving progression towards androgen-independent prostate cancer, finding ways to disrupt this progression, and developing novel strategies to treat prostate cancer patients who no longer respond to hormone therapy. Concurrently, determining the clinically significant definition of castration level T and optimizing ADT to achieve the best patient outcome would greatly impact the field.

Declaration of interest

ED Crawford is a consultant or advisor for Bayer, MDx, Genomic Health, Janssen, Dendreon, Ferring, and TOLMAR. JW Moul has received honoraria from Dendreon, Ferring, Janssen and TOLMAR, is a consultant or advisor for Myriad, Genomic Health, Theralogix, and is part of the speaker's bureau for Myriad, Genomic Health, Dendreon, Ferring, Janssen, Sanofi, and TOLMAR. ND Shore is a consultant or advisor for Astellas, Bayer, Dendreon, Ferring, Janssen, Medivation, TOLMAR, Sanofi, and Millennium. O Sartor has been a consultant for TOLMAR, AbbVie, and Atrix, and has been an investigator for Atrix. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Medical writing support by Drs. Jocelyn Hybiske and Mark Rocco of Xelay Acumen, Inc. was utilized in the production of this manuscript and funded by TOLMAR Inc, Fort Collins, CO.

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