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Short Communication

6-Month Formulations of Androgen Deprivation Therapy for Advanced Prostate Cancer: Effectiveness and Rationale for Extended Dosing

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DESCRIPTION

Androgen Deprivation Therapy (ADT), which reduces serum T to castration levels, is recognized as the standard treatment approach for the management of advanced Prostate Cancer (PCa). The most common ADT are Luteinizing Hormone-Releasing Hormone (LHRH) agonists and Gonadotropin-Releasing Hormone (GnRH) antagonists [1]. Elevated T concentrations are linked to a poor prognosis and increased risk of mortality in PCa [2]. Therefore, it is critical that LHRH and GnRH therapies achieve and maintain T levels below 50 ng/dL, ideally reaching below 20 ng/dL [1,3].

Adherence to dosing schedules consistently is crucial for the success of ADT. However, real-world data indicate a high rate of nonadherence to LHRH therapies, which can lead to T levels exceeding 50 and/or 20 ng/dL [4,5]. Barriers to adherence include dosing frequency, Health Care Provider (HCP) availability, appointment transportation difficulties, and cost [6]. Therefore, clinicians should evaluate which LHRH therapies provide the best balance of effectiveness and feasibility to address these common barriers, thereby avoiding nonadherence, treatment failure, and potential disease progression.

6-month LHRH formulations are proven effective for T suppression

Formulations of LHRH lasting 6 months are as effective in suppressing T compared to shorter formulations (1-, 3-, and 4 months) and compare favorably against competing products [7-12]. Research has shown that 90% of PCa patients receiving 6-month Intra-Muscular (IM) Leuprolide Acetate (LA) achieved T levels of 50 ng/dL or lower [8]. In a study of 6-month Sub-Cutaneous (SC) LA, 99% of PCa patients achieved T levels at or below 50 ng/dL by the 12th month, and 93% achieved a T nadir of ≤ 5 ng/dL [9,10]. Additionally, 93% of patients administered 6-month triptorelin pamoate maintained T levels at or below 50 ng/dL from the 2nd to the 12th month, and a pooled post hoc analysis from three phase 3 studies of triptorelin pamoate found that 96% achieved a T nadir below 0.35 nmol/L (<10 ng/dL) [11,12]. The T suppression outcomes for 6-month leuprolide mesylate were equivalent to those of other 6-month LHRH formulations [13]. However, when comparing studies, caution is advised, due to variations (e.g., different patient populations) between trials that may impact results.

Late dosing negatively impacts clinical outcomes

In real-world clinical settings, late dosing is common and has been observed to adversely affect clinical outcomes [2,5]. Therefore, LHRH formulations that minimize the possibility of delayed dosing may be preferable. A study involving 22,860 PCa patients in the United States showed that 84% of LHRH injections were administered beyond the 28-day month defined by the FDA for clinical trials, and average T levels were higher for late injections compared to those given early or on time (79 *vs.* 21 ng/dL) [5]. Additionally, for late injections compared to early or on-time injections the proportion of patients with T concentrations exceeding 50 ng/dL was much higher (27% *vs.* 4%) [5]. Consequently, LHRH formulations with longer durations of action (e.g., 6-month), which minimize the frequency of dosing, are likely to lead to more effective T suppression and improved clinical outcomes (Figure 1).

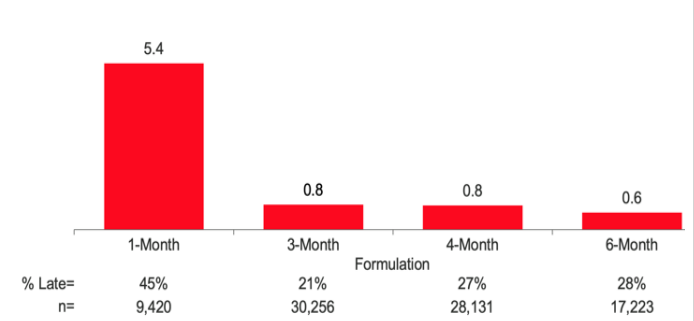

Figure 1: Expected[1] number of late[2] injections per year (n=85,030) by formulation [14]. **Note:** 1. Expected number calculated by the proportion of late injections multiplied by the number of injections per year for each formulation; 2. "Early/On-Time" if prior to, or "Late" if on/after day 33 (1-M formulation), 98 (3-M formulation), 129 (4-M formulation), or 195 (6-M formulation).

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6-month LHRH formulations minimize office visits

Beyond minimizing the chances of late dosing, 6-month LHRH treatments reduce the number of annual office visits, a change that might be favored by some HCPs and patients. A reduction in the number of visits for injections can potentially alleviate the workload for HCPs, which is important due to recent labor shortages; over 60% of US counties do not have a practicing urologist, 20% of the US population live in a rural area but only 10% of the urology workforce practices in a rural area, and federal authorities project a shortage of almost 80,000 full-time registered nurses in 2025 [15-17]. 6-month LHRH formulations also allow clinicians to maintain control over the use of ADT in their patients (*vs.* daily oral therapies that are self-administered by patients). Additionally, a decrease in the number of in-person appointments might be convenient for patients who face challenges accessing healthcare facilities, such as those living in areas with limited medical services, or for patients with dual residences like "snowbirds," patients who live in nursing homes, and patients without reliable transportation. Patients can leverage resources such as telemedicine, oncology nurse navigators, care partners, and mobile technologies to ensure ongoing care between office visits.

6-month LHRH formulations options have unique profiles

Due to the unique properties of each formulation, 6-month LHRH therapies are not necessarily interchangeable. Subcutaneous LA has a small injection volume (0.375 mL) and a short 18-gauge needle. Intramuscular LA has a 1.5 mL injection volume and a 1.5-inch 23-gauge needle [18]. A pharmacokinetic comparison between these two formulations found that 1-month SC LA had longer T suppression than 1-month IM LA (56 *vs.* 42 days), which is likely due to the different delivery systems for each long-acting injectable (polymeric gel for SC LA *vs.* Lyophilized Microspheres for IM LA) [19]. Triptorelin pamoate uses a larger injection volume (2 mL) and needle (21-gauge), and must be injected immediately after reconstitution to avoid separation of the suspension. In comparison to IM LA, triptorelin decreased T levels more slowly; by day 29%, 91% of patients on triptorelin achieved castrate T concentrations *vs.* 99% for IM LA, yet maintained castration T levels just as effectively [20]. Leuprolide mesylate comes as a pre-filled, pre-mixed emulsion that must be refrigerated and is administered with an 18-gauge needle. Clinicians and patients should select the LHRH formulation with features that best suit the patients' needs and preferences.

6-month formulations may generate health care cost savings

Despite 6-month formulations being more expensive per unit, they've been associated with reduced overall costs in comparison to shorter-acting formulations [7,21]. One study identified the reduced frequency of required treatments as a cost driver [21]. Additionally, the lowered risk of late dosing and consequent T breakthrough linked to longer-acting formulations can lower the likelihood of treatment failures and the extra costs they incur. These longer-acting formulations might also safeguard against unforeseen short-term product shortages.

CONCLUSION

The efficacy, safety, and practicality provided by 6-month LHRH formulations might render them a favored option for both patients and HCPs. Despite potential limitations in the types of ADT available to clinicians, they can still work with patients to explore all available treatment options and choose the best-suited therapy.

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