

REVIEW

# An Update on Triptorelin: Current Thinking on Androgen Deprivation Therapy for Prostate Cancer

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## ABSTRACT

Androgen deprivation therapy (ADT) is the mainstay palliative treatment for men with locally advanced and metastatic prostate cancer, and aims to reduce testosterone to levels obtained by surgical castration. Use of gonadotropin-releasing hormone (GnRH) agonists predominates among the ADT options. The GnRH agonist, triptorelin is a first-line hormonal therapy that has demonstrated efficacy and safety in clinical trials of patients with locally advanced non-metastatic or metastatic disease. Sustained-release 1-, 3- and 6-month formulations of triptorelin, administered intramuscularly or subcutaneously, have been developed to provide improved flexibility and convenience for the patient. Head-to-head studies of GnRH agonists are lacking in the field of prostate cancer. Despite the

inevitable progression to castration-resistant prostate cancer (CRPC) in most patients receiving ADT, monitoring of testosterone levels needs to improve in routine practice and physicians should not overlook the benefits of continued ADT in their patients when introducing one of the various new treatment options for CRPC. For improved survival outcomes, there remains a need to tailor ADT treatment regimens, novel hormonal agents and chemotherapy according to the individual patient with advanced prostate cancer.

**Keywords:** Androgen deprivation therapy; Oncology; Prostate cancer; Sustained-release formulations; Triptorelin

## INTRODUCTION

Prostate cancer is the most frequently occurring cancer among European men, with an estimated incidence of 416,700 (varying from 25 to 193 per 100,000 populations in different European countries) and an estimated 92,200 deaths in 2012 [1]. In the USA, incidence of prostate cancer is within this European range at

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138 per 100,000 populations according to the Surveillance, Epidemiology, and End Result program [2]. Hereditary factors are important for determining the risk of developing prostate cancer and exogenous factors may have an impact on the risk of progression. However, in general, the risk factors for prostate cancer are poorly understood and consequent advice on prevention is not possible [3]. Therefore, the management of prostate cancer focuses on treating the disease, and the hormone dependence of prostate cancer has been recognized for decades [4]. As a consequence, testosterone suppression has been the standard palliative treatment in men with advanced prostate cancer for many years. Orchiectomy is a simple, low-cost surgical procedure that effectively and quickly achieves castration, but because it is irreversible and does not allow intermittent treatment, it has become less popular than hormonal therapies among patients.

The selection of appropriate treatment is mainly dependent on the stage of disease and the risk of progression. Prostate cancer is generally described as localized, locally advanced (when the tumor has extended beyond the capsule of the prostate) and metastatic disease, and is classified using the Tumor-lymph Nodes-Metastasis (TNM) system [5]. Patients are also categorized into low, high, or intermediate risk of progression according to clinical stage, Gleason score, and prostate-specific antigen (PSA) level [6], and this will continue with the adoption of the recent International Society of Urological Pathology (ISUP) modified Gleason grading patterns [7]. However, a recent assessment of a large cohort found that while high levels of PSA (>100 ng/ml) at diagnosis were associated with a reduction in survival after 5 and 10 years, within this high-risk group PSA level was not

associated with prostate cancer-specific mortality [8]. Gleason score and the presence of metastasis were the strongest predictors of prostate cancer-specific mortality in this group with high PSA at presentation [8]. What is clear is that patients classified as having low or intermediate risk prostate cancer (Gleason score <8 and PSA <20 ng/ml) may have a 10-year prostate cancer-specific mortality of <5% [9, 10], and avoiding unnecessary treatment is a challenge in these patients [11, 12]. Patients with high-risk prostate cancer make up a considerable proportion of newly diagnosed patients and have much higher mortality rates, and therefore, the challenge in these men is to increase overall survival while reducing any adverse effects of treatment. However, this high-risk population is heterogeneous and more information is needed on the validity of suggested prognostic indicators, such as the number and location of bone metastases, visceral metastases, Gleason score, and the initial PSA level [3, 13].

This article reviews the current and ongoing role of androgen deprivation therapy (ADT) in the management of prostate cancer, with a particular focus on clinical trial and real-world evidence supporting the use of the gonadotropin-releasing hormone (GnRH) agonist triptorelin in men with locally advanced or metastatic prostate cancer. As such, this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

## THE ROLE OF ADT IN PROSTATE CANCER MANAGEMENT

ADT aims to reduce testosterone levels to the levels achieved with surgical castration [defined

as <50 ng/dl (<1.7 nmol/l) by regulatory authorities and used in clinical trials, but <20 ng/dl may be a more clinically meaningful definition of castration] [3].

ADT is recommended for patients with locally advanced prostate cancer and metastatic prostate cancer [3]. In the case of locally advanced prostate cancer, ADT is recommended only when patients are unwilling or unable to receive any form of local treatment and who are symptomatic or asymptomatic with a PSA doubling time (PSA-DT) <12 months and a poorly differentiated tumor. ADT is also recommended for lymph node positive (N1) prostate cancer whether newly diagnosed or after extended lymph node dissection. In both situations, additional radiation therapy may have a role. ADT using GnRH agonists should be combined at treatment initiation with the short-term administration of anti-androgens to prevent flare-up of symptoms due to the initial pituitary stimulation and increase in testosterone levels [3].

Androgen deprivation can be achieved with a number of different types of ADT, including GnRH agonists, GnRH antagonists, and oestrogens. Anti-androgens are also sometimes used to inhibit the action of androgens. GnRH agonists, of which the most widely used include triptorelin, goserelin, and leuprolide, stimulate gonadotropins from the anterior pituitary gland and the production of testosterone in men, but continued administration leads to the downregulation of pituitary GnRH receptors, which quickly results in the suppression of gonadotropins [luteinising hormone (LH) and follicle stimulating hormone (FSH)] followed by a decrease in testosterone levels [14, 15]. GnRH antagonists (e.g., degarelix) competitively bind to the pituitary GnRH receptors and directly

inhibit the release of gonadotropins and lead to reduced testosterone levels [16]. Oestrogens induce pituitary suppression of gonadotropin secretion and inhibit the production of androgens in the testicles but are rarely used due to their side effect profile [17]. Anti-androgens, which bind to androgen receptors and thereby block the effect of endogenous androgens, are used in combination with GnRH agonists to achieve complete androgen blockade (CAB) [18]. In the short term, the concomitant use of anti-androgens prevents the flare-up that can occur when initiating GnRH agonist therapy [18]. Anti-androgens include bicalutamide, flutamide, and the more recently developed enzalutamide [19]. Moreover, abiraterone is a novel androgen synthesis inhibitor that has been shown to block androgen synthesis in adrenal glands and prostate cancer cells. Both abiraterone and enzalutamide are generally indicated for second-line treatment when castration resistance develops with ADT [20–22].

While ADT is effective for reducing testosterone and PSA levels, almost all men treated in the long term develop castrate-resistant prostate cancer (CRPC) [23, 24], with more than 80% exhibiting bone metastases upon diagnosis of CRPC.

## TRIPTORELIN AS ADT

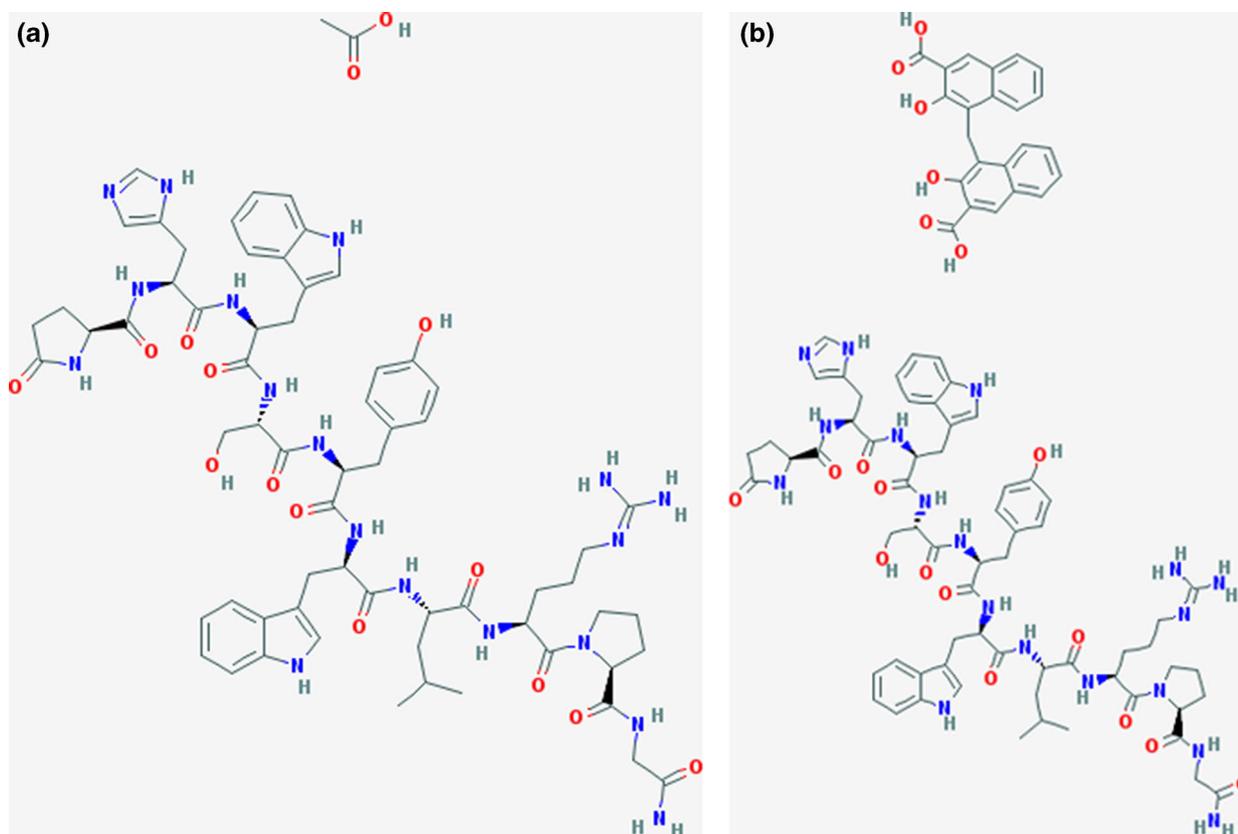
The most widely used ADT in clinical practice is GnRH agonist therapy, and one frequently prescribed agent is triptorelin (Decapeptyl<sup>®</sup>, Pamorelin<sup>®</sup>, Diphereline<sup>®</sup>, Arvekap<sup>®</sup>, Ipsen, Paris, France). In line with European Association of Urology (EAU) guidelines [3], triptorelin is indicated as the first-line

hormonal therapy in patients with locally advanced non-metastatic or metastatic disease as an alternative to surgical castration; and as add-on to external-beam radiation therapy.

Triptorelin is administered to patients in the form of acetate or pamoate (also known as embonate) salts, and in response to the need for ADT regimens that improve convenience and treatment adherence, sustained-release 1-month (3 or 3.75 mg), 3-month (11.25 mg), and 6-month (22.5 mg) formulations of triptorelin have been developed (Fig. 1) [25–27]. Sustained-release formulations of triptorelin comprise microparticles of the decapeptide incorporated within a biocompatible and biodegradable copolymer (polylactide-co-glycolide) [28].

## Pharmacokinetics

Following intravenous bolus administration, triptorelin is distributed and eliminated by hepatic and renal routes according to a three-compartment model that corresponds to plasma half-lives of 6 min, 45 min, and 3 h [27]. Sustained-release intramuscular (IM) administration of triptorelin initially stimulates LH and FSH secretion, with the subsequent production of testosterone [27]. Bioequivalence studies suggest a maximal increase in testosterone at around 4 days post-triptorelin administration. Testosterone levels progressively decline after this initial increase with continuous exposure to triptorelin [27]. Romero et al. developed a



**Fig. 1** Structure of triptorelin acetate (a) and pamoate (b) [82, 83]

pharmacokinetic/pharmacodynamics model indicating that 95% of patients with steady-state concentrations of triptorelin ( $C_{\min}$ ) higher than 0.0609 ng/ml were kept castrated [29].

Triptorelin is usually administered by IM injection. After the first month, mean serum levels of triptorelin are stable at 0.06 ng/ml for approximately 12 weeks after a single IM injection of a triptorelin pamoate 3-month formulation, with mean (standard deviation)  $C_{\max}$  of 35.7 ng/ml (18.3 ng/ml) and  $C_{\min}$  of 0.063 ng/ml (range 0.021–0.174 ng/ml) [30]. A single IM administration of the 6-month formulation of triptorelin pamoate produced a  $C_{\max}$  of 40.0 ng/ml (range 22.2–76.8 ng/ml) [15].

Patients are also offered greater flexibility by the availability of subcutaneous (SC) injections of triptorelin [31]. The IM route of administration may not be suitable for all patients (for example, the risk of excessive bleeding or haematomas in those receiving anticoagulants) [32], and so SC injections provide an alternative delivery option. The key pharmacokinetic parameters (such as  $C_{\max}$  and  $C_{\min}$ ) with the SC injection of a triptorelin pamoate 11.25 mg 3-month formulation are in the same range as observed for the IM injection [30, 31].

### Clinical Efficacy

A significant body of evidence supports the efficacy and safety of sustained-release formulations of triptorelin for the treatment of patients with locally advanced non-metastatic or metastatic prostate cancer (Table 1).

The biochemical effectiveness of ADT is measured by determining if testosterone levels are reduced by treatment to castrate levels (serum testosterone <50 ng/dl or <1.7 nmol/l).

In addition, more stringent definitions of castration have been proposed, such as serum testosterone <20 ng/dl [33]. Other cut-offs, such as 30 or 32 ng/dl, have also been proposed [34–36]. PSA levels are also utilized as a measure of treatment response. However, PSA measurement has many limitations; for example, there is little precision on the predictive value of PSA levels, there is no consensus on the magnitude or duration of PSA decline that can be used to define response, and PSA kinetics have little value in guiding management decisions. Nevertheless, in the absence of better surrogate markers, PSA decline is used as a secondary efficacy criterion in clinical trials of ADT. Ultimately, a decrease in testosterone level remains the primary biochemical surrogate efficacy parameter of medical castration.

Following promising data from early trials of depot formulations of triptorelin [37], the ability of the triptorelin 3.75 mg 1-month and the triptorelin 11.25 mg 3-month formulations to achieve castration 3–4 weeks after administration and to maintain it between the injections was demonstrated in key clinical trials encompassing 14–140 men with advanced prostate cancer [30, 38–41]. In the largest of these studies, castrate levels of testosterone were reached after 28 days in 91.2% of 140 men randomized to treatment with the triptorelin 3.75 mg 1-month formulation [40]. Moreover, in an open-label, non-comparative, Phase III study of 120 men with locally advanced or metastatic prostate cancer, the triptorelin 22.5 mg 6-month formulation was shown to achieve castrate levels of testosterone in 97.5% of patients after 28 days and in 98.3% after 12 months [15]. Similarly, >90% of patients achieved castrate levels of testosterone 1, 3, and 6 months after injection of triptorelin 22.5 mg in the recent

**Table 1** Overview of studies of triptorelin in patients with prostate cancer

Study	Patients and design	Treatments and route of administration	Efficacy outcomes
Clinical trials			
Boccardo et al. [37]	N = 95 Men with Stage C or D prostate cancer Up to 39 months	Triptorelin microcapsules, depot injections	<i>Effect on testosterone</i> Of 88 evaluable patients, about 50% showed an objective response <i>Effect on PSA</i> NR <i>Other</i> Subjective improvement with relief of bone pain and/or urinary symptoms Median PFS was 13.1 and 16.4 months in patients with stage D2 and D1, respectively Median survival of 27.6 months in stage D2 patients
Abbou et al. 1997 [41]	N = 68 Men with metastatic prostate cancer Randomized 6 months	Triptorelin 3.75 mg 1-month, six IM injections Leuprolide 3.75 mg	<i>Effect on testosterone</i> Castrate levels ( $\leq 50$ ng/ml) were achieved in 90–100% and 97–100% of patients treated with triptorelin and leuprolide, respectively <i>Effect on PSA</i> PSA declined similarly in the triptorelin and leuprolide groups (3 and 2 ng/ml, respectively, at 6 months) <i>Other</i> IPSS score decreased by 37% and 49% from baseline to 6 months in triptorelin- and leuprolide-treated patients, respectively After 6 months, 46% and 50% of the triptorelin and leuprolide groups, respectively, experienced a reduction in bone pain
Kuhn et al. [39]	N = 67 Men with prostate cancer, unsuitable for surgery Open-label, randomized 3 months	Triptorelin 3.75 mg 1-month, IM injection every 4 weeks Leuprolide 3.75 mg	<i>Effect on testosterone</i> By month 2, testosterone levels $<1.0$ nmol/l achieved in 77% and 48% of triptorelin and leuprolide groups, respectively <i>Effect on PSA</i> PSA declined similarly in both treatment groups <i>Other</i> Evolution of clinical symptoms (pain, obstructive urinary symptoms, need for analgesic drugs) did not differ between triptorelin and leuprolide at 3 months

Table 1 continued

Study	Patients and design	Treatments and route of administration	Efficacy outcomes
Bouchot et al. [30]	N = 14 Men with locally advanced and/or metastatic prostate cancer, previously untreated Open-label, phase I-II 3 months	Triptorelin 11.25 mg 3-month, single IM injection	<i>Effect on testosterone</i> Mean time to castration (testosterone <2 nmol/l) was 22 days <i>Effect on PSA</i> Mean PSA level declined to 16 ng/ml from month 1 through month 3 46.1% with PSA below normal range at 3 months <i>Other</i> Stable triptorelin plasma levels (0.06 ng/ml) from month 1 until 91 days
Minkov et al. [38]	N = 20 Men with prostate cancer requiring GnRH agonists Open-label, non-randomized, phase II 3 months	Triptorelin 11.25 mg 3-month, single IM injection	<i>Effect on testosterone</i> Castration (testosterone <1.735 nmol/L) was achieved within 3 to 4 weeks post-injection and maintained until end of month 3 <i>Effect on PSA</i> NR <i>Other</i> Improved dysuria at day 84 in one patient; micturition difficulties remained stable in other patients Improvement in performance status in 6 patients; no change in remaining patients
Heyns et al. [40]	N = 284 Men with advanced prostate cancer Single-blind, parallel group, randomized 9 months	Triptorelin 3.75 mg 1-month, nine IM injections Leuprolide 7.5 mg 1-month, nine IM injections	<i>Effect on testosterone</i> At day 29 and 57, medical castration (testosterone ≤50 ng/dl) was achieved in 91% and 98% of triptorelin-treated patients, respectively, and 99% and 97% of leuprolide-treated patients, respectively Mean testosterone concentrations were maintained below 50 ng/dl in 99% and 97% of the triptorelin and leuprolide groups, respectively <i>Effect on PSA</i> Median PSA declined from baseline to endpoint for triptorelin (46.8–1.3 µg/l) and leuprolide (36.7–1.1 µg/l); no significant differences between groups <i>Other</i> Median bone pain values on the VAS were low throughout the study in both groups No changes in QoL from baseline to endpoint in either treatment group

**Table 1** continued

Study	Patients and design	Treatments and route of administration	Efficacy outcomes
Teillac et al. [46]	N = 131 Men with locally advanced or metastatic prostate cancer, amenable to hormone therapy Open-label, parallel group, equivalence, randomized 91 days	Triptorelin 3 mg 1-month, IM injection every 28 days Triptorelin 11.25 mg 3-month, single IM injection	<i>Effect on testosterone</i> Similar proportions of patients achieved castration (testosterone $\leq 50$ ng/dl) at day 84 in the 1-month (96%) and 3-month (98%) groups Median time to chemical castration was 18.5 days in the 1-month group and 18.8 days in the 3-month group <i>Effect on PSA</i> Mean PSA concentrations decreased by 91.7% and 91.0% in the 1- and 3-month groups, respectively <i>Other</i> Few patients experienced dysuria, and the incidence of this symptom decreased with time
Bortto et al. [43]	N = 80 Men with locally advanced or metastatic prostate cancer, ADT naïve Open-label 1 year	Triptorelin 3.75 mg 1-month, IM injection every 28 days Bilateral pulpectomy	<i>Effect on testosterone</i> Castration (testosterone $< 50$ ng/dl) was achieved in 35 and 38 patients from the triptorelin and pulpectomy groups, respectively <i>Effect on PSA</i> NR <i>Other</i> Median survival was 37.5 months in the triptorelin group and 33 months in the pulpectomy group
Lundstrom et al. [15]	N = 120 Men with locally advanced or metastatic prostate cancer and/or increased PSA after failed local therapy Open-label, phase III 48 weeks	Triptorelin 22.5 mg 6-month, two IM injections	<i>Effect on testosterone</i> 97.5% achieved castration (testosterone $\leq 50$ ng/dl) at day 29 93.0% maintained castration between months 2 and 12 <i>Effect on PSA</i> Median decrease from baseline of 97% and 96% at 6 and 12 months, respectively
Mounedji et al. [47]	N = 120 Men with locally advanced or metastatic prostate cancer and/or increased PSA after failed local therapy Open-label, phase III 48 weeks	Triptorelin 22.5 mg 6-month, two IM injections	<i>Effect on testosterone</i> Castrate levels (testosterone $< 20$ ng/dl) were achieved in $> 90\%$ of patients on day 169 and 337 <i>Effect on PSA:</i> NR <i>Other</i> NR

Table 1 continued

Study	Patients and design	Treatments and route of administration	Efficacy outcomes
Kao et al. [45]	N = 41 Men with newly diagnosed locally advanced or metastatic prostate cancer amenable to hormone therapy Open-label, phase IV 180 days	Triptorelin 11.25 mg 3-month, two IM injections	<i>Effect on testosterone</i> Testosterone decreased to $\leq 50$ ng/dl in 97.5% and 100% of patients by day 90 and 180, respectively <i>Effect on PSA</i> Median PSA level decreased by 99.2% on days 90 and 180 <i>Other</i> Incidence of clinical symptoms (such as urinary symptoms, localization of pain) decreased at day 90 and further reduced by day 180 Global health status significantly improved by study endpoint
Martinez-Pineiro et al. [42]	N = 326 Men with locally advanced or metastatic prostate cancer, ADT naïve Open-label, phase III 6 months	Triptorelin 22.5 mg 6-month, IM injection	<i>Effect on testosterone</i> >90% of patients achieved castration ( $<50$ ng/dl) from 1 through to 6 months <i>Effect on PSA</i> Median PSA levels decreased from baseline (45.5 ng/ml) to 6 months (1.2 ng/ml) <i>Other</i> Baseline age, presence of metastasis, PSA level and Gleason score were not associated with a significant difference in the proportion of TMPRSS2-ERG-positive scores Gleason score was the only variable associated with non-assessability of PCA-3 score
de la Taille et al. [44]	N = 180 Men with locally advanced or metastatic prostate cancer, ADT naïve Non-interventional, longitudinal Extension of Triptocare study 3 years	Initiated on triptorelin 22.5 mg 6-month, IM injections Long term treatment at physician's discretion	<i>Effect on testosterone</i> Median testosterone levels remained low during the extension study (3 years) <i>Effect on PSA</i> Median PSA levels remained low during the extension study (3 years) <i>Other</i> Progression to CRPC occurred in 16.7% of patients at 3 years

**Table 1** continued

Study	Patients and design	Treatments and route of administration	Efficacy outcomes
Lebret et al. [31]	N = 126 Men with locally advanced and/or metastatic prostate cancer, ADT naïve Open-label 26 weeks	Triptorelin 11.25 mg 3-month, two SC injections	<i>Effect on testosterone</i> 97.6% achieved castration (testosterone <50 ng/dl) at 4 weeks; of these, 96.6% maintained castration at 26 weeks 90% probability of maintaining testosterone level <20 ng/dl up to 26 weeks <i>Effect on PSA</i> Median PSA levels were reduced by 64.2% and 96.0% at 4 and 26 weeks, respectively <i>Other</i> Decreases in LH and FSH were maintained until end of study
Observational studies			
Lebret et al. [57]	N = 1438 Men with prostate cancer initiating LHRH agonist therapy in everyday practice Prospective, observational 1 year	LHRH agonists 3- or 6-month formulations	<i>Effect on testosterone</i> NR <i>Effect on PSA</i> NR <i>Other</i> LHRH agonist therapy was initiated more frequently with a 6-month (62.8%) than with a 3-month (37.2%) formulation 'Simplification of therapeutic regimen' (86.9%) or 'fewer unnecessary visits' (46.8%) were the most frequent physician reasons for selecting the 6-month formulation More than 80% of patients were satisfied/very satisfied with their LHRH agonist treatment
Lebret et al. [56]	N = 1276 Men with prostate cancer initiating GnRH agonist therapy, aged ≥ 75 years Prospective, observational, longitudinal Up to 6 months	GnRH agonists	<i>Effect on testosterone</i> NR <i>Effect on PSA</i> NR <i>Other</i> Significant improvement in urinary symptoms, incontinence aid, emotional-functioning, social-functioning, global HRQL, sleep-disturbance, appetite-loss, and pain ( $P \leq 0.02$ ) Worsening in treatment-related symptom, sexual-activity, and sexual-functioning ( $P < 0.001$ )

Table 1 continued

Study	Patients and design	Treatments and route of administration	Efficacy outcomes
Cornford et al. [55]	<p><i>N</i> = 115</p> <p>Men with prostate cancer initiating triptorelin or switching therapy</p> <p>Retrospective chart review and prospective</p> <p>24 months (12 months before and 12 months following initiation/switch)</p>	Triptorelin 22.5 mg 6-month, IM injections	<p><i>Effect on testosterone</i></p> <p>NR</p> <p><i>Effect on PSA</i></p> <p>NR</p> <p><i>Other</i></p> <p>Significant reductions in the number of reviews (by 48.4%; <i>P</i> &lt; 0.0001), injections (by 48.4%; <i>P</i> &lt; 0.0001), and PSA tests (by 29.8%; <i>P</i> &lt; 0.0001) in the 12 months following switch versus 12 months prior</p> <p>At 12 months, median PSA was 1.30 ng/ml (23.50 ng/ml at diagnosis) for newly treated patients and 0.24 ng/ml (0.35 ng/ml at switch) for switch patients</p>
Eisenhardt et al. [58]	<p><i>N</i> = 608</p> <p>Men with locally advanced or metastatic prostate cancer</p> <p>Prospective, non-interventional, longitudinal</p> <p>1 year</p>	Triptorelin 22.5 mg 6-month, IM injections	<p><i>Effect on testosterone</i></p> <p>NR</p> <p><i>Effect on PSA</i></p> <p>NR</p> <p><i>Other</i></p> <p>Most patients demonstrated stable QoL over 1 year</p> <p>About one-quarter of patients experienced a clinically relevant improvement in global QoL</p>
Gil et al. [52]	<p><i>N</i> = 2461</p> <p>Men with advanced prostate cancer initiating triptorelin therapy in clinical practice</p> <p>Prospective, non-interventional, observational</p> <p>48 weeks</p>	<p>Triptorelin 3.75 mg 1-month, IM injections every 4 weeks</p> <p>Triptorelin 11.25 mg 3-month, IM injections every 12 weeks</p>	<p><i>Effect on testosterone</i></p> <p>NR</p> <p><i>Effect on PSA</i></p> <p>Mean PSA levels were reduced from 117.9 ng/ml at baseline to 16.6 ng/ml at 48 weeks</p> <p><i>Other</i></p> <p>Mean IPSS score decreased from 18.2 at baseline to 10.6 at 48 weeks</p> <p>QoL significantly improved following triptorelin treatment (<i>P</i> &lt; 0.001)</p>

**Table 1** continued

Study	Patients and design	Treatments and route of administration	Efficacy outcomes
Peltier et al. [53]	<p><i>N</i> = 325</p> <p>Men with locally advanced or metastatic prostate cancer scheduled to receive triptorelin therapy</p> <p>Prospective, non-interventional, open-label</p> <p>1 year</p>	<p>Triptorelin 3.75 mg 1-month, IM injections every 4 weeks</p> <p>Triptorelin 11.25 mg 3-month, IM injections every 12 weeks</p>	<p><i>Effect on testosterone</i></p> <p>NR</p> <p><i>Effect on PSA</i></p> <p>Mean PSA levels were reduced from 117.9 ng/ml at baseline to 16.6 ng/ml at 48 weeks</p> <p><i>Other</i></p> <p>Mean IPSS score decreased from 18.2 at baseline to 10.6 at 48 weeks</p> <p>QoL significantly improved following triptorelin treatment (<i>P</i> &lt; 0.001)</p>

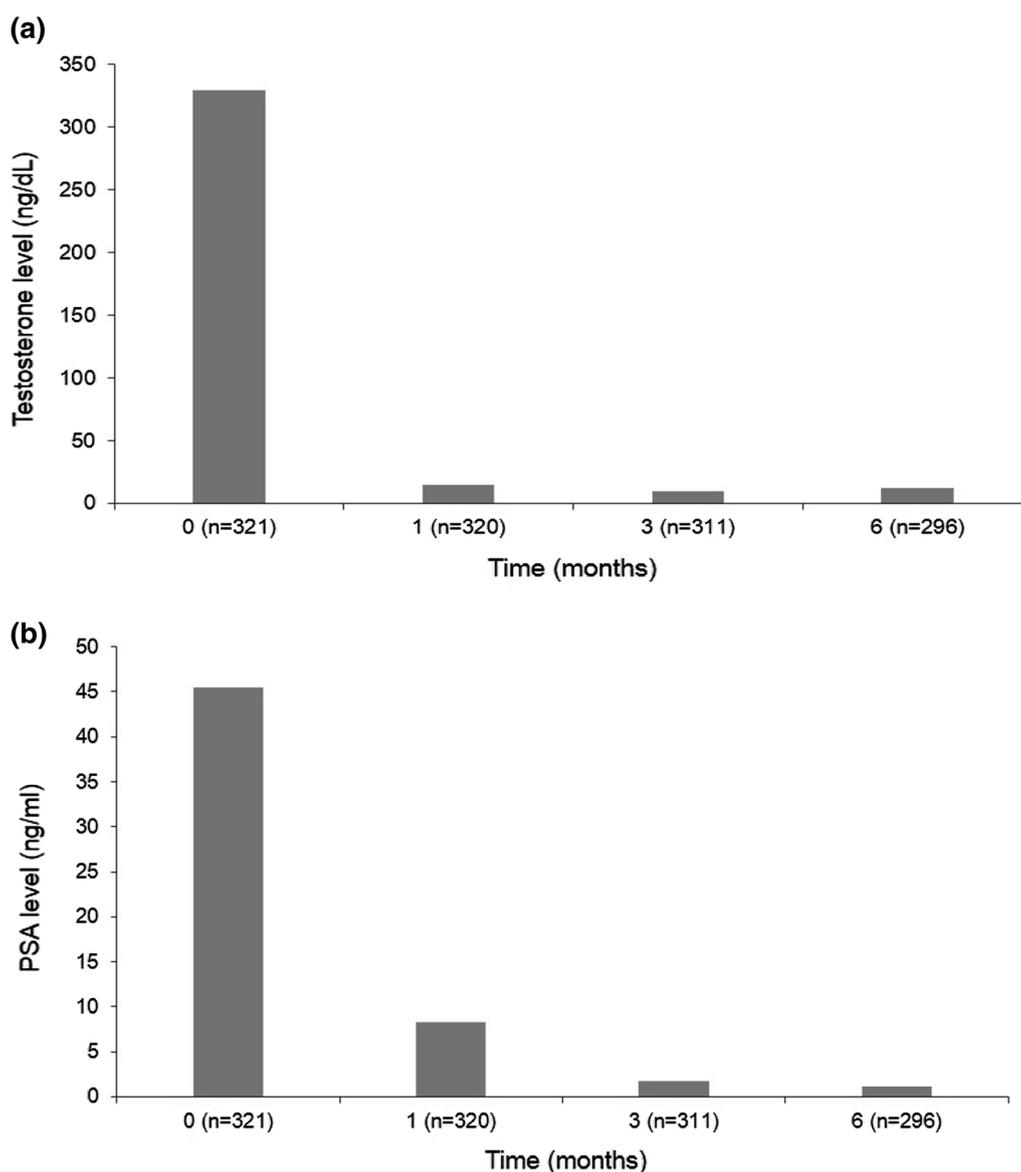
*ADT* androgen deprivation therapy, *CRCP* castrate-resistant prostate cancer, *D1 and D2* prostate cancer stage defined by the Jewett staging system, *FSH* follicle stimulating hormone, *GnRH* gonatropin-releasing hormone, *HRQoL* health-related quality of life, *IM* intramuscular, *IPSS* International Prostate Symptom Score, *LH* luteinizing hormone, *LHRH* luteinizing hormone-releasing hormone, *NR* not reported, *PCA-3* prostate cancer antigen-3, *PSA* prostate-specific antigen, *QoL* quality of life, *SC* subcutaneous, *TMPRSS2-ERG* gene fusions of the type 2 transmembrane serine protease with v-erythroblastosis virus E26 oncogene homolog, *VAS* visual analog scale

Triptocare study in 326 adult men with locally advanced or metastatic prostate cancer who were naïve to ADT [42] (Fig. 2). Castration is also maintained in the longer term [43]. The Triptocare LT study (ClinicalTrials.gov identifier, NCT01383863) showed that castrate levels of testosterone were maintained 3 years after starting ADT in men recruited into the Triptocare study; however, regular measurement of testosterone levels was infrequent in routine clinical practice [44].

In general, similar results have been reported internationally in ethnically different populations [15, 45, 46].

In addition to the standard castrate testosterone threshold of <50 ng/dl, the 1-, 3-, and 6-month formulations of triptorelin have been shown to achieve the most stringent definition of castration (i.e., serum testosterone <20 ng/dl) in >90% of patients at 6, 9, and 12 months post-IM injection [28, 47]. Although this more stringent definition of castration has not been widely adopted, the EAU guidelines state that a <20 ng/dl cut-off would be more appropriate, as better results are observed with lower levels of testosterone compared to 50 ng/dl [3]. It is, therefore, important to demonstrate in clinical trials that a high proportion of patients achieves this lower level with ADT.

The sustained suppression of testosterone with these triptorelin formulations leads to reductions in PSA levels. The triptorelin 3.75 mg 1-month formulation was shown to reduce median PSA levels from 46.8 ng/ml at baseline to 1.3 ng/ml at 9 months in 140 men with advanced prostate cancer [40]. Likewise, triptorelin 11.25 mg 3-month formulations reduced serum PSA level in treated patients [39, 45]. In one of these studies, 41 patients with newly diagnosed locally advanced or metastatic prostate cancer were administered a



**Fig. 2** Change in testosterone (a) and serum PSA (b) levels from baseline with sustained-release 22.5 mg 6-month triptorelin in men with advanced prostate cancer [42]. *PSA* prostate-specific antigen

triptorelin 11.25 mg 3-month formulation and showed reductions in median PSA from 112.7 ng/ml at baseline to 10.4 and 11.6 ng/ml at 3 and 6 months, respectively [45]. Substantial PSA decreases were also observed with the triptorelin 22.5 mg 6-month formulation from 84 days post-injection [15, 42] (Fig. 2). The longer term Triptocare LT study, which included 180 patients who had participated in and received triptorelin treatment in the

Triptocare study, showed that median serum PSA reductions were maintained after 3 years of ADT [44]. The median time to PSA nadir was 185 days [44].

All of the aforementioned efficacy data were reported with the IM administration of triptorelin. Recently, SC administration of triptorelin pamoate 11.25 mg 3-month formulation was shown to achieve castrate levels of testosterone within 4 weeks of the

first injection in 97.6% of men with locally advanced or metastatic prostate cancer [31]. Treated patients reached testosterone levels of <50 ng/dl after a median of 22 days and maintained castration until study end at 26 weeks (in 96.6% of those who achieved castration at 4 weeks) [31]. Most patients (77.7%) also met the stringent castration definition of testosterone concentration <20 ng/dl at 4 weeks, increasing to 90.8% after 26 weeks. In this study, PSA levels were also reduced from baseline by 64.2% and 96.0% at 4 and 26 weeks after injection, with median PSA levels below 4 ng/ml from week 8 through week 26 [31]. These data suggest that the route of triptorelin administration can be switched from IM to SC without compromising efficacy.

### Effect on Symptoms

Up to 40% of men with localized prostate cancer may have moderate or severe lower urinary tract symptoms (LUTS) [48], but data on the impact of ADT on LUTS are limited [49–51]. Recently, the preliminary results of an observational study in six countries suggested that treatment with triptorelin 1- and 3-month formulations improved LUTS after 6 and 12 months, as measured by a significant reduction in the International Prostate Symptom Score (IPSS) [52]. Interestingly, the improvement in LUTS after triptorelin therapy, correlated with reductions in PSA levels [52]. Similar results were observed in a prospective observational study that included 325 Belgian patients with locally advanced or metastatic prostate cancer, the majority of whom (62%) had moderate (IPSS 8–19) to severe (IPSS  $\geq$  20) LUTS at study entry [53]. After 24 and 48 weeks of treatment with triptorelin 3.75 mg and/or

11.25 mg formulations, mild or no LUTS were reported in 25.7% and 33.5% of patients, respectively [53].

The triptorelin 1- and 3-month formulations have also been associated with improvement in other clinical symptoms, including bone pain [40, 41, 45], but further study on bone pain relief is needed.

### Tolerability

Across clinical trials of patients with advanced prostate cancer, sustained-release triptorelin 1-, 3- and 6-month formulations were generally well tolerated, and the safety profile is consistent between the sustained-release formulations [15, 28, 31, 40, 42, 54]. The most frequently occurring treatment-related adverse events (AEs) with both IM and SC administrations of triptorelin were characteristic of those observed following any GnRH agonist treatment and are due to the expected pharmacological effect of the drug, i.e., castration [15, 31]. Such AEs with IM administration included hot flushes (50% of patients), erectile dysfunction (4%), and decreased libido (3%) [26, 27]. Similarly, hot flushes (10.3%) were the most frequently reported AE with the SC administration of triptorelin followed by increased weight (5.6%) [31].

Despite these AEs, discontinuation rates while receiving triptorelin are infrequent. For example, the IM administered triptorelin 22.5 mg 6-month formulation led to no withdrawals due to AEs in the pivotal trial of this formulation [15]. Equally, triptorelin 11.25 mg 3-month treatment did not lead to discontinuations due to AEs when administered by SC injection to patients with locally advanced or metastatic prostate cancer [31].

### Triptorelin in Routine Clinical Practice

Reports of triptorelin efficacy in clinical trials translate to real-world studies. For example, in a grouped analysis of 1241 men from six countries, mean PSA levels were 117.9 ng/ml before the men initiated triptorelin therapy and this was reduced to 8.5 and 16.6 ng/ml after 6 and 12 months treatment, respectively [52]. A recent preliminary report from the UK indicated that PSA remained suppressed when patients switched from any 3-month formulation of GnRH agonist to the triptorelin 22.5 mg 6-month formulation, and this switch may help reduce hospital resource use [55].

Studies of sustained-release formulations of triptorelin during routine clinical practice also demonstrate improvements in some aspects of health-related quality of life (HRQoL) and satisfaction in patients [52, 53, 55–58]. In an observational study of everyday practice in France, 1438 patients initiating treatment with triptorelin 3- or 6-month formulations for prostate cancer were evaluated for reasons for prescription and patient preference. Most patients initiated the 6-month formulation (62.8% vs 37.2% for the 3-month formulation), primarily for physician-reported reasons relating to the simplification of the treatment regimen and fewer unnecessary visits. Most patients (~80%) were satisfied with their prescribed formulation [57]. A second French longitudinal, prospective study of elderly men aged 75 years or older with prostate cancer observed that 3–6 months of triptorelin treatment did not adversely influence HRQoL. Notably, triptorelin treatment improved HRQoL related to urinary symptoms and incontinence [56].

One notable observation in many studies in routine practice is the low frequency of testosterone measurement—for example, in the Triptocare LT study, less than 20% of patients had testosterone levels measured at all time points [44]. Since testosterone level remains the primary biochemical surrogate efficacy parameter of medical castration in prostate cancer, the low frequency of testosterone measurement in practice is a concern. Greater efforts should be made to ensure testosterone measurement in future observational studies and registries to improve the quality of outcomes data, and initiatives, such as the Prostate Cancer Outcomes Registry-Australia and New Zealand, may help in this respect [59].

### ARE ALL ADTS THE SAME?

Several head-to-head trials have been conducted of sustained-release 1-month triptorelin acetate or pamoate versus leuprolide acetate [39–41]. In the most recent study, 284 men with advanced prostate cancer were randomly assigned to receive triptorelin pamoate 3.75 mg or leuprolide 7.5 mg every 28 days for 9 months (252 days). Triptorelin and leuprolide demonstrated clinical equivalence in the proportion of men maintaining castrate serum testosterone levels, defined as  $\leq 50$  ng/dl, between 2 and 9 months after starting treatment (mean levels maintained below castration limit in 98.8% vs 97.3% of the patients; cumulative maintenance castration rates of 96.2% vs 91.2%, respectively). Changes in the secondary endpoints of LH levels, bone pain, PSA levels, and quality of life were also not significantly different between treatment

groups. However, triptorelin was associated with a significantly higher 9-month survival rate than leuprolide (97.0% vs 90.5%;  $P = 0.033$ ) [40].

However, in general, there is a lack of head-to-head evaluations of GnRH agonists in advanced prostate cancer, and the aforementioned studies all used a 1-month formulation of triptorelin. In the absence of head-to-head data, cross-study comparisons suggest similar efficacy of the sustained-release 6-month formulations of the GnRH agonists triptorelin pamoate and leuprolide acetate, with medical castration rates (serum testosterone  $\leq 50$  ng/dl) of 97.5% and 97.0% at 29 days and 98.3% and 99.0% at 12 months, respectively [60].

A technology appraisal commissioned by the National Institute for Health Care and Excellence (NICE) in the UK reviewed the evidence supporting the use of the GnRH antagonist degarelix for the treatment of advanced prostate cancer and selected leuprolide, goserelin, and triptorelin as comparators [61]. A mixed treatment comparison meta-analysis of a total of six studies of the selected agents revealed that leuprolide and goserelin were associated with increased mortality compared with degarelix (odds ratio [OR] 1.8 and 1.9, respectively). In contrast, mortality with triptorelin was lower than with degarelix (OR 0.5), leading the NICE Evidence Review Group to consider that the treatment effect of triptorelin on overall survival may differ from that of leuprolide and goserelin [61]. While this analysis is intriguing, more large-scale head-to-head comparisons would be needed to draw firm conclusions on the effects of different ADTs on survival.

## THE ONGOING PLACE OF ADT IN PROSTATE CANCER MANAGEMENT

Two important topics on the role of ADT in prostate cancer management continue to be debated. First, whether tolerance and side effects of ADT can be diminished by altering the regimens used, for example, with intermittent ADT. Second, with the introduction of newer treatment options, mainly indicated for metastatic CRPC, there is a concern among clinical experts that some physicians may disregard the need for continued ADT (i.e., 'backbone ADT') [62].

The feasibility of intermittent ADT, as an alternative to continuous androgen deprivation for improving quality of life while maintaining disease control, was examined in 2013 in 1535 men with newly diagnosed metastatic hormone-sensitive prostate cancer, and was found to be inferior to continuous ADT on survival outcomes [63]. However, intermittent ADT may still have a role when patients are not metastatic, the patient profile fits the choice of strategy, or because of the strong belief that toxicity is reduced. This was tested in a secondary analysis of the trial mentioned above, with regard to toxicity. The analysis of intermittent versus continuous ADT suggested that the 10-year cumulative incidence of ischaemic and thrombotic events was significantly higher with intermittent ADT (33%) versus continuous ADT (24%,  $P = 0.02$ ). In conclusion, older men with metastatic prostate cancer who received intermittent ADT had no reduction in bone, endocrine or cognitive events, but ischemic and thrombotic events were more frequent compared with continuous ADT [64].

However, the results from these studies should be interpreted with caution, and there is a trend for improved HRQoL with intermittent versus continuous ADT and intermittent treatment may have reduced treatment costs [65]. These uncertainties have led the EAU to suggest that intermittent ADT may be an option in patients with metastatic disease after a standardized induction period [3].

Another strategy for the management of asymptomatic disease is to defer ADT until the development of symptoms. A Cochrane review of studies from the pre-PSA era suggested that early ADT in a metastatic population significantly reduced disease progression and associated complications [66]. However, the EAU guidelines highlight the difficulties in making any recommendations due to the lack of quality data [3].

On the issue of backbone ADT, the need to eliminate or suppress as many parts of the androgen receptor signaling pathway as possible provides a rationale for continuing androgen deprivation while inhibiting androgen biosynthesis with abiraterone [62]. Data suggest that the combination of abiraterone and ADT provides more sustained suppression of testosterone than abiraterone monotherapy [67–69]. Specifically, the use of abiraterone alone is not able to maintain decreased levels of testosterone in men who have not achieved castration, whereas the addition of abiraterone to backbone ADT results in sustained suppression of testosterone to low levels [67–69]. Likewise, the continuation of ADT when initiating enzalutamide therapy may help achieve greater CAB.

The rationale for continuing ADT when starting chemotherapy in metastatic CRPC (mCRPC) is that cessation of ADT may cause

renewed testosterone release and stimulation of the remaining androgen-sensitive elements of the tumor [62]. Although survival benefits of lowered testosterone in the setting of metastatic prostate cancer have not been conclusively demonstrated, improved overall survival by 13.6 months was shown with the inclusion of ADT during chemotherapy initiation compared with ADT alone in men with metastatic prostate cancer naïve to hormonal therapy from the CHAARTED (ChemoHormonal therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer) study (ClinicalTrials.gov identifier, NCT00309985) [70]. This study also showed an 8.5 month increase in median time to biochemical, symptomatic or radiographic progression with the addition of chemotherapy. In addition, the addition of chemotherapy to the first-line hormonal therapy for high-risk, locally advanced, metastatic or recurrent prostate cancer was shown to increase median overall survival by 10 months in the STAMPEDE trial (ClinicalTrials.gov identifier, NCT00268476) [71]. However, the incidence of Grade 3–5 AEs was considerably higher in the group receiving chemotherapy than in the group not receiving chemotherapy [71]. Thus, it seems the combination of ADT and chemotherapy should be initiated earlier in the treatment algorithm for high-risk disease. In patients who have already initiated ADT, it may be less clear if potential survival advantages exist by continuing ADT when chemotherapy is initiated, but it seems logical to follow expert guidance that advocates maintaining ADT when initiating chemotherapy for metastatic prostate cancer [62].

Irrespective of the above arguments in favor of maintaining backbone ADT, continuation of ADT, and maintenance of testosterone levels <50 ng/dl were stipulated as inclusion criteria

for entry into all randomized controlled trials of newer agents (e.g., abiraterone and enzalutamide) [20, 21, 72, 73], and therefore, there is no evidence to support stopping ADT when initiating these other agents. An important question that requires more data is whether certain sequences of these treatments or combinations of ADT and abiraterone and enzalutamide may benefit some patients. Several studies have assessed the optimal sequencing of treatments in different patient groups [74–77], but firm guidance is not currently possible.

As well as these issues surrounding ADT, the use of adjuvant ADT after radical prostatectomy when nodal involvement is detected continues to have an important role [3]. Similarly, adjuvant or neo-adjuvant ADT plus radiotherapy is established as standard practice for locally advanced prostate cancer, especially when disease is classified as high risk [3, 78–81].

## CONCLUSION

ADT remains the mainstay of treatment for advanced prostate cancer, with GnRH agonists predominating as a hormonal therapy of choice. Triptorelin is a GnRH agonist that is indicated as the first-line hormonal therapy in patients with locally advanced non-metastatic or metastatic disease. The availability of sustained-release 1-, 3- and 6-month formulations of triptorelin delivered via IM or SC routes offers the potential for improved flexibility and convenience for the patient with advanced prostate cancer. Moreover, sustained-release triptorelin treatment has a proven efficacy and safety profile in clinical trials, with observations from routine practice indicating patient satisfaction lending credence to clinical trial data. It is imperative that the

emergence of new treatment options for castration-resistant prostate cancer does not lead physicians to overlook the benefits of continuing ADT in their patients. However, it is also clear that optimum treatment sequencing of ADT, novel hormonal agents, and chemotherapy needs to be defined and individualized for men with advanced prostate cancer.

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