ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 33 (2015) 270–274

UROLOGIC ONCOLOGY

Seminar article

Bench-to-bedside development of agonists and antagonists of luteinizing hormone–releasing hormone for treatment of advanced prostate cancer

Ferenc G. Rick, M.D., Ph.D.[a,b,*], Andrew V. Schally, Ph.D., M.D.h.c.[a,c,d,e,f]

[a] *Veterans Affairs Medical Center and South Florida Veterans Affairs Foundation for Research and Education, Miami, FL*
[b] *Department of Urology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL*
[c] *Department of Pathology, Miller School of Medicine, University of Miami, Miami, FL*
[d] *Division of Hematology/Oncology, Department of Medicine, Miller School of Medicine, University of Miami, Miami, FL*
[e] *Division of Endocrinology, Department of Medicine, Miller School of Medicine, University of Miami, Miami, FL*
[f] *Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Miami, FL*

Received 29 September 2014; received in revised form 3 November 2014; accepted 11 November 2014

Abstract

Background: Androgen deprivation therapy (ADT) has been the standard of care for treating patients with hormone-sensitive advanced prostate cancer (PCa) for 3 decades. The agonists of luteinizing hormone–releasing hormone (LHRH), also called gonadotropin-releasing hormone, are still the most frequently used form of medical ADT.

ADT and LHRH analogs: The application of agonists of LHRH has improved and modernized the treatment of advanced PCa; millions of patients have benefited from therapy with LHRH agonists as a preferred alternative to surgical castration, as the psychological effects and perpetuity of orchiectomy are undesirable for most men. Despite their efficacy, agonists of LHRH have several shortcomings, including initial surge in testosterone, producing exacerbation of clinical symptoms, and microsurges in testosterone that might occur after each administration. A new, alternate approach to ADT is emerging with the improvements in antagonists of LHRH. This class of LHRH analogues produces a direct and immediate blockade of pituitary LHRH receptors and leads to a more rapid suppression of testosterone without an initial surge or subsequent microsurges. Degarelix, a third-generation LHRH antagonist, is the only antagonist with a low histamine-releasing activity that is currently on the market for clinical use in advanced PCa with improved testosterone suppression, better control of follicle-stimulating hormone and prostate-specific antigen, and which offers a prolonged delay to progression and more favorable effects on serum alkaline phosphatase.

Conclusions: Although LHRH agonists are still the mainstay for treatment of advanced PCa, antagonists of LHRH offer an alternative as a pharmacological approach.

Keywords: LHRH; GnRH; Hormonal therapy; Advanced prostate cancer

Basic discovery

The first landmark for the treatment of advanced prostate cancer (PCa) was the report by Huggins and Hodges [1] in 1941 that the growth of PCa cells requires testosterone. This discovery led to the use of orchiectomy or estrogens as the predominant method of androgen deprivation therapy (ADT) for patients with advanced PCa until the late 1970s [2]. The next major advance in ADT was based on the discovery of the hypothalamic neurohormone, luteinizing hormone–releasing hormone (LHRH), by one of us (A.V.S.). Our laboratory accomplished the isolation and structural identification of LHRH in 1971 [3]. Our group was also the first to show that both natural and synthetic forms of LHRH stimulate the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in mammals and humans [4]. These fundamental discoveries on the

The studies on LHRH agonists and antagonists cited in this review were supported by the Medical Research Service of the Veterans Affairs Department, Departments of Pathology, and Medicine, Division of Hematology/Oncology of the Miller Medical School, Sylvester Comprehensive Cancer Center, University of Miami, and South Florida Veterans Affairs Foundation for Research and Education (all to A.V.S.). F.G.R. was supported by the Urology Care Foundation Research Scholars Program and the American Urological Association (AUA) Southeastern Section.

* Corresponding author. Tel.: +1-305-575-3477; fax: +1-305-575-3126.
E-mail address: ferencrick@gmail.com (F.G. Rick).

http://dx.doi.org/10.1016/j.urolonc.2014.11.006
1078-1439/

hypothalamic control of the pituitary gland and the key reproductive functions of LHRH were recognized in 1975 by the Lasker Award, Gairdner and Mickle Award in 1976, and the 1977 Nobel Prize in Medicine.

Since 1971, more than 6,000 agonists of LHRH and hundreds of LHRH antagonists have been synthesized with a view to their potential medical applications. Hormonal therapy for PCa, based on agonistic analogues of LHRH, was also developed in our laboratory [2]. In addition to agonistic analogues of LHRH, our group has also developed antagonistic analogues and cytotoxic analogues of LHRH [2,5–7].

Mechanisms of action

LHRH agonists, acting on pituitary receptors for LHRH, initially produce a powerful stimulation of release of LH and FSH, which in men causes a marked elevation in testosterone [8]. Ultimately, overstimulation induced by an agonist overcomes the natural pulsatile control of LH release, leading to desensitization or down-regulation of pituitary receptors for LHRH. This phenomenon in turn suppresses LH and FSH secretion and consequently diminishes testosterone-to-castrate levels [9,10]. Antagonists of LHRH, in comparison, exert their effects directly by competitively binding to and blocking pituitary LHRH receptors, prompting an instant blockade of LH and FSH secretion [11]. This causes immediate suppression of testosterone, without any initial stimulation [12].

Synthesis of clinical-grade substance

LHRH agonists

After the discovery of LHRH, thousands of agonists of LHRH have been produced. Our group demonstrated that both native and synthetic LHRH agonists have high LH-releasing and FSH-releasing activity [2,8,13,14]. Several agonistic LHRH analogues are up to 100 times more active than native LHRH and endowed with prolonged activity [9].

The inconvenience of daily injections of LHRH agonists to suppress LH and testosterone and variations in blood levels [15] encouraged the development of sustained-release delivery systems. Long-acting depot formulations of LHRH agonists dispersed in biodegradable and biocompatible polymers offered controlled delivery of these peptides into the blood stream over extended time periods. This convenient delivery of LHRH agonists results in a persistent down-regulation and desensitization of the pituitary [2,16].

In 1986, triptorelin became the first commercialized sustained-release preparation of an LHRH agonist [16]. An initial plasma peak of the agonist in the first few hours after injection is followed by a decrease in plasma levels over 10 hours, eventually displaying a plateau level for 28 days. Testosterone levels initially increase, then decrease to lower than the castration level and persist that way for a month [16,17]. Present depot formulations of triptorelin and leuprolide in microcapsules of poly(D,L-lactide-co-glycolide) for intramuscular injection are now available in forms that release the drug over 3 to 12 months [2,16]. In addition, goserelin/Zoladex implants (dispersed in poly(D,L-lactide-co-glycolide) rods) are intended for subcutaneous administration into abdominal wall and produce continuous release for either a 4- or 12-week period [9].

LHRH antagonists

Since 1972, hundreds of LHRH antagonists have been synthesized and assayed in animals. Early inhibitory analogues were hydrophilic; however, these hydrophilic antagonists with D-Arg or related basic residues in position 6 induced histamine liberation, resulting in transient edema and other anaphylactoid reactions [13].

To eliminate the undesirable edematogenic effect, new analogues with neutral D-ureidoalkyl amino acids were synthesized in our laboratory [5]. Among these antagonists devoid of any significant edematogenic effects, cetrorelix had the highest overall inhibitory activity and receptor binding affinity [13].

Other groups have also synthesized LHRH antagonists with diminished anaphylactoid activity. Among antagonists that were developed are antide (Ares-Serono) and Nal-Glu antagonist (NIH), azaline-B, ganirelix (Organon), abarelix (Precis), and degarelix (Ferring Pharmaceuticals) [9].

Clinical trials, pharmaceutical in-licensing, and Food and Drug Administration approval

LHRH agonists

The discovery that continuous treatment with LHRH agonists resulted in testicular inhibition and chemical castration encouraged our group to apply this method to induce the regression of prostate tumors in rat models [18]. Treatment of male rats bearing the Dunning R3327H prostate adenocarcinoma with triptorelin (D-Trp^6-LHRH) decreased tumor volume and tumor weight and markedly reduced serum LH, FSH and testosterone levels [18]. Based on these findings, the first successful palliative treatment of patients with hormone-sensitive advanced PCa by LHRH agonists triptorelin and buserelin was completed at the Royal Victoria Hospital in Montreal, Canada, in collaboration with Tolis et al. [19] in 1981. A randomized controlled trial of a long-acting formulation of triptorelin injected once a month (3.75 mg, designed to release 100 μg/d) compared with bilateral orchiectomy in 41 patients with advanced PCa, provided comparative data that therapy with sustained-release LHRH agonists offers a therapeutic alternative to surgical castration [20]. Both treatments resulted in comparable reductions in testosterone and prostatic acid phosphatase, and they were considered therapeutically