Pre-clinical evidence and clinical translation of benign prostatic hyperplasia treatment by the vitamin D receptor agonist BXL-628 (Elocalcitol)

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ABSTRACT. The active form of vitamin D, 1,25-dihydroxyvitamin D3, is a secosteroid hormone that binds to the vitamin D receptor (VDR), a member of the superfamily of nuclear receptors, and exerts a number of diverse biological functions. The natural hormone and synthetic VDR agonists are well known for their capacity to control calcium and bone metabolism, but they also regulate proliferation and differentiation of many cell types, and possess exquisite immunoregulatory properties, mostly by targeting dendritic cells (DC) and T cells. These properties have been clinically exploited in the treatment of different diseases, from secondary hyperparathyroidism to osteoporosis to psoriasis. The VDR is expressed by most cell types, including cells of the urogenital system such as prostate and bladder cells. In particular, the prostate has been recognized as a target organ of VDR agonists and represents an extra-renal synthesis site of 1,25-dihydroxyvitamin D3, but its capacity to respond to VDR agonists has, so far, been proven only for the treatment of prostate cancer. We have taken a different approach, and have analysed the capacity of VDR agonists to treat benign prostatic hyperplasia (BPH), a complex syndrome characterized by a static component related to prostate overgrowth, a dynamic component responsible for urinary irritative symptoms, and a possible inflammatory component. Pre-clinical data reviewed here demonstrate that VDR agonists, and notably BXL-628 (Elocalcitol), reduce the static component of BPH by inhibiting the activity of intra-prostatic growth factors downstream of the androgen receptor, and the dynamic component by targeting bladder cells. These data have led to a proof-of-concept clinical study that has successfully shown arrest of prostate growth in BPH patients treated with BXL-628. Ongoing clinical studies will assess the capacity of this VDR agonist to reduce symptoms and ameliorate flow parameters in BPH-affected individuals. The pronounced effects of BXL-628 on bladder smooth muscle cells and its anti-inflammatory properties indeed anticipate beneficial effects also on BPH-related lower urinary tract symptoms.

INTRODUCTION

The human prostate is a urogenital accessory organ of the male reproductive tract, surrounding the urethra below the bladder neck and producing prostatic fluid, a secrete rich in fibrinolytic enzymes. Prostatic fluid contributes to 30% of the total ejaculate, and provides nutrients and optimal pH for sperm survival. Although it is generally believed that prostate secretion is essential for male reproduction, its specific function in humans is still unknown, since sperm directly derived from epididymis are still fertile (1). The prostate weight is only a few grams at birth, increases during puberty, and reaches approximately 20 g in young adults. During puberty, the prostate undergoes extensive growth and remodelling, characterized by branching of ducts and development of new gland buds, followed by acini formation within fibromuscular stroma. In contrast to the pubertal growth phase which involves the entire gland, in
about 75% of men, during the 5th decade of life there is a second growth phase selectively involving one of the three anatomically distinct prostate zones, the periurethral one. Conversely, the peripheral and central zones, which represent up to 95% of the total prostate volume, are usually unaffected.

In humans, enlargement of the periurethral zone gives rise to the most common and costly age-related disease of the male: benign prostate hyperplasia (BPH). It has been estimated that in the US private sector, direct and indirect costs related to BPH treatment approach $4 billion (2). Clinically, BPH is often associated with the development of lower urinary tract symptoms (LUTS). BPH can cause LUTS because of compression of the prostatic urethra, which, in the earliest stages, is relatively compensated by the hypertrophy of the bladder smooth muscle. However, later on, the hypertrophic bladder becomes dysfunctional with the occurrence of non-voiding contraction during the filling phase and deterioration of the ability to generate adequate voiding pressure. These symptoms have a negative impact on the quality of life of the patients. Frequency and severity of LUTS due to prostate enlargement increase with age. As the age of the world's population is progressively increasing, health-related quality of life of elderly men becomes more and more important.

The pathophysiological mechanisms underlying BPH-related end-stage bladder decompensation are still unclear, but it is likely that both increased urethral narrowing and bladder smooth muscle overactivity might be involved (3). Hence, in the development of BPH, and its related bothering symptoms, at least two distinct components can be defined: a static component, related to the overgrowth of the prostate gland, and a dynamic component, associated with smooth muscle hypercontractility. The static component is mostly responsible for obstructive symptoms, because the enlarged prostate is a mechanical obstacle to the physiological urinary outflow resulting in complaints of weak stream, intermittent urinary flow, and/or straining to void. The dynamic component is responsible for the occurrence of storage (irritative) symptoms as urinary frequency, urgency and nocturia. Recently, a third component has been recognized, the inflammatory component, related to prostatic inflammatory infiltrates observed in a large percentage of BPH surgical specimens (4, 5). The latter component might be responsible for several biological changes leading to prostate overgrowth (6, 7) and for prostatitis-like symptoms associated with BPH in at least 20% of patients (8).

The present review aims at demonstrating that 1,25-dihydroxyvitamin D3 analogs, and in particular BXL-628 (Eocalcitol), might positively impact all these three components.

**THERAPEUTIC PROPERTIES OF VITAMIN D RECEPTORS AGONISTS**

The vitamin D family comprises a series of fat-soluble bioactive secosteroids with antirachitic properties, having as classic targets the kidney, the intestine and the skeleton, where they regulate calcium absorption and metabolism. The most active vitamin D hormone is 1,25-dihydroxyvitamin D3 (1,25-dihydroxyvitamin D3). 1,25-dihydroxyvitamin D3 is generated through the combined hydroxylative activities of liver and kidney, which transform precursors as vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) obtained from animal and plant sources, respectively. However, the most important source of 1,25-dihydroxyvitamin D3 is the conversion of 7-dehydrocholesterol, present in the skin, which upon the action of ultraviolet sunlight, becomes previtamin D.

1,25-dihydroxyvitamin D3 binds with high affinity to the vitamin D receptor (VDR), a ligand-activated nuclear transcription factor, regulating specific DNA sequence in target tissues. Agonist binding induces conformational changes in the VDR, which promote heterodimerization with the retinoid X receptor (RXR) and recruitment of a number of co-repressor and co-activator proteins, including steroid receptor co-activator family members and a multimeric co-activator complex, the D-receptor interacting proteins. These co-activators induce chromatin remodelling through intrinsic histone-modifying activities and direct recruitment of key transcription initiation components at regulated promoters. Thus, the VDR functions as an agonist-activated transcription factor that binds to specific DNA sequence elements in vitamin D responsive genes (vitamin D responsive elements, VDRE) and ultimately influences the rate of RNA polymerase II-mediated gene transcription (9).

VDR agonists have different clinical applications, and they are currently used in the treatment of secondary hyperparathyroidism, osteoporosis and psoriasis (10, 11). More recently, the biological actions of VDR agonists have been shown to extend well beyond calcium metabolism to include regulation of immunity, angiogenesis, and growth differentiation as well as apoptosis of many cell types, including malignant cells (9-13).

The discovery of VDR expression in most cell types of the immune system (12), in particular in antigen-presenting cells (APC), such as macrophages and DC, as well as in activated T and B lymphocytes, prompted a number of studies investigating the capacity of VDR agonists to modulate immune responses. Following the pioneering work of Bhalla et al. (13), VDR agonists were subsequently found to be selective inhibitors of Th1 cell development (14,