



European Association of Urology



Editorial

Drug treatment for LUTS and BPH: New is not always better

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Medical therapy for lower urinary tract symptoms (LUTS), the most common manifestation of benign prostatic hyperplasia (BPH), has been firmly established in our therapeutic armamentarium for nearly 15 years. It was in the early 1990's that the selective long-acting alpha blocker terazosin and doxazosin were introduced, and just a few years later that the first 5 alpha reductase inhibitor finasteride entered the market place. These two classes of drugs have dominated the field ever since then, slashing the number of transurethral resections of the prostate (TURP) performed drastically in most developed countries around the world [1,2].

Our understanding of the natural history of the disease was at best rudimentary in 1990, and has increased equally as dramatic over the last decade. Increasing clinical experience with alpha blockers and 5 alpha reductase inhibitors, and a better understanding of the etiology, pathophysiology and natural history have refined also our understanding of the mechanism(s) of actions of these classes of drugs, as well as our ability to use them in a logical and differentiated manner [3]. While initially it was thought that both classes of drugs improve LUTS symptomatology – some to a larger degree than others – carefully done clinical trial work and practical experience coupled with long-term population based natural history studies have taught us that these early views were naïve at best and simply wrong at worst.

LUTS and BPH are progressive conditions in many men, and such progression is characterized by increased prostate size, worsening of symptoms,

bother, quality of life, deterioration of flow rate and urodynamics, and finally development of outcomes such as acute urinary retention (AUR) and surgical interventions [4,5]. Reasonably reliable predictors of progression have been identified in both population based studies and placebo control groups in long term clinical trials, such as age of the patient, symptom severity, baseline prostate size and serum PSA levels [6].

The improved understanding when BPH is or is not likely to progress allowed for a differential use of the two classes of drugs depending on initial presentation and risk profile. Patients with moderate to severe symptoms and bother who have a small prostate size and relatively low serum PSA are best treated with an alpha blocker as monotherapy as their risk for progression is very small and symptom relief is the main therapeutic goal. Moderate to severely symptomatic patients with larger glands and higher serum PSA levels, however, are best served with combination therapy, as they benefit from the disease modification induced by the 5 alpha reductase inhibitors in addition to the symptomatic improvement due to the alpha blockers.

Naturally, there are limitations regarding the use of these compounds both in terms of their clinical efficacy as well as in regards to the observed adverse events. The primary goal of all therapy is usually an improvement in symptoms, measured by the International Prostate Symptom Score or IPSS, which runs from 0–35 points. Under the best circumstances an improvement of up to six points may be achieved,

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but in many clinical trials the actual improvement under active therapy has been considerably less. An improvement of at least three points has been suggested as being the minimum change noticeable to patients as subjective improvement. Similarly, improvements in the maximum urinary flow rate have been in the range of 1.5 to 3.0 ml/sec, and it is not at all clear that patients can actually distinguish flow rates of 10 versus 12 ml/sec. The 5 alpha reductase inhibitors finasteride and dutasteride are capable of shrinking the prostate volume by 15–30% over a period of 3 to 6 months, and, remarkably, long term studies demonstrate that from that time forward there is neither significant ongoing shrinkage nor any increase in size as long as patients continue on the medication. These drugs also reduce the risk of progression to AUR and surgery by 50% or more, but the risk reduction is not linked to the extent of prostate shrinkage.

It is my conviction that we have done as well as we can with alpha blocking agents and 5 alpha reductase inhibitors alone or in combination, and that a glass ceiling in terms of efficacy has been reached. Nothing would therefore be more welcome than new therapeutic targets and compounds with an innovative mechanism of action addressing any or all of the many measurable signs and symptoms of LUTS and BPH.

Both rat and human prostate cells express the Vitamin D receptor (VDR) and respond to VDR agonist by decreasing proliferation, thus allowing the potential that VDR ligands might be a novel therapeutic avenue for LUTS and BPH. However, the active form of vitamin D, calcitriol, induces hypercalcemia and hyperphosphatemia, limiting its therapeutic potential. A newer calcitriol analogue, BXL-353, had been shown to reduce the growth rate of human BPH cells, induce apoptosis, block certain growth factors and androgen dependent cellular proliferation without causing hypercalcemia [7,8]. Encouraged by these findings, another analogue, BXL-628, was intensely studied and found to inhibit human BPH cell proliferation and induce apoptosis even in the presence of androgens or growth factors. It also decreased prostate growth to an extent similar to finasteride, inducing DNA fragmentation and apoptosis, both in intact and in testosterone-supplemented castrated rats. Accordingly, BXL-628, like finasteride, increased the expression of clusterin, a prostatic atrophy marker. However, BXL-628 did not inhibit 5 α -reductase 1 and 2, did not bind to the androgen receptor (AR) in BPH homogenates and did not affect AR-coupled luciferase activity. In addition, BXL-628 did not affect rat pituitary and testis activity or calcemia [8].

In this issue of European Urology the first randomized, placebo-controlled, multi-center trial using BXL-628 in men with BPH for a 12 week treatment duration is reported [9]. Given the pre-clinical data and our understanding of the natural history of LUTS and BPH, what might we expect from such a compound in the clinical setting? Certainly an influence on further prostate growth, perhaps a volume reduction, and hopefully some improvement in symptoms or a reduction in the rate of AUR or surgery. To state it upfront and quite clearly, very few if any of these goals are achieved in the current trial. However, one might ask, what could one expect in a three months trial? All 5 alpha reductase inhibitor studies were at least of 6 months duration, most of them one, two or even four years long, given ample opportunity for the placebo treated prostate to exhibit their natural growth characteristics and for the actively treated prostates to shrink, and secondarily, for beneficial effects of the volume reduction to take place such as symptom relief and reduction in the risk for AUR and surgery. The authors recognized the potential mechanism of action and took it into consideration when designing the trial: patients had to have a prostate volume of greater than 40 ml, and the mean volume was 74 and 80 cc in the 62 placebo and 57 BXL-628 treated patients, respectively. As expected the mean serum PSA was quite high at 4.4 and 4.1 ng/ml, respectively, in the two groups. Symptom scores were not evenly distributed with the mean score being 15.3 and 13.5 points for the placebo and BXL-628 groups. The primary outcome was presumably a change in the prostate volume measured by MRI, and a decrease in volume by more than 5% from baseline was considered a “responder” while an increase by more than 5% a “non-responder”. This was partially based on a 20% volume reduction over one year in finasteride trials, and the authors assumed a linear effect, ie a decrease by 5% in the first 3 months continued out over 12 months and resulting in a 20% decrease. Sample size calculation was based on a –1.9% change in volume in the placebo and a –15% change in the BXL-628 treated groups with a standard deviation of 20%, resulting in the need for 50 patients in each group.

After 12 weeks of treatment the placebo group experienced a 4.3% volume increase while the BXL-628 treated group a decrease by –2.9%, for a difference of –7.22% ($p < 0.0001$). There were 28.9% responder in the BXL-628 group vs. 7.7% non-responder, while there were 51.7% non-responder in the placebo group ($p < 0.0001$). Changes in IPSS (–3.5 vs. –1.8 for placebo vs. BXL-628) and maximum flow rate (+1.5 vs. –0.3 ml/sec) were not significant,

but the trend was unfavorable for the active treatment group. Both groups experienced slight PSA increases and no change in serum testosterone. It is perhaps unexpected if not disturbing that the placebo group experienced a rather large decrease in serum dihydrotestosterone by 182.5 pg/ml, and also a rather large increase in urine calcium and phosphate excretion, neither one of these being presumably significant.

How does one interpret these “mixed” results? First, it is hard for me to accept the discrepancy between the responder definition and the sample size calculation. It is simply not justified to assume a linear, i.e. continuing decrease in prostate volume as there is no precedence for it. The shrinkage is achieved at 6 mo and there is very little further change in volume noted with either finasteride or dutasteride. Secondly, why did they assume a -1.9% decrease in the placebo group? Should the volume not slightly increase? A -15% decrease in the BXL-628 group was assumed to take place over 12 weeks. This would be - assuming as they did a linear response - a 60% decrease over one year, and such observation appears overly optimistic. What ultimately was seen was a 4.3% increase in volume in the placebo group. Assuming a linear increase in size - in this case certainly reasonable - it would translate into a 17.2% increase in one year, which is greater as in most other clinical trials such as PLESS or MTOPS! The 2.9% decrease in the BXL-628 group would translate into a disappointing 11.6% decrease over one year - assuming linear decrease - or less if the shrinkage would end after 3-6 months analogously to finasteride data. These differences are statistically significant, but are they clinically meaningful? One has to doubt this very much indeed. A 2.9% decrease from a baseline of 80 cc is about 2.3 cc or just under 10 cc over a year, a shrinkage from 80 to 70 cc. If patients would be offered a classic trade off: take a tablet every day and shrink your prostate by 12% or 10 cc, no effect on symptoms and uncertain effect on risk of AUR or surgery, I doubt that many would buy into this option.

No doubt, we are all looking for new therapeutic targets and exciting molecules in the treatment of LUTS and BPH. A safe compound capable of significant shrinkage and elimination of further

growth might be acceptable, provided the safety profile is acceptable and it is not too expensive. The current trials with BXL-628, however, is less than convincing, and it would take a substantial change in the observed outcomes in a trial of at least one year duration to convince me that this represents a reasonable therapeutic option.

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