Emerging therapies: what's new is old and what's old is new

Jack Barkin, MD,[1] Christine Folia, PharmD[2]

[1]Department of Surgery, University of Toronto, Humber River Regional Hospital, Toronto, Ontario Canada

[2]Agro Health Associates In., Burlington, Ontario, Canada

BARKIN J, FOLIA C. Emerging therapies: what's new is old and what's old is new. *Can J Urol* 2012;19 (Suppl 1):49-53.

Researchers are constantly seeking ways to improve existing drugs, drug mechanisms of activity, find new indications for old drugs or to develop new drugs to treat urological diseases and conditions. In Canada, tadalafil in a 5 mg daily dosage (old drug), and a new drug, silodosin, have recently become available to treat patients who have benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS). In clinical studies, silodosin has shown promise as a treatment for ureteral stones, whereas it has shown conflicting results as a potential treatment for prostatitis. Two new therapies have emerged for treating overactive bladder (OAB): Mirabegron (not yet available in Canada) and fesoterodine (newly introduced in the marketplace). New therapies—denosumab (to prevent skeletal events) and abiraterone acetate and enzalutamide—were recently approved to treat certain patients with advanced prostate cancer. With the advent of new therapies to treat urological diseases, in many cases, primary management of the patient is often shifted from the urologist to the family physician, and sometimes moved from the oncologist to the urologist.

Key Words: indications, ED/LUTS, silodosin, cialis, abiraterone, denosumab, enzalutamide, fesoterodine

Introduction

In the evolution of drug development there are often surprises where an investigator might serendipitously discover that the indication a drug is primarily being tested for will not be the therapeutic area for which the drug will ultimately be determined to be most effective. A very good example is in the development of phosphodiesterase-type 5 (PDE-5) inhibitors. Initially, because of their known impact on nitric oxide metabolism, these drugs were being tested as a potential treatment for angina. However, it became evident that they were more effective for treating erectile dysfunction (ED), and that is their current approved primary indication.[1,2] The evolution of the use of this class of drugs did not stop here. As predicted[1] and reported[3] elsewhere, one of the PDE-5 inhibitors (daily tadalafil) has now been approved for men with ED and lower urinary tract symptoms (LUTS). However, first-line therapy for men with small prostates and LUTS remains an alpha blocker.[4]

The current article reviews some of the published data about new drugs for old conditions and new, non-approved (but trial-suggested) uses for older approved drugs.

Address correspondence to Dr. Jack Barkin, Department of Surgery, University of Toronto, 404-960 Lawrence Avenue West, Toronto, Ontario M6A 3B5 Canada

BPH/LUTS

Silodosin (Rapaflo)

Dr. Kapoor provides an overview of the management of benign prostatic hyperplasia (BPH)/LUTS elsewhere in this supplement.[3] The choice of one of the two most commonly accepted medical therapies for BPH is based on prostate volume and symptom severity (degree of bother) that the patient is reporting. For patients with small prostates and moderate symptoms, alpha blockers are most often indicated. Investigators have determined that there are three main alpha receptors: α1A, α1B, and α1D. It appears that α1A receptors are more specific for smooth muscle in the urinary tract, whereas α1B receptors are more often found in blood vessels.[5]

Since the early 1990s when patients who were being treated with the non-selective alpha blocker terazosin for hypertension reported an improvement in their urinary flow and BPH symptoms, there has been a quest to develop a more uro-selective alpha blocker to mitigate vascular side effects such as orthostatic hypotension and nasal stuffiness, which are commonly reported by patients.[6] Tamsulosin is one of the most prescribed uro-selective alpha blockers.

In Canada, the selective alpha blocker silodosin was recently approved for the treatment of BPH/LUTS. Dr. Kapoor describes the indications and advantages of silodosin in an article in this supplement.[3] In vitro experiments have demonstrated that silodosin's α1A-to-α1B binding ratio is extremely high (162:1), whereas tamsulosin's α1A-to-α1B binding ratio is only 50:1.[7]

The European clinical study led by Chapple that compared tamsulosin to silodosin to placebo with the aim of demonstrating non-inferiority showed some interesting results.[8] Most notably, silodosin was proven to be non-inferior to tamsulosin and better than placebo for the reduction of International Prostate Symptom Score (IPSS) and improvement in quality of life. It was also slightly better than tamsulosin in improving Qmax response and in possibly reducing nocturia episodes. The major difference was in the reported incidence of ejaculatory dysfunction: 14% with silodosin versus only 2% with tamsulosin. However, the rates of withdrawal from the study due to this side effect were virtually identical for both alpha blockers.

Daily tadalafil (Cialis)

A new approval/indication for an "old" drug became a reality in Canada recently, when 5 mg daily tadalafil was approved for men with ED and LUTS, secondary to BPH. This approval had been predicted in a previous article,[1] in which Barkin had discussed guidelines for the management of patients with BPH, which recommend stratifying patients by symptoms and prostate size. Men with small prostates (< 30 cc) and moderate symptoms should be offered an alpha blocker, whereas men with enlarged prostates (> 30 cc) and moderate symptoms should be offered the combination of an alpha blocker and a 5-alpha reductase inhibitor (5-ARI) from day one. This provides the greatest reduction in the risks of clinical progression, acute urinary retention, and need for surgery.[1]

Some men who are receiving combination therapy may still have LUTS or may experience ED as a side effect of the 5-ARI. ED has been shown to be associated with more severe LUTS, where the degree of LUTS is a risk factor for ED.[9] To treat ED, 5 mg daily tadalafil represents a paradigm shift from on-demand PDE-5 inhibitors. A 1 year, open-label study reported that patients who were treated with 5 mg daily tadalafil had improved International Prostate Symptom Score (IPSS) results, quality of life, and International Index of Erectile Dysfunction (IIEF) scores.[10]

Daily tadalafil is now approved as monotherapy for men who have ED and BPH/LUTS, simultaneously. In my opinion, it should also be indicated for men with enlarged prostates, ideally given in combination with the 5-ARI (if they have stopped the alpha blocker because of side effects or lack of efficacy).[1]

Ureteral stones

Silodosin (Rapaflo)

For many years, research suggested that there are alpha receptors in the human ureter. This theory was tested clinically to determine if the use of alpha blockers might encourage the passage of ureteral stones.[11]

Recently, a Japanese study of 187 patients looked at ureteral stone management and compared the standard approach of high fluid intake and watchful waiting (control group) versus high fluid intake and use of silodosin (sildosin group).[12] This was the first published study to report the efficacy and potential utilization of silodosin in the management of ureteral stones. The results were very encouraging. Overall, the stone expulsion rate was 50.0% (92 patients) in the control group versus 66.3% (89 patients) in the silodosin group ($p = 0.056$). The mean expulsion times were 15.19 ± 7.14 days in the control group versus 10.27 ± 8.35 days in the silodosin group, ($p = 0.0058$). The study stratified the stones into six categories depending on their size and location. For stones in the distal ureter that were 6 mm to 9 mm in diameter, the

expulsion rate was 30.4% (46 patients) in the control group versus 52.2% (44 patients) in the sildosin group, (p = 0.036). The mean expulsion times were 21.00 days in the control group versus 11.33 days in the sildosin group, (p = 0.038). The mean number of times that narcotic pain medications were necessary was 1.7 times in the control group versus 1.1 times in the sildosin group, (p = 0.151).

Prostatitis

Silodosin (Rapaflo)

Chronic prostatitis, which has been proven to be abacterial and which is commonly termed chronic pelvic pain syndrome (CPPS), is a highly prevalent, very difficult-to-treat disease.[13] Because LUTS accompanies pain in CPPS, a number of studies have looked at whether using alpha blockers might ameliorate symptoms. Although the studies suggested that these drugs might help, the findings have been inconclusive and inconsistent.[14]

Nickel et al recently reported results from a randomized, double-blind, placebo-controlled trial in which 151 patients with CPPS were randomized to receive 4 mg silodosin, 8 mg silodosin, or placebo once daily for 12 weeks.[15] The study endpoints were the change in National Institutes of Health Chronic Prostatitis Symptom Index total score and the impact on urinary symptoms and quality of life. For all parameters tested, the patient response with silodosin was significantly better than with placebo, and there was a marked improvement in quality of life. There were no significant incremental improvements in patients who received an 8 mg dose versus those who received a 4 mg dose. Although the results need to be confirmed in further studies, they are very encouraging, and suggest a potential alternate treatment approach for men with this very difficult-to-treat disease.

Overactive bladder

Radomski and Barkin provide an overview of the diagnosis and management of overactive bladder (OAB) elsewhere in this supplement.[16] OAB is a very common disorder that has received a lot of attention in the past few years. The primary treatment approach is to use a medication that decreases the sensitivity of the bladder and thereby improves the symptom of urgency, which may or may not be accompanied by incontinence and frequency.

The main class of drug for managing OAB has been the anticholinergic/antimuscarinic medications. The first significant agent for OAB was the anticholinergic agent oxybutynin, and the gold standard therapy for OAB is still immediate-release, oral oxybutynin. The most common deficiency of these agents is not their efficacy, but their side effect profiles, which include increased risk of dry mouth and constipation, aggravation of narrow-angle glaucoma, and a potential impact on cognition in the elderly. Over the years, because of bothersome side effects and a lack of compliance due to the multiple doses per day required with these agents, attempts have been made to develop new, long-acting compounds.

Mirabegron

Mirabegron is a β3-adrenoceptor agonist, the first in a new class of agents developed for the treatment of OAB. It has a direct impact on this condition by causing relaxation of the detrusor muscle. In the normal urination cycle, there are storage, voiding, and post-micturition phases. By acting on the detrusor muscle during the urine storage phase, the drug increases bladder capacity and lengthens the interval between voiding. It does not prevent bladder contraction during the voiding phase.[17] The drug can also reduce the sensation of urgency. Mirabegron, given as once daily doses of 25 mg or 50 mg, has been approved in Japan and the United States for treating symptoms of OAB. A study of Mirabegron (Astellas) was recently completed in Canada.

Fesoterodine (Toviaz)

Fesoterodine was recently approved by Health Canada and launched in the marketplace. It is an interesting drug, because it is the metabolite of tolterodine (Detrol). It does not impact the liver, since under the influence of serum esterases it is rapidly hydrolyzed to its active moiety, 5-hydroxymethyl tolterodine—which is also the active metabolite of tolterodine. Tolterodine has a maximum dosage of 4 mg/day due to concerns about potential QT prolongation. In clinical trials, fesoterodine did not prolong patients' QT intervals, and this added safety feature allows for dose titration from the recommended starting dose of 4 mg daily to 8 mg daily, in certain patients.[18] This may provide better efficacy; however, as with all drug dose titrations, the clinician balances the efficacy response against the potential for increased side effects.

Prostate cancer

The article by Shayegan[19] in this supplement provides insight into the urologist's approach for diagnosing and managing different stages of prostate cancer. For invasive,

aggressive, bulky disease, or early metastatic disease, the first therapeutic approach is hormonal ablation. The accepted theory is that the growth and spread of prostate cancer is stimulated by testosterone. By inducing surgical or medical castration in a patient, the clinician commonly sees a lowering of prostate-specific antigen (PSA) levels and regression or stabilization of the prostate cancer.[20] However, the use of the anti-testosterone agents can cause bone-related and metabolic problems. The onset of bone metastases signals impending skeletal-related events and pain or death.[21]

Denosumab (Xgeva)

As mentioned, the primary treatment approach for extensive prostate cancer is hormonal ablation. However, when a patient no longer responds to this treatment, he is said to have castration-resistant prostate cancer and is usually offered chemotherapy.[19]

The treatment approach for men with prostate cancer and bone metastasis has been to give intravenous agents such as zoledronic acid (Zometa) to reduce the progression of the bone metastasis. The problem with this agent is that the patient's renal function must be carefully monitored, and the drug must be given in a chemotherapy unit, in most cases.[22]

Denosumab is a synthetic human monoclonal antibody against RANK ligand (RANKL), which is the main driver of osteoclast formation. It is believed that in bone metastasis, osteoclasts cause the bone destruction.[23] The benefit of denosumab is that it is given subcutaneously, the clinician only needs to monitor the patient's calcium levels for the first few months, and it avoids concerns about potential renal or liver effects.

In a study of 1904 patients with castration-resistant prostate cancer who were randomized to denosumab or zoledronic acid, the median time to the first on-study, skeletal-related event was 20.7 months with denosumab and 17.1 months with zoledronic acid. The conclusion was that denosumab represents a novel, easily used treatment option that was better than zoledronic acid in preventing skeletal-related events in men with castration-resistant prostate cancer.[24] Denosumab is now approved and covered by many provincial insurance plans for that indication.

Abiraterone acetate (Zytiga)

Abiraterone acetate targets extragonadal androgen production by inhibiting the CYP17 lyase enzyme, which is a potentiator of androgen biosynthesis. It represents a new approach to more efficient hormonal ablation in an ORAL agent, compared to the injectable anti-hormonal agents LHRH analogues and antagonists.

Recently Health Canada and the US Food and Drug Administration (FDA) have approved Zytiga for men with prostate cancer who have not responded to chemotherapy. Based on a recent study, the drug's manufacturer is applying to broaden the indication to include men with castration-resistant prostate cancer who have not yet had chemotherapy. At the American Society of Clinical Oncology (ASCO) meeting this summer, an investigator presented this study, which compared abiraterone plus prednisone to placebo plus prednisone in chemotherapy-naïve patients with castration-resistant prostate cancer. Progression-free survival in the placebo arm was 8.3 months, but it was estimated to be double that in the treatment arm. Progression-free survival was "estimated," because the benefit was so obvious that the study was terminated early and the patients on placebo were given abiraterone. It appears that overall survival in this difficult-to-treat population is increased by 25% in the treatment arm compared to placebo.[25]

Enzalutamide (Xtandi)

At the end of August 2012, the FDA approved enzalutamide (Xtandi [formerly called MDV3100]), an anti-androgenic/chemotherapeutic agent for men with castration-resistant prostate cancer who have not responded to chemotherapy. The approval was largely based on a study of patients with castrate-resistant prostate cancer after attempts at salvage with chemotherapy, where it was found that those who were treated with enzalutamide had a median survival of 18.4 months, whereas those receiving placebo had a median survival of 13.6 months. Enzalutamide is an oral agent that provides competitive binding at the level of the androgen receptor, prevents the translocation of the androgen receptor from the cytoplasm to the nucleus, and, within the nucleus, inhibits binding at the DNA level.[26]

Conclusion

In all areas of the management of urological diseases, there is constant investigation to determine if the mechanism of action of older drugs can be enhanced, or if older drugs can be applied to new indications, or if newer drugs can be developed to attack "old" diseases for which we still do not have an ideal, reliable cure. The initial diagnosis and management of some of these conditions, because of the ease of utilization and safety of some of these newer agents, is now often shifting to the family physician from the urologist or sometimes to the urologist from the medical oncologist.

Disclosure

Dr. Jack Barkin has been a clinical investigator, speaker and medical advisory board member and consultant for Abbott, Lilly, Bayer, Paladin, Watson Pharma, Bayer, AstraZeneca , Astellas, Solvay, Pfizer and Triton.
Dr. Christine Folia has no potential conflict of interest. □

References

1. Barkin J. Benign prostatic hyperplasia and lower urinary tract symptoms: evidence and approaches for best case management. *Can J Urol* 2011;18(Suppl 1):14-19.
2. Greenspan MB, Barkin J. Erectile dysfunction and testosterone deficiency syndrome: the "portal to men's health". *Can J Urol* 2012; 19(Suppl 1):18-27.
3. Kapoor A. Benign prostatic hyperplasia (BPH) management in the primary care setting. *Can J Urol* 2012;19(Suppl 1):10-17.
4. Nickel JC, Mendez-Probst CE, Whelan TF, Paterson RF, Razvi H. 2010 Update: Guidelines for the management of benign prostatic hyperplasia. www.cua.org/guidelines/bph.
5. Hatano A, Takahashi H, Tamaki M, Komeyama T, Koizumi T, Takeda M. Pharmacological evidence of district a1-adrenoceptors subtypes mediating the contraction of human urethra and peripheral artery. *Br J Pharmacol* 1994;113(3):723-728.
6. Barkin J. Medical management of BPH. *Perspectives in Cardiology* 1993;Suppl:25-32.
7. Tatemichi S, Kobayashi K, Maezawa A et al. a1-Adenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213). *Yakugaku Zasshi* 2006;126:209-216.
8. Christopher R. Chapple, Francesco Montorsi, Teuvo LJ et al on behalf of the European Silodosin Study Group. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. *Eur Urol* 2011;59(3):342–352.
9. Rosen R, Altwein J, Boyle et al. Lower urinary symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7) *Eur Urol* 2003;44(6):637-649.
10. Donatucci CF, Brock GB, Goldfischer ER et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open label extension study. *BJU Int* 2011;107(7):1110-1116.
11. Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol* 2003;170(6 Pt 1):2202-2205.
12. Itoh Y, Okada A, Yasui T et al. Efficacy of selective a1A adrenoceptor antagonist Silodosin in the medical expulsive therapy for ureteral stones. *Int J Urol* 2011;18(9)672-674.
13. McNaughton Collins M. The impact of chronic prostatitis/ chronic pelvic pain syndrome on patients. *World J Urol* 2003;21(2) 86-89.
14. Nickel JC, Narayan P, McKay J, Doyle C. Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. *J Urol* 2004;171(4):1594-1597.
15. Nickel JC, O'Leary MP, Lepor H et al. Silodosin for men with chronic prostatitis/chronic pelvic pain syndrome: results of a phase II multicenter, double-blind, placebo controlled study. *J Urol* 2011;186(1):125-131.
16. Radomski SB, Barkin J. Medical management of overactive bladder. *Can J Urol* 2012;19(Suppl 1):2-9.
17. Takasu T, Ukai M, Sato S et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]ethyl} acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. *J Pharmacol Exp Ther* 2007;321(2):642-647
18. Gomella LG Lallas CD, Perkel R et al. Uropharmacology in primary care: 2010 update. *Can J Urol* 2010;17(Suppl 1); 35-51.
19. Rehsia S, Shayegan B. PSA implications and medical management of prostate cancer for the primary care physician. *Can J Urol* 2012;19(Suppl 1):28-35.
20. Barkin J. PSA and the family physician. *Can J Urol* 2011;18 (Suppl 1):20-23.
21. Liu XS, Folia C, Gomella LG. Pharmacology for common urologic diseases: 2011 review for the primary care physician. *Can J Urol* 2011;18(Suppl 1):24-38.
22. Saad F, Gleason DM, Murray DM et al. Long term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone refractory prostate cancer. *J Natl Cancer Inst* 2004;96(11):879-882.
23. Percival RC, Urwin GH, Harris S et al. Biochemical and histologic evidence that carcinoma of the prostate is associated with increased bone resorption. *Eur J Surg Oncol* 1987;13(1):41-49.
24. Fizazi K, Carducci M Smith M et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castrate-resistant prostate cancer: a randomized, double blind study. *Lancet* 2011;377(9768):813-822.
25. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364(21):1995-2005.
26. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012 DOI:10.1056/NEJMoa 1207506.