A Report on Comparative Safety and Efficacy of Vibegron in the treatment of Overactive Bladder (OAB)

Dr. Mohammad Younus Mohiuddin – Portfolio Management

Introduction

Overactive bladder (OAB) is a chronic symptom syndrome characterized by urgency with or without urgency incontinence, often with increased daytime frequency and nocturia, in the absence of an underlying pathologic or metabolic condition that may cause or mimic the symptoms[1].

Urinary incontinence has been defined by the International Continence Society as "the complaint of any involuntary leakage of urine"[2]. The prevalence of urinary incontinence has been estimated as 13.1% in women and 5.4% in men [3]. Epidemiological studies have estimated the prevalence of OAB to be 14%–16% after the age of 40 years and prevalence increases inexorably with age for both men and women. It is estimated that one third of OAB patients have urgency incontinence[3].

The etiology of OAB is multifactorial. Although a large proportion of cases are idiopathic, recognized contributing factors include lower urinary tract pathology (infection, calculi, and stones), neurological conditions (stroke, dementias, multiple sclerosis), systemic conditions (congestive heart failure, diabetes mellitus), functional and behavioral conditions (caffeine and alcohol consumption, mobility), and side effects of medication[4].

The primary treatment for OAB and urgency incontinence is a combination of behavioral measures (including bladder retraining) and antimuscarinic drug therapy. Despite the proven efficacy of these drugs for the relief of OAB symptoms, side effects impair tolerability and persistence with therapy[5].

Older antimuscarinic agents such as oxybutynin are neither bladder nor muscarinic receptor subtype selective and are thus associated with greater generalized anticholinergic side effects. Commonly reported side effects of all antimuscarinic drugs include dry mouth, constipation, blurred vision, gastro-esophageal reflux, and cognitive

impairment[6]. Recently concern has arisen regarding the potential for significant cognitive impairment of patients receiving antimuscarinic drugs which exert an effect on M1 receptors and which can cross the blood brain barrier[7].

Antimuscarinic drugs are still the mainstay of oral pharmacological treatment for OAB, relaxing the detrusor muscle and reducing sensory symptoms during the storage phase of the micturition cycle by inhibiting muscarinic receptor subtypes, M3 and M2. Both subtypes are expressed in multiple tissues, increasing the risk of bothersome, anticholinergic adverse events (AEs) such as dry mouth, which along with lack of efficacy, is the most frequently cited reason for discontinuation of antimuscarinic treatment[8]. Due to these reasons approximately 50% and 75% patients discontinue treatment at 3 - 6 months and 1 year respectively[8, 9].

However, anticholinergic medication for an OAB is not the only medication with anticholinergic activity. There have been concerns that polypharmacy with multiple anticholinergic medications that have some anticholinergic action may lead to a significantly raised anticholinergic burden and reduced cognitive function or dementia in the long term[10]. Several papers have also linked anticholinergic burden to dementia or Alzheimer's disease[11, 12].

The ideal antimuscarinic agent should effectively relieve the symptoms of OAB, with the minimum of side effects; it should be available as a once daily sustained release formulation and in dosage strength that allows easy dose titration for the majority of sufferers. Solifenacin succinate is a relatively new antimuscarinic which has been shown in both short and long term clinical trials to fulfill these requirements[5]. Solifenacin a competitive M3 receptor antagonist, in in-vivo and in-vitro studies have shown greater bladder selectivity than tolterodine and oxybutynin. This relative bladder selectivity was the rationale for development of Solifenacin in the treatment of OAB[13, 14].

Studies in the pathophysiology of OAB have demonstrated three subtypes of beta-adrenoceptors in the detrusor muscle and urothelium. The β3 subtype was identified in 1989 and is the predominate adrenoceptor in the bladder[15]. β3 adrenoceptor agonists have shown a pronounced effect on spontaneous contractile activity in the

detrusor muscle in vitro therefore reducing the bladder tone and afferent input which is related to the storage symptoms of the OAB syndrome[16].

Mirabegron is the first β3 adrenoceptor agonist to be approved for the treatment of OAB symptoms and is the first in a new class of therapy for OAB symptoms for over 30 years. It is licensed in Japan, USA, Europe and Canada. It has a particular affinity for β3 adrenoceptors and improves the storage capacity of the bladder with little effect on the contractile ability of the bladder[17].

Vibegron is Urovant's lead investigational product candidate; it is an oral, once-daily, small molecule beta-3 agonist. The beta-3 adrenergic receptor is the most prevalent beta-adrenergic receptor subtype on the smooth muscle around the bladder. In March 2019, Urovant announced positive topline results from an international double-blind, placebo-controlled, multicenter Phase 3 clinical trial evaluating the efficacy and safety of Vibegron 75mg in 1,518 adults with symptoms of overactive bladder. Urovant filed a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) in Dec, 2019 and approval is projected in Dec, 2020. In addition to OAB, Vibegron is being developed for two additional potential indications: the treatment of OAB in men with benign prostatic hyperplasia (BPH) and the treatment of pain associated with irritable bowel syndrome (IBS) [18-20].

Pharmacokinetic data[18-21]

Innovator	Urovant Sciences (US - 2020); Kyorin Pharma, Kissei Pharma (Japan)
Regulatory Approval	PMDA – 2018, USFDA - NDA submitted in December 2019 (Approval projected December 2020)
Patent Information (INH - IPM)	DP Expiry – 01/12/2030 (US), 02/04/2034 (JP), 02/04/2029 (IND/EU/KR/CN), NCE: 23/12/2025
Pregnancy Category	Not Specified
Dose & Dosage form	Tablet – 50mg, 75mg – OD; (US – 75mg)
ROA	Oral

Approved Indications	Indicated for the treatment of Overactive Bladder (OAB)
Indications under trial	Phase III: OAB in men with BPH; Phase II: IBS associated Pain

Note – Pharmacokinetic data for this product is not available

Comparison of Safety[22-26]

Adverse effects	Vibegron[22]	Mirabegron 25mg – 50mg[23,24]	Solifenacin 5mg – 10mg[24,25]	Tolterodine[22]	Fesoterodine[2] [6]
Dry mouth	1.7%	7.5% - 11.3%	10.9% - 27.6%	6.5%	34.6%
Constipation	-	1.6%	5.4% - 13.4%	-	6%
Nausea	2.2%	-	1.7% - 3.3%	1.2%	1.9%
Dyspepsia	-	-	1.4% - 3.9%	-	2.3%
Abdominal Pain	-	0.6% - 1.4%	1.2% - 1.9%	-	0.5%
Diarrhea	2.2%	-	-	2.1%	-
Vomiting	-	-	0.2% - 1.1%	-	-
Tachycardia	-	1.2% - 1.6%	1.8%	-	-
Hypertension	1.7%	-	-	2.6%	-
UTI	5%	2.9% - 4.2%	2.8% - 4.8%	5.8%	4.2%
URTI	-	1.5% - 2.1%	0.9% - 2.2% (Influenza)	-	1.8%
Pharyngitis	2.8% (Nasopharyngitis)	3.5% - 3.9% (Nasopharyngitis)	0.3% - 1.1% (Pharyngitis)	2.6% (Nasopharyngitis)	Liver enzymes elevation – 1.2%
Headache	4%	2.1% - 3.2%	2.4%	2.6%	-
Dizziness	-	-	1.8% - 1.9%	-	-
Blurred vision	-	-	3.8% - 4.8%	-	-
Dry eyes	-	-	0.3% - 1.6%	-	-

Urinary retention	0.6%	-	0 – 1.4%	0.7%	-
Lower limb Edema	-	-	0.3% - 1.1%	-	1.2%
Fatigue	-	1.2% - 1.4%	1.0% - 2.1%	-	-
Depression	-	-	0.8% - 1.2%	-	-
Cough	-	-	0.2% - 1.1%	-	0.9%

Comparison of Efficacy[22, 23, 25, 26]

Outcome	Vibegron 75mg[22]	Mirabegron 50mg[23]	Solifenacin 10mg[25]	Tolterodine 4mg[22]	Fesoterodine 8mg[26]
Daily Urge Incontinence Episodes (Baseline Mean)	3.43	2.83	2.60	3.42	3.7
Daily Urge Incontinence Episodes (Mean Change from Baseline at 12 weeks)	-2.0 (58.3%)	-1.57 (55.4%)	-1.50 (57.6%)	-1.80 (52.6%)	-2.27 (61.3%)
Daily Micturitions (Baseline Mean)	11.31	11.65	12.3	11.48	11.9
Daily Micturitions (Mean Change from Baseline at 12 weeks)	-1.8 (15.9%)	-1.93 (16.5%)	-2.60 (21.1%)	-1.60 (13.9%)	-1.94 (16.3%)

It was reported that due to adverse effects generally about 50% and 75% patients discontinue treatment with Antimuscarinics (Solifenacin/Tolterodine/Fesoterodine) at 3 - 6 months and 1 year respectively[8,9].

Conclusions

- Vibegron is Urovant's lead investigational product candidate; it is an oral, once-daily, small molecule beta-3 agonist. Urovant announced positive topline results from an international double-blind, placebo-controlled, multicenter Phase 3 clinical trial evaluating the efficacy and safety of Vibegron 75mg in 1,518 adults with symptoms of overactive bladder.
- The drug was approved by PMDA in 2018 for use in Japan and in 2020 in the US. Further, the drug is in Phase III for treating OAB in men with BPH and in Phase II for treating IBS associated Pain.
- The result suggests the efficacy of all the comparators is more or less similar to each other in reduction of both daily incontinence and daily micturition. No single drug expressed a significant superiority or inferiority to the other comparator.
- Safety wise, Solifenacin being an antimuscarinic; has a major drawback of adverse effects and larger treatment withdrawal. Whereas, Vibegron and Mirabegron are β3 adrenoceptor agonists, and comparatively they don't carry the risk of worrying adverse effects and treatment withdrawal.
- As per trials data, Vibegron and Mirabegron had a well balanced Safety vs. Efficacy profile. Hence, it can be stated that all the above mentioned conclusions are in favor of Vibegron followed by Mirabegron over the others.

References

1. Abrams P., Artibani W., Cardozo L., Dmochowski R., Van Kerrebroeck P., Sand P. (2009) Reviewing the ICS 2002 terminology report: the ongoing debate. Neurourol Urodyn 28: 287.
2. Abrams P, Kelleher CJ, Kerr LA, et al. Overactive bladder significantly affects quality of life. Am J Manag Care. 2000;6(11 Suppl):S580–90.

3. Irwin D, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: Results of the EPIC study. Eur Urol. 2006;50:1306–14.
4. Ouslander JG. Management of overactive bladder. N Engl J Med. 2004;350:786–99.
5. Chapple CR. Muscarinic receptor antagonists in the treatment of overactive bladder. Urology. 2000;55(5A Suppl):33–46.
6. Kelleher CJ, Cardozo LD, Khullar V, et al. A medium term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. Br J Obstet Gynaecol. 1997a;104:988–93.
7. Kay G, Crook T, Rekeda L, et al. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. Eur Urol. 2006;50:317–26. Epub Apr 19.
8. Benner J., Nichol M., Rovner E., Jumadilova Z., Alvir J., Hussein M., et al. (2010) Patient-reported reasons for discontinuing overactive bladder medication. BJU Int 105: 1276–1282.
9. Wagg A., Compion G., Fahey A., Siddiqui E. (2012) Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. BJU Int 110: 1767–1774.
10. Shah R., Janos A., Kline J., Yu L., Leurgans S., Wilson R., et al. (2013) Cognitive decline in older persons initiating anticholinergic medications. PLoS One 8: e64111.
11. Jessen F., Kaduszkiewicz H., Daerr M., Bickel H., Pentzek M., Riedel-Heller S., et al. (2010) Anticholinergic drug use and risk for dementia: target for dementia prevention. Eur Arch Psychiatry Clin Neurosci 260(Suppl. 2): S111–S115.
12. Carriere I., Fourrier-Reglat A., Dartigues J., Rouaud O., Pasquier F., Ritchie K., et al. (2009) Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-City Study. Arch Intern Med 169: 1317–1324.
13. Hatanaka T, Ukai M, Ohtake A, et al. In vitro tissue selectivity profile of solifenacin succinate (YM905) for urinary bladder over salivary gland in rats and monkeys [poster]. ICS; Florence Italy. 2003.
14. Ohtake A, Hanataka T, Ikeda K, et al. In vivo bladder selective profile of solifenacin succinate (YM905) over salivary gland in mice and rats [poster]. ICS; Florence Italy. 2003.

15. Michel M., Ochodnicky P., Homma Y., Igawa Y. (2011) β-adrenoceptor agonist effects in experimental models of bladder dysfunction. Pharmacol Ther 131: 40–49.
16. Andersson K., Martin N., Nitti V. (2013) Selective beta(3)-adrenoceptor agonists for the treatment of overactive bladder. J Urol 190: 1173–1180.
17. Rossanese M., Novara G., Challacombe B., Iannetti A., Dasgupta P., Ficarra V. (2015) Critical analysis of phase II and III randomised control trials (RCTs) evaluating efficacy and tolerability of a beta(3)-adrenoceptor agonist (mirabegron) for overactive bladder (OAB). BJU Int 115: 32–40.
18. Vibegron. Pipeline. UROVANT SCIENCES. Available online: https://urovant.com/pipeline/.
19. Urovant Sciences Announces U.S. FDA Acceptance of New Drug Application for Vibegron for the Treatment of Overactive Bladder. Mar 05, 2020. Available online: https://www.biospace.com/article/releases/urovant-sciences-announces-u-s-fda-acceptance-of-new-drug-application-for-vibegron-for-the-treatment-of-overactive-bladder/#:~:text=)%20News%20(642)-,Urovant%20Sciences%20Announces%20U.S.%20FDA%20Acceptance%20of%20New%20Drug%20Application,the%20Treatment%20of%20Overactive%20Bladder&text=Vibegron%2C%20if%20approved%2C%20would%20be,patients%20another%20potential%20treatment%20option.%E2%80%9D.
20. 40th Online Healthcare Conference. UROVANT SCIENCES. Available online: https://ir.urovant.com/static-files/103361b6-2f3f-4f65-8c73-6c9b7f55d162.
21. Vibegron. Newport. Available online: https://www.apicomesfirst.com/newport/Product/doseform.do?apiGrpId=193570&showPrdtFmly=0.
22. AUA 2019: International Phase 3, Double-Blind, Placebo- and Active (Tolterodine)-Controlled Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms in patients with Symptoms of Overactive Bladder: EMPOWUR. Available online: https://www.urotoday.com/conference-highlights/aua-2019-annual-meeting/aua-2019-lower-urinary-tract-conditions/112454-aua-2019-international-phase-3-double-blind-placebo-and-active-tolterodine-controlled-study-to-evaluate-the-safety-and-efficacy-of-vibegron-in-patients-with-symptoms-in-patients-with-symptoms-of-overactive-bladder-empowur.html.

23. Label (PDF)-FDA. MYRBETRIQ (mirabegron). PRESCRIBING INFORMATION. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202611s000lbl.pdf.
24. Jose E. Batista et al, on behalf of the BEYOND study group. The efficacy and safety of mirabegron compared with solifenacin in overactive bladder patients dissatisfied with previous antimuscarinic treatment due to lack of efficacy: results of a noninferiority, randomized, phase IIIb trial. Ther Adv Urol 2015, Vol. 7(4) 167 –179.
25. Label (PDF)-FDA. VESIcare (solifenacin). PRESCRIBING INFORMATION. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021518s016lbl.pdf.
26. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. TOVIAZ (Fesoterodine fumarate). PRESCRIBING INFORMATION. Available Online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022030s009lbl.pdf.