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## Review article

### NEW DRUGS IN THE PIPELINE: A REVIEW

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## INTRODUCTION

Pharmacology is a rapidly advancing science. The essence of rational pharmacotherapeutics is to maximize the efficacy of a pharmaceutical interventional product for a specific indication, with a simultaneous minimization of its adverse effects. With this primary objective in mind, research and development activities of pharmaceutical companies and other healthcare research organizations focus on the development and screening of new chemical entities (NCE). Once a definite pharmacological action of the NCE has been discovered, which is expected to be of satisfactory therapeutic value, the molecule is taken for a thorough pre-clinical animal testing in order to determine its feasibility for human clinical trials. Positive outcomes of the animal studies facilitate the submission of an Investigational New Drug (IND) application with the requisite drug regulatory authority of that particular country. The molecule then undergoes Phase I-III Clinical Trials before it can get a marketing approval. Alternatively, an existing molecule can be modified as per the structure activity relationships to enhance its efficacy or safety. There are numerous examples of structural modifications yielding much better pharmacokinetic and or pharmacodynamic profiles. Introduction of new and better drugs ensure a continuous improvement in the management of patients with all types of ailments. A post marketing surveillance facilitates evidence based medicine, so also in the detection, assessment and analysis of adverse events which constitutes the discipline of Pharmacovigilance.

**Keywords:** Abiraterone, Avanafil, Canagliflozin, Daclatasvir, Linaclotide, Pasireotide, Tafluprost

### New drugs in the pipeline

A few important drugs which have got US FDA approval very recently are discussed below :-

#### 1. Abiraterone<sup>1</sup>

Abiraterone acetate has been a recently approved drug for metastatic, castration resistant (hormone resistant / refractory) prostatic carcinoma. It is the first oral drug for this indication, given in

combination with Prednisolone, even in those patients who have received docetaxel previously and have not responded adequately.

This drug is a 17- $\alpha$ -hydroxylase / C17, 20 lyase inhibitor, thereby inhibiting testosterone production. 17- $\alpha$ -hydroxylase / C17, 20 lyase is an enzyme expressed in the testis, adrenal glands and prostate tumor tissues, responsible for the

eventual production of testosterone in sequential steps. Reduction in circulating testosterone brings about an inhibition in the further growth of the prostate cancer.

The recommended dose of abiraterone is 1000 mg per day in combination with 5mg of Prednisolone bid. Reported adverse effects include mineralocorticoid related effects (joint swelling, hypokalemia, fluid retention) and altered Liver Function Tests.

## 2. Avanafil

This drug has been a recently approved, fast acting phosphodiesterase-5 (PDE-5) inhibitor<sup>2</sup>, useful in the treatment of erectile dysfunction. It acts on a specific PDE-5 found mainly in the corpus cavernosum of the penis, so also in the retina. PDE-5 is the enzyme responsible for the degradation of cyclic GMP (cGMP); its inhibition leads to increased levels of cGMP in the corpus cavernosum. cGMP (produced via the action of guanylate cyclase stimulated by nitric oxide [NO]) mediates smooth muscle relaxation of the penile blood vessels, which causes increased blood flow into the corpus cavernosum and subsequently penile erection. Maintenance of penile erection requires sustained levels of cGMP in the corpus, which is lacking in patients with erectile dysfunction.

The recommended starting dose of avanafil is 100 mg 30 mins prior to sexual activity; can be increased to a maximum of 200 mg or reduced to 50 mg.

The drug is relatively quite safe but may rarely cause cardiovascular effects like angina, DVT & palpitations. Other common side effects are minor and comparable with the placebo.

## 3. Canagliflozin

Canagliflozin is a new Sodium-Glucose co-Transporter-2 (SGLT-2) blocker, which inhibits the resorption of glucose from the kidneys, thereby causing loss of glucose in the urine and reduction of blood sugar levels and weight loss<sup>3</sup>. An additional justification for using this drug is

the belief that the kidney of diabetics reabsorbs more glucose, as compared to normal individuals, which contributes to a further rise in blood sugar levels. Canagliflozin is awaiting approval as an adjuvant therapy for patients with Type-2 Diabetes Mellitus (T2DM). Even though cardiovascular risk was projected as a significant safety issue, the drug has been recommended for approval by the US FDA drug safety committee. The previous congener, Dapagliflozin, did not get FDA approval due to a concern of causing malignancies.

The suggested dose of canagliflozin is 100-300 mg per day orally. In addition to the cardiovascular side effects, it may also lead to genital mycotic infections and urinary tract infections.

This drug may be a valuable addition in the armamentarium of drugs against T2DM, especially in obese diabetics.

## 4. Daclatasvir<sup>4</sup>

The standard regimen for the treatment of Hepatitis-C Virus (HCV) infection has been a combination of pegylated interferon and ribavirin. However, the overall success rates with this combination have not been very good, which led to a search for potential new targets to inhibit viral replication. The DAAs (Directly acting Antiviral Agents) like telaprevir and boceprevir were a new addition in the armamentarium against HCV. However, another novel class of DAAs includes the NS5a replication complex inhibitors like Daclatasvir, which has recently received US FDA approval for multi-drug therapy of HCV infection<sup>5</sup>.

Even though the exact mechanism has not been outlined, daclatasvir probably inhibits the production of certain non-structural proteins of the HCV required for viral replication. Thus, the inhibition of NS5a replication complex indirectly inhibits viral replication. For optimal effect, daclatasvir has to be administered concurrently with a polymerase inhibitor like Sofosbuvir. As such, daclatasvir is expected to be a component of

a multi-drug regimen in the treatment of HCV infection, which would include ribavirin & interferon.

The suggested optimum dosage of daclatasvir is 60 mg per day, in combination. ADR profile was found to be comparable with placebo. Long term safety in patients has to be evaluated.

### **5. Linaclotide**

Linaclotide, a peptide agonist of guanylate cyclase 2C, was approved by the US FDA in Aug 2012 for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). The drug increases the concentration of cGMP both intracellularly and extracellularly, which causes increased fluid secretion in the gut lumen and an increased motility<sup>6</sup>. In addition, higher levels of cGMP reduce the sensitivity of sensory nerves, which in turn diminishes intestinal pain.

The exact mechanism of action is by an enhanced pumping of Cl<sup>-</sup> ions into the gut lumen by increased cGMP levels. Water follows the chloride ions by osmotic action, which leads to a higher water content in the stools.

The recommended doses are 290 µg for IBS-C patients and 145 µg for CIC patients.

The expected side effect of linaclotide is diarrhea. It is not recommended in individuals <16 yrs of age, and is contraindicated in children below 6 yrs. Long term toxicity of the drug needs further evaluation.

### **6. Lomitapide<sup>7</sup>**

US FDA has very recently approved a new drug - Lomitapide - as an adjunctive treatment of Homozygous Familial Hypercholesterolemia. It is a Microsomal Triglyceride Transfer Protein-1 (MTP-1) inhibitor, thereby inhibiting the assembly and secretion of Very Low Density Lipoproteins (VLDL) in the liver. This in turn leads to a reduction in the total cholesterol (TC), Low Density Lipoprotein - Cholesterol (LDL-C), apolipoprotein-B (Apo-B) and non-High Density Lipoprotein Cholesterol (non-HDL-C) levels in

the blood, which has a definite beneficial effect on the serum lipid profile in patients with homozygous familial hypercholesterolemia. This gives additional benefit to patients who are already on other lipid lowering agents, including LDL-apheresis, if required.

Dosage range for lomitapide is 5-60 mg per day orally. The biggest concern with its use is a risk of hepatic toxicity. Other ADRs include GIT side effects including abdominal pain, nausea, vomiting, diarrhea, bloating and flatulence.

### **7. Pasireotide**

A somatostatin analogue, Pasireotide blocks the release of Adrenocorticotrophic Hormone (ACTH) from the Anterior Pituitary gland by stimulating somatostatin receptors therein<sup>8</sup>. This leads to a subsequent reduction in the secretion of glucocorticoids & mineralocorticoids from the adrenal glands.

The drug is indicated for the treatment of Cushing's disease in patients for whom surgery is either not an option or has been unsuccessful. The recommended dose is 600µg or 900µg subcutaneously twice a day. In addition to the alleviation of the signs & symptoms of Cushing's disease, the drug is also associated with improvements in systolic & diastolic blood pressure, low density lipoprotein (LDL) cholesterol, weight and overall quality of life.

Hyperglycemia was the commonest adverse effect. Other side effects include nausea, diarrhea, abdominal pain and gallstones.

Currently, the drug has an orphan drug status in the USA.

### **8. Tafluprost**

Tafluprost is Prostaglandin F<sub>2α</sub> (PG F<sub>2α</sub>) analog, approved for the treatment of Chronic Open angle Glaucoma (Ocular hypertension)<sup>9</sup>. It facilitates the outflow of aqueous humor from the anterior chamber, thereby reducing the intra-ocular pressure.

It is available as preservative free eye drops, in a concentration of 15 mcg per ml, so also as a single dose formulation containing 0.3 ml per dose.

### 9. Teduglutide<sup>10</sup>

Another orphan drug (USA), Teduglutide is a Glucagon like Peptide-2 (GLP-2) analog, which enhances the absorption of nutrients & water in patients of Short Bowel Syndrome (SBS). This is an alternative to parenteral nutrition which is commonly required in patients of SBS.

SBS results from partial or complete surgical resection of the small intestine (ileum) due to any indication mandating it. This leads to poor absorption of nutrients and water from the ileum, leading to malnutrition, for which the only remedy was parenteral nutrition or total parenteral nutrition (TPN). Teduglutide is expected to be a suitable alternative to TPN.

Currently recommended dose of teduglutide is 0.05mg/kg/day subcutaneously.

The major concern with teduglutide is the possibility of intestinal malignancies & polyposis, so also intestinal obstruction, gallbladder disease and biliary tract / pancreatic disease. The drug may not get suitable marketing status till these issues are satisfactorily resolved.

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