DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Eleventh, Jul– Sep 2023

Dear Readers,
The purpose of this bulletin is to disseminate important information related to drugs and medical devices likely to be of interest to everyone, involved directly or indirectly in patient care. The current issue highlights novel drug targets for dyslipidaemia management, newer drugs for Alzheimer's disease, few interesting preclinical/ clinical research and new drug approvals. Feedback and suggestions, if any, may be send at email Id: thepillboxafmc@gmail.com .

World Heart Day: 29 Sep 2023

Newer Drugs for Dyslipidemia

Dyslipidaemia is a well-known risk factor for the development of cardiovascular disease, a leading cause of morbidity and mortality in developed countries. For decades, the traditional statin therapy remains the cornerstone therapeutic approach. However, clinical trials have observed remarkable results for a few agents effective in the treatment of elevated serum lipid levels. This section intent to provide a short summary of new agents currently used or being developed for lipid lowering treatment.

Bempedoic Acid

- An ATP citrate lyase inhibitor that inhibits cholesterol biosynthesis and increases LDL receptor expression. Inhibition of ATP citrate lyase prevents endogenous cholesterol synthesis and indirectly increases the expression of LDL receptors, thereby increasing the clearance of LDL cholesterol.
- It is a prodrug, converted to its active metabolite ESP15228.
- Administered orally once a day at a dose of 180 mg.
- Approved for the treatment of hypercholesterolemia (FDA approval 21 Feb 2020).
- Studies have shown a 15 to 16.5% reductions in LDL cholesterol levels after 12 weeks of therapy.
- Advantage is the lack of myopathies observed sometimes with prolonged statin therapy.

PCSK9 Inhibitors

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new generation of lipid-lowering drugs.
- PCSK9 plays an important role in LDL receptor downregulation. PCSK9 protein binding to LDL receptor starts process of degrading the receptor, thus increasing LDL cholesterol levels.
- Monoclonal antibodies viz **alirocumab** and **evolocumab** inhibit PCSK9 binding to LDL receptors, decreasing circulating LDL cholesterol levels and has a preventive effect on cardiovascular incidents.
- Approved for use in patients with high cardiovascular risk and high LDL cholesterol levels.
- Both are administered subcutaneously once every two weeks in doses starting from 75 mg to 300 mg.
- Presently cost is a limiting factor for their wider use.

Inclisiran

- It is a small interfering ribonucleic acid (siRNA) that targets PCSK9.
- It interferes with the translation of PCSK9 by cleaving messenger RNA, thereby decreasing PCSK9 production.
- Approved for the treatment of mixed dyslipidaemia and hypertriglyceridemia (FDA approval 15 Dec 2021).
- Dosage schedule: 284 mg is administered subcutaneously on days 1, day 90, day 180, and afterwards once every six months.
- LDL cholesterol levels were reduced by approximately 50% compared to placebo groups.

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World Heart Day: Use Heart, Know Heart

New Treatment Options Are on the Horizon for Dyslipidemia

Volanesorsen:

- An important protein found in chylomicrons is the apolipoprotein C-III (apoC-III).
- Target for this new class of drugs is apoC-III aimed to lower triglyceride levels and indirectly preventing cardiovascular incidents and pancreatitis episodes in patients with hypertriglyceridemia.
- It is an antisense oligonucleotide that binds to the apoC-III mRNA and disrupts apoC-III translation. This leads to lower apoC-III levels and lower levels of chylomicrons and triglycerides.
- Clinical studies observed reduction in triglyceride levels by 71.8% compared to the placebo group after a three -month period. In addition, pancreatitis events were reduced.
- Initially, the FDA kept the approval of volanesorsen pending due to concerns regarding drug induced thrombocytopenia and risk of bleeding. Finally, it was approved on 07 May 2019.

ANGPTL3 Inhibitors

- One of the new possible targets for the treatment of dyslipidaemia is angiopoietin-like 3 protein (ANGPTL3).
- ANGPTL3 acts as an inhibitor of lipoprotein lipase (LPL) and endothelial lipase (EL) enzymes. Both enzymes are important in the increase in serum triglycerides and LDL cholesterol.
- The first drug in the class of ANGPTL3 inhibitors is **evinacumab (**FDA approved Feb 2021) , a monoclonal antibody for the treatment of familial hypercholesterolemia.
- It is administered intravenously every four weeks.
- Another possibility to target ANGPTL3 is the antisense oligonucleotide **vupanorsen** (FDA approved Jan 2022).

Olezarsen:

- An antisense oligonucleotide targeting apoCIII currently in phase III clinical trials.
- Olezarsen is administered subcutaneously.
- Studies have observed promising results with safety profile being the biggest benefit of olezarsen when compared to volanesorsen, with no platelet count reduction.

Pelacarsen:

- It is an antisense oligonucleotide that binds to hepatocyte apo(a) mRNA and forms an ASO/mRNA complex that prevents the translation of apolipoprotein(a). This leads to decreased apolipoprotein(a) production and lower circulating Lp(a) levels.
- Phase II clinical trials already completed, and phase III currently ongoing.
- Phase II observed dose-dependent and regiment-dependent reductions in Lp(a) levels compared to the placebo group. It is observed to lower levels of not only Lp(a), but also lower levels of oxidized phospholipids on apolipoprotein(a) and apolipoprotein(b), lower levels of apolipoprotein(b), and LDL cholesterol.

Lerodalcibep

- Inhibits PCSK9 by gene editing, using CRISPR-Cas9 techniques.
- In phase III clinical trials.
- It is a recombinant fusion protein of a PCSK9-binding domain (adnectin) and human serum albumin.
- Clinical studies have observed up to 70% reduction of circulating LDL levels at the end of 12 weeks.

Vaccines against PCSK9

- It triggers the generation of host anti-PCSK9 antibodies and consequently neutralize PCSK9/LDL receptor interactions.
- A novel antiPCSK9 vaccine formulation, called liposomal immunogenic fused PCSK9-tetanus peptide plus alum adjuvant (L-IFPTA), undergoing preclinical studies.

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World Alzheimer's Day (21 Sep 2023)
Theme: Never too early, Never too late

Dementia is increasingly being recognized as one of the most important prevalent medical problems in older people. Alzheimer's disease (AD) is the most prevalent subtype, accounting for about 60% of all dementias . To date, established treatments are only symptomatic in nature, trying to counterbalance the neurotransmitter disturbance of the disease. Most of the available drugs are inhibitor of acetylcholinesterase (AChE) like Tacrine, Donepezil, Galantamine and Rivastigmine. Memantine is N-methyl D-aspartate (NMDA) antagonist and Aducanumab targets accumulated Aβ plaques. Some newer potential drugs are in pipeline and presently are in different phases of development. Below is the summary of new potential disease-modifying therapies for AD.

New Potential Disease Modifying Agents For Alzheimer's Disease

Drug	Mechanism of Action	Stage of AD	Target	Phase of Trial
Disease-Modifying Biologics				
Pepinemab	Monoclonal antibody directed at semaphoring 4D to reduce inflammation	Mild	Inflammation	I
Gantenerumab	Monoclonal antibody acts at Aβ plaques and oligomers	Mild to moderate	Amyloid	II
LY3372689	Tau protein aggregation inhibitor	Moderate	Tau	II
BCG vaccine	Vaccination against tuberculosis infection; immunomodulator	Prevention	Inflammation/ Immunity	II
IVIG (New Gam 10%)	Polyclonal antibody	Mild	Amyloid	II
Disease-Modifying Small Molecules				
Trehalose	Induces autophagy and promotes clearance of aggregated proteins	Mild to moderate	Cell death	I
Suvorexant	Dual orexin receptor antagonist; improves sleep with effects on CSF Aβ	Mild to moderate	Neurotransmitter receptors	II
Nicotine	Nicotinic acetylcholine receptor agonist	Mild	Cognitive enhancer Neurotransmitter receptors	II
Sumifilam	Alters conformation of filamin A	Mild to moderate	Filamin A	II
Tricaprilin	Induces ketosis and improves mitochondrial and neuronal function	Mild to moderate	Metabolism and bioenergetics	III
Nabilone	Synthetic cannabinoid; antiemetic	Mild to moderate	Neurotransmitter receptors	III
Hydralazine	Antioxidant	Mild to moderate	Oxidative stress	III

Pre-clinical Research

Mushroom-derived product may be the future of lung cancer prevention

- Lung cancer is one of the leading causes of cancer mortality worldwide.
- Benzo[a]pyrene (B[a]P) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are known procarcinogens in tobacco smoke that can lead to deoxyribonucleic acid (DNA) mutations and, eventually, lung cancer.
- A medicinal mushroom, *Ganoderma lucidum* (GL), is known to have anticancer and immuno-modulating properties and being used as a nutraceutical in the treatment of various chronic ailments, including cancer.
- The potential chemo-preventive effects of the GL-derived commercial product named GLSF were investigated *in vitro* and in mice with lung carcinogenesis induced by (B[a]P) and NNK.
- The mice treated with GLSF had lower B[a]P-induced lung toxicity and reduced NNK-induced lung tumor development in the sort-term and long-term carcinogenesis study. While inflammatory and angiogenesis markers were found to decrease in the GLSF group , apoptotic markers were found to increase, indicating GLSF's promising preventive potential against lung cancer.
- As a nutraceutical, GLSF is not known to be associated with any severe adverse event, making it an ideal candidate for future clinical studies aimed at lung cancer prevention.
- Subject to trial results, GLSF could potentially be utilized in individuals with an increased risk of developing lung cancer, such as heavy smokers.

Journal reference: The medicinal mushroom *Ganoderma lucidum* prevents lung tumorigenesis induced by tobacco smoke carcinogens. Shahid A, Chen M, Yeung S, Parsa C, Orlando R, Huang Y., *Frontiers in Pharmacology*, Vol. 14 (2023) .

New compound could offer an alternative to injections for people suffering from wet AMD

- Wet age-related macular degeneration (AMD) causes vision loss due to the uncontrolled growth and leakage of blood vessels in the posterior part of the eye.
- Aging causes inflammation and hypoxia in the eye that leads to changes in gene expression associated with the cellular effects and symptoms of wet AMD.
- Inhibition of microtubule-associated end binding protein 3 (EB3) in endothelial cells may prevent reverse these epigenetic changes, restoring gene expression to a normal, healthy state.
- It was hypothesized that inhibiting EB3 can activate the regenerative program in wet AMD and promote regenerative and healing processes.
- Using computational drug design methods, a small EB3 inhibitor was developed that could be delivered externally via eye drops instead of by injection.
- The effectiveness of new drug was tested in animal models of wet AMD, where they found that twice-daily treatment reduced eye damage within 2 to 3 weeks.
- EB3 inhibitor is also being investigated in models of acute lung injury, diabetic retinopathy, stroke, heart disease and even the general effects of aging on the brain.

Journal reference: Lee, Q., *et al.* (2023) End binding-3 inhibitor activates regenerative program in age-related macular degeneration. *Cell Reports Medicine.* doi.org/10.1016/ j.xcrm. 2023 .101223.

Pre-clinical Research

Development of new weight-loss drug that mimics exercise

- A new drug class known as "exercise mimetics", tested in mice, shows promising new results that could lead to the development of a new weight-loss drug that mimics exercise without increasing physical activity.
- SLU-PP-332 is an estrogen receptor-related (ERR) agonist. ERRs are responsible for activating some of the most important metabolic pathways in energy-gobbling tissues like muscles, the heart, and the brain. The ERRs are more active when people exercise.
- Normal-weight mice receiving SLU-PP-332 ran 70% longer and 45% further than mice not receiving the drug.
- Obese mice treated with SLU-PP-332 for a month showed 10% less fat and lost 12% of their body weight than untreated mice. The mice were provided with the same amount of food and no exercise during the period of study.
- No serious adverse effect has been seen with the drug during preclinical study.
- The preclinical study results have shown SLU-PP-332 to be a potential candidate for treating diseases like obesity, diabetes, and age-related muscle loss.

Journal reference: Billon, C., et al. (2023). A Synthetic ERR Agonist Alleviates Metabolic Syndrome. Journal of Pharmacology and Experimental Therapeutics.

New injectable solution could help manage HIV unlike any current treatment methods

- The primary challenge in HIV treatment is the adherence to lifelong anti-retroviral therapy and maintaining blood drug levels at concentrations that suppress virus load in the body.
- One way to address this is to reduce dosing frequencies so as to increase patient compliance to therapy.
- A new injectable solution that self-assembles into a gel under the right conditions and releases a steady dose of the anti-HIV drug lamivudine over six weeks, suggests people living with HIV could have new therapy that doesn't require a daily pill regimen to prevent AIDS.
- By injecting the gel in the backs of mice, the researchers found one injection was sufficient to maintain effective and lasting drug concentrations for 42 days with nearly no side effects.
- Hydrogels have unique water-absorbing properties that give them a jellylike consistency resembling biological tissue. The new gel undergoes self-formulation, stays close to the site of injection, and separates into molecules that can kill the virus without the need for additional carriers or delivery materials.
- The development of hydrogel containing medications used in combination therapies along with lamivudine is in the process, as most of these treatments involve a cocktail of two or more drugs.
- Because lamivudine is an FDA-approved drug to treat HIV and hepatitis B, the hydrogel could also be explored in the treatment of hepatitis B.

Journal reference: Wang, H., et al. (2023) Constructing Antiretroviral Supramolecular Polymers as Long-Acting Injectables through Rational Design of Drug Amphiphiles with Alternating Antiretroviral-Based and Hydrophobic Residues. Journal of the American Chemical Society.

New Drugs Corner

(Reference: USFDA)

Name (FDA approval date)	MOA	Indication	Dose
Nirsevimab-alip (17 Jul 2023)	Respiratory syncytial virus (RSV) F protein-directed fusion inhibitor	Prevention of RSV lower respiratory tract disease	200 mg IM
Lotilaner ophthalmic solution (25 Jul 2023)	Gamma-aminobutyric acid (GABA)-gated chloride channel inhibitor	Demodex blepharitis	0.25% (2.5mg/mL): 1 drop BD
Avacincaptad pegol intravitreal solution (04 Aug 2023)	Complement inhibitor	Geographic atrophy (GA) secondary to age related macular degeneration	2mg (0.1mL) intravitreal injection
Zuranolone (04 Aug 2023)	Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator	Postpartum depression in adults	50mg PO
Talquetamab-tgvs (09 Aug 2023)	Bispecific GPRC5D-directed CD3 T-cell engager	Patients with heavily pretreated multiple myeloma	Day 1 (step-up dose 1): 0.01 mg/kg SC x 1 dose Day 4 (step-up dose 2): 0.06 mg/kg SC x 1 dose Day 7 (first treatment dose): 0.4 mg/kg SC x 1 dose
Elranatamab-bcmm (14 Aug 2023)	B-cell maturation antigen (BCMA) CD3-targeted bispecific antibody (BsAb)	Relapsed or refractory multiple myeloma	Day 1(step-up dose 1): 12 mg, Day 4 (step-up dose 2): 32 mg, Day 8 (first treatment dose): 76 mg; 76 mg weekly, thereafter.
Natalizumab-sztn (24 Aug 2023)	Integrin receptor antagonist	Multiple sclerosis and Crohn's disease	300 mg IV
Motixafortide (11 Sep 2023)	Haematopoietic stem cell mobilizer	In combination with filgrastim to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma	1.25 mg/kg SC
Momelotinib (15 Sep 2023)	JAK1/JAK2 and activin A receptor type 1 (ACVR1) inhibitor	Myelofibrosis patients with anemia	100 - 200 mg SC
Phentolamine mesylate (27 Sep 2023)	Alpha adrenergic blocker	Pharmacologically-induced mydriasis	1% - 1 drop
Gepirone (28 Sep 2023)	5-HT1A receptor agonist	Adults with major depressive disorder	10-45mg/day PO

The Pill Box Quiz: 11

Instructions:
Scan the QR code to access the quiz.