DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Sixth, Apr– Jun 2022

Dear Readers,
The purpose of this bulletin is to disseminate some 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 investigational agents for asthma, drugs updates in psychiatry, recent drug approvals and few interesting potential preclinical research. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com .

World Asthma Day: 03 May 2022; Theme: *Closing Gaps in Asthma Care*

Investigational agents for asthma: A glimpse

The standard treatment of patients with asthma is based upon trigger avoidance, bronchodilation, and anti-inflammatory therapy. Beta agonists, inhaled and systemic glucocorticoids, leukotriene modifiers, omalizumab, anti-interleukin (IL)-5 agents, anti-IL-4 receptor alpha subunit antibody, anti-thymic stromal lymphopoietin, and, to a lesser extent, methylxanthines and muscarinic antagonists (anticholinergic agents) all have a role in the conventional treatment of asthma. However, some patients do not achieve adequate control of their asthma with conventional therapy or experience adverse effects with conventional agents. Ongoing research is attempting to identify more effective and less toxic agents to control asthma. Investigational approaches to asthma management, both promising and unsuccessful, are mentioned below:-

Biologic agents: Several biologic agents targeting steps in the cascade of cytokines implicated in asthma inflammation have been developed in hopes of ameliorating the inflammation that underlies chronic asthma. These agents are as follows:-

Anti-IgE agents: Immunoglobulin E (IgE) plays a central role in the mechanism of immediate bronchoconstriction and the influx of inflammatory cells in allergic asthma. **Ligelizumab** (QGE031) is an investigational monoclonal anti-IgE antibody that binds IgE with higher affinity than omalizumab.

Anti-IL-2R antibody: Activation of type 2 helper T lymphocyte (Th2) cells by allergen leads to production of interleukin (IL)-2 and its receptor IL-2R. Binding of IL-2 to Th2 cells expressing IL-2R leads to proliferation of that clone of specifically sensitized Th2 cells. The humanized monoclonal antibody to the CD25 subunit of IL-2R, **daclizumab**, inhibits various T cell functions, including T cell proliferation and cytokine production. In a randomized trial, 115 patients with moderate to severe asthma were assigned (3:1) to intravenous daclizumab or placebo every two weeks for 12 weeks . Daclizumab treatment was associated with small improvements in pulmonary function and asthma control. Daclizumab, approved for relapsing forms of multiple sclerosis, has been voluntarily withdrawn by the manufacture from the market worldwide due to adverse benefit-risk profile.

Anti-IL-13 antibodies: IL-13 promotes IgE production by B cells, generation of eosinophil chemoattractants, and contractility of airway smooth muscle cells, among other effects, and is therefore of interest as a potential target for asthma therapy. Clinical studies, however, have not documented a benefit to anti-IL-13 monoclonal antibodies, **lebrikizumab** and **tralokinumab**.

Reference: GINA & UpToDate

The Pill Box Quiz: 06

Instructions:
Scan the QR code or click below link to access the quiz.
https://docs.google.com/forms/d/e/1FAIpQLSfruH9siXu3HaqIc Xm4pzzTirXSmykNwE4T-m4FeTSCdT_IPHQ/viewform?usp=sf_link

SCAN ME

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Investigational agents for asthma: A glimpse...

[Reference: GINA and UpToDate]

Anti-IL-23 antibody: IL-23 appears to contribute to airway inflammation through elaboration of cytokines from Th2 lymphocytes and proliferation of Th17 lymphocytes. **Risankizumab**, an anti–interleukin-23p19 monoclonal antibody, is used in the treatment of psoriasis. However, risankizumab was not beneficial in a randomized trial in 212 patients with severe asthma in which the time to the first asthma worsening was shorter and the annualized rate of asthma worsening was higher with risankizumab than placebo. This observation indicates that IL-23 has a limited role in augmenting type 2 inflammation and is not critical for the development of Th17 cells.

Anti-IL-33 and anti-IL-33/ST2 monoclonal antibodies: IL-33 is released by several cell types, including airway epithelial and endothelial cells and mast cells, in response to cell stress or damage (eg, from exposure to viruses, tobacco smoke, air pollution, allergens) and is categorized as an "alarmin". IL-33 activates a number of effector cells, such as eosinophils, mast cells, basophils, innate lymphoid type 2 cells (ILC2s), and Th2 lymphocytes, thus involving both the innate and adaptive immune systems. Strategies targeting IL-33, such as **itepekimab**, an anti-IL-33 antibody, and **astegolimab**, an IL-33/ST2 receptor antibody, may be beneficial in patients with a component of non-type 2 asthma that does not respond to agents focused on type 2 cytokines.

Toll like receptor 9 agonist: Toll-like receptor 9 (TLR9), a component of the innate immune system primarily located in B cells and plasmacytic dendritic cells, recognizes cytosine guanine dinucleotide (CpG) motifs in microbial DNA and shifts T lymphocyte responses from Th2-dominant to Th1-dominant. **AZD1419** is an investigational oligonucleotide containing immunostimulatory CpG motifs that activates TLR9; it is administered by inhalation.

Prostaglandin D2 receptor antagonist: Prostaglandin D2 (PGD2) is the predominant prostaglandin produced by mast cells and is also produced by Th2 lymphocytes and dendritic cells. It has bronchoconstrictive and chemokinetic effects that may contribute to asthma pathogenesis, such as being a potent eosinophil chemoattractant. PGD2 acts on the PGD2 receptor 2 (DP2 receptor) on mast cells, eosinophils, and basophils. The DP2 receptor mediates migration of Th2 lymphocytes, delays Th2 cell apoptosis and stimulation of Th2 cells to produce interleukin-4 (IL-4), IL-5, and IL-13 among other effects. A clinical trial to assess the effect of **GB001** and **Fevipiprant** as an investigational oral DP2 receptor antagonist as part of asthma maintenance therapy is in progress.

Novel glucocorticoid receptor agonist: The novel glucocorticoid receptor agonist **AZD5423** is a nonsteroidal compound that binds to the glucocorticoid receptor and appears to suppress production of proinflammatory proteins (like traditional glucocorticoids), but with reduced adverse effects in animal models. Additional studies are needed to determine the safety and efficacy of AZD5423 compared with inhaled glucocorticoids.

GATA3 specific DNAzyme: GATA3 is a transcription factor, essential for Th2 lymphocyte differentiation and activation. **SB010** is a synthetic DNA molecule (DNAzyme) that binds uniquely to GATA3 messenger RNA and cleaves it. In a clinical trial, the late asthmatic response to allergen bronchoprovocation was significantly attenuated by SB010.

- **Macrolide antibiotics:** have anti-inflammatory effects in addition to their antibacterial effects, guidelines suggest **not** using macrolides for severe asthma unless indicated for treatment of specific infections as widespread use of macrolides would promote development of macrolide-resistant bacteria.
- A number of agents that have anti-inflammatory effects in other diseases (eg, rheumatic diseases, inflammatory bowel disease, psoriasis) do not appear to be of benefit in asthma, or their adverse effects outweigh the modest benefits. These agents include **methotrexate**, **gold**, **cyclosporine**, **hydroxychloroquine**, **immunoglobulin**, and **dapsone**.
- **Lidocaine** and **heparin** are thought to have anti-inflammatory effects in addition to their respective anesthetic and anticoagulant effects. Attempts to administer these agents by nebulization, and thus achieve anti-inflammatory effects in the airways without the adverse effects of systemic therapy, have not been of sufficient benefit to pursue further.

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Drug updates: Psychiatry

[Reference: USFDA and UpToDate]

Sublingual dexmedetomidine for agitation in bipolar disorder

The US Food and Drug Administration recently approved a sublingual formulation of dexmedetomidine for agitation in bipolar disorder. Evidence supporting the indication includes a randomized trial in 378 patients of bipolar disorder with mild to moderate agitation, in which dexmedetomidine reduced agitation more than placebo, and improvements begin within 20 minutes after administration. However, adverse events were twice as common with dexmedetomidine and included somnolence, dry mouth, hypotension, and dizziness. Use of the drug should be limited for mild to moderate agitation in patients who cannot tolerate as needed antipsychotics or benzodiazepines. Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist.

Ketamine for suicidal ideation in bipolar disorder

Suicidal ideation in bipolar disorder that does not respond to standard treatments may resolve with ketamine. In a placebo-controlled randomized trial of 52 patients with bipolar depression hospitalized for suicidal ideation and receiving usual pharmacotherapy, two doses of add-on ketamine (40 minute IV infusion 0.5 mg/kg at baseline and 24 hours apart) resulted in a higher rate of remission of suicidal ideas at day 3 (85 versus 28 percent), and the benefit appeared to persist at the six-week follow-up. Ketamine was well tolerated and did not induce switching to mania. Ketamine remains an investigational treatment for bipolar depression due to limited evidence of efficacy and concerns about adverse effects, including addiction.

Lumateperone for bipolar depression

Drawbacks to antipsychotics currently used for treatment of bipolar disorder include poor efficacy for associated depression, which often accounts for a high proportion of morbidity in such patients, and frequent undesirable side effects. In a clinical trial of individuals with type I or II bipolar depression, lumateperone , an atypical antipsychotic with a novel mechanism, led to greater rates of response (51 versus 37 percent) and remission (40 versus 34 percent) compared with placebo. Treatment emergent side effects occurred at similar rates to placebo. While lumateperone may be a promising new option with minimal side effects for the treatment of bipolar disorder, further studies are needed in order to define its optimal role.

Dental problems associated with oral dissolving buprenorphine

There are >300 reports of dental problems associated with use of buprenorphine formulations—mouth dissolving, buccal formulation and sublingual preparations. Reported problems include dental caries, abscesses, and damaged teeth, many of which have required tooth removal. The incidence of dental problems with buprenorphine is unknown. Patients who use orally dissolving buprenorphine should swish and swallow water after the drug has dissolved, see a dentist soon after starting the drug, and make sure the dentist knows they are taking the drug. The US Food and Drug Administration (FDA) has issued a related safety advisory and will mandate a label change.

Daridorexant for treatment of insomnia in adults

Daridorexant, a dual orexin receptor antagonist (DORA), has been approved by the US Food and Drug Administration (FDA) for treatment of insomnia in adults. Like lemborexant and suvorexant , daridorexant improves both subjective and objective measures of sleep onset and sleep maintenance compared with placebo. Among the three DORAs, daridorexant has the shortest half-life (approximately eight hours). For adults who fail or do not have access to cognitive behavioral therapy, DORAs to be considered an acceptable first-line option for sleep maintenance insomnia, along with benzodiazepine receptor agonists (BZRAs) and low-dose doxepin.

Medications used to treat psychiatric disorders are commonly referred to as psychotropic drugs.

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Dostarlimab

'Dostarlimab trial: Light at the end of tunnel.' ..'Every patient in experimental drug trial saw their rectal cancer disappear.'..These are the few headlines of the newspapers in recent past. Below mentioned are some of the salient information about the miracle drug –Dostarlimab.

- **Drug class**: Antineoplastic Agent, Anti-PD-1 Monoclonal Antibody
- **Mechanism of Action**: Dostarlimab is an anti-PD-1 humanized IgG4 monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signalling .
- **Pharmacokinetics**: Distribution: Vdss: ~5.3 L; Metabolism: Expected to be metabolized by catabolic pathways into small peptides and amino acids; Half-life elimination: 23.5 days; Excretion: Clearance: 0.007 L/hour (at steady state).
- **Labelled Indications:** Select patients for treatment based on the presence of deficient mismatch repair (dMMR) in tumor specimens (as determined by an approved test) . **Endometrial cancer (recurrent or advanced):** Treatment of mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer in adults that has progressed on or following prior treatment with a platinum-containing regimen. **Solid tumors (recurrent or advanced):** Treatment of dMMR recurrent or advanced solid tumors in adults that has progressed on or following prior treatment and who have no satisfactory alternative treatment options.
- **Dosing: IV:** 500 mg every 3 weeks for 4 doses, followed by 1,000 mg every 6 weeks for dose 5 and beyond (administer dose 5 beginning 3 weeks after dose 4) until disease is not responding to treatment or unacceptable toxicity occurs. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance.
- **Warnings/Precautions/ *Adverse effects:***
- **Immune-mediated adverse reactions**:

- Severe and fatal immune-mediated adverse reactions may occur during treatment and even after discontinuation.

- Early identification and management of immune-mediated adverse reactions are necessary.

- Withhold dostarlimab for severe (grade 3) immune-mediated adverse reactions.

- Permanently discontinue dostarlimab for life-threatening (grade 4) immune-mediated adverse reactions, recurrent severe (grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or inability to reduce corticosteroid dose to prednisone ≤10 mg/day (or equivalent) within 12 weeks of initiating corticosteroids.

- **Dermatologic toxicity**: Immune-mediated rash or dermatitis, bullous and exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis have occurred.
- **Endocrinopathies**: *Adrenal insufficiency*; *Diabetes mellitus*: Type 1 diabetes mellitus may occur (which may present with diabetic ketoacidosis); *Hypophysitis:* Immune-mediated hypophysitis may occur and may present with acute mass effect symptoms (headache, photophobia, or visual field defects); *Thyroid disorders:* Immune-mediated thyroid disorders may occur. Hypothyroidism may follow hyperthyroidism.
- **GI toxicity**: Immune-mediated colitis; pancreatitis , gastritis, and duodenitis have been reported.

Approximately 5-10% of rectal cancers are molecularly characterized as being deficient in mismatch repair enzymes

New Drugs Corner

Ganoxolone
MOA: Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator
Indication: To treat seizures in cyclin-dependent kinase-like 5 deficiency disorder in patients 2 years of age and older.

Baricitinib
MOA: Janus kinase (JAK) inhibitor
Indication: To treat adult patients with severe alopecia areata (oral).

Alpelisib
MOA: Kinase inhibitor
Indication: For the treatment of adult and pediatric patients 2 years and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy.

Osteoconazole
MOA: Oral azole antifungal
Indication: To reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC and who are not of reproductive potential.

Trientine tetrahydrochloride
MOA: Copper chelator
Indication: Adult patients with stable Wilson's disease.

Mevacamten
MOA: Cardiac myosin inhibitor
Indication: For treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.

Amoxicillin, clarithromycin and vonoprazan Co-packaged
MOA: Amoxicillin (Beta-lactam class antibacterial), clarithromycin (macrolide antimicrobial), vonoprazan (potassium-competitive acid blocker)
Indication: Treatment of Helicobacter pylori infection in adults.

Edaravone oral suspension
MOA: Free radical scavenger
Indication: For treatment of amyotrophic lateral sclerosis.

Tirzepatide
MOA: Glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist
Indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is also found to cause substantial and sustained reductions in body weight at once weekly dose.

Tapinarof
MOA: Topical aryl hydrocarbon receptor (AhR) modulating agent
Indication: For treatment of plaque psoriasis in adults.

Pegfilgrastim-pbbk
MOA: Leukocyte growth factor biosimilar
Indication: To reduce the incidence of neutropenia in patients undergoing chemotherapy.

Reference: USFDA

Pre-clinical research : Potential news

A new method to combat malaria with novel ML901

Every year, at least 200 million new malaria infections are diagnosed worldwide, causing more than 600,000 deaths in Africa and Southeast Asia. Over the past 50 years, ever increasing levels of resistance to antimalarials has led to an impending crisis, with breakthrough drugs desperately needed. The University of Melbourne-led research has identified an anti-malarial compound, ML901, which inhibits the malaria parasite but does not harm mammalian -- human or other mammals' – cells. ML901 works by an unusual reaction-hijacking mechanism. Once ML901 entered the parasite, it attached itself to an amino acid and attacked the protein synthesis machinery from the inside, rapidly grinding the parasite to a halt. ML901 finds a particular chink in the machinery that the malaria parasite uses to generate the proteins needed to reproduce itself and stops it doing so. The molecular structure of human cells means they are not susceptible to attack by ML901. In tests using both human blood cultures and an animal model of malaria, the team found ML901 killed malaria parasites that had resistance to currently used drugs and showed rapid and prolonged action resulting in excellent parasite killing. As it was active against all stages of the lifecycle, meaning it could be used to prevent malaria infections as well as to treat the disease. These results are really encouraging in the search for new antimalarials.

Journal Reference: Stanley C. Xie, Riley D. Metcalfe, Elyse Dunn *et al*. Reaction hijacking of tyrosine tRNA synthetase as a new whole-of-life-cycle antimalarial strategy. *Science*, 2022; 376 (6597): 1074.

Ketamine: speedster of antidepressants

The study in mice shows ketamine works as a rapid antidepressant by increasing the activity of the very small number of newborn neurons, which are part of an ongoing neurogenesis in the brain. New neurons are always being made at a slow rate. It's been known that increasing the number of neurons leads to behavioral changes. Other antidepressants work by increasing the rate of neurogenesis, in other words, increasing the number of neurons. But this takes weeks to happen. By contrast, ketamine produces behavioral changes simply by increasing the activity of the existing new neurons. This can happen immediately when the cells are activated by ketamine. When we give ketamine to patients, it affects multiple regions of the brain and causes a lot of adverse side effects. The side effects of ketamine include blurred or double vision, nausea, vomiting, insomnia, drowsiness and addiction. But since mow it is known exactly which cells to target, one design drugs to focus only on those cells.

Journal Reference: Radhika Rawat, Elif Tunc-Ozcan, Tammy L. McGuire et al. Ketamine activates adult-born immature granule neurons to rapidly alleviate depression-like behaviors in mice. *Nature Communications*, 2022; 13 (1) DOI: 10.1038/s41467-022-30386-5

Gut bacteria can reduce the effectiveness of certain blood pressure drugs

Hypertension is a major risk factor for heart disease and stroke. There are individuals (an estimated 20%) who know they have hypertension but still cannot get it under control, even though they're taking anti-hypertensive drugs. Why do some people not respond well to medication? This study is the first to examine the impact of gut bacteria on blood pressure medication itself. The study compared the effectiveness of the antihypertensive drug quinapril in rats with normal gut bacteria against those whose gut microbiota had been depleted by high doses of antibiotics. Researchers found that animals that were given antibiotics first responding much better to quinapril. Analysis of the gut bacteria composition in the animals identified the bacteria *Coprococcus* as the culprit. Laboratory experiments proved that *Coprococcus comes*, a dominant bacteria species in this genus, can break down quinapril and ramipril, resulting in the compromised blood pressure-lowering effects. More research needed for studying the interaction between additional blood pressure medications and other common types of gut bacteria.

Journal Reference: Tao Yang et al. Identification of a Gut Commensal That Compromises the Blood Pressure-Lowering Effect of Ester Angiotensin-Converting Enzyme Inhibitors. *Hypertension*, 2022 DOI: 10.1161/HYPERTENSIONAHA.121.18711