DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Tenth, Apr– Jun 2023

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 novel drug targets for malaria, newer drugs for thalassemia, drug-food interactions and new drug approvals. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com .

World Malaria Day: 25 Apr 2023

Novel drug targets for Malaria

Malaria is a prevalent infectious disease, affecting about 150 million people globally and responsible for around 4, 45,000 deaths annually. Chemotherapy against the malaria parasite had been a vital component. However, resistance to existing medicines is always a risk and that needs attention from drug discovery scientists to investigate novel compounds with high drug efficacy, safety and low cost to encounter the malaria parasites that are resistant to existing drug molecules. The fight against malaria may soon have two new weapons: malaria vaccines and novel drugs for malaria.

Malaria Vaccines

RTS,S/AS01

-RTS,S/AS01 is the first and currently the only malaria vaccine recommended for use by WHO.
-It was named RTS as it was engineered using genes from the repeat (R) and T-cell epitope (T) of the pre-erythrocytic circumsporozoite protein (CSP) of the Plasmodium falciparum malaria parasite together with a viral surface antigen (S) of the hepatitis B virus (HBsAg).
-In trials, the vaccine was non-inferior to seasonal malaria chemoprevention (SMC); the combination of the vaccine and SMC was significantly better than either SMC alone or RTS,S/AS01 alone.
Indication: The vaccine should be provided to infants and young children aged 5—17 months of age living in malaria-endemic settings of moderate to high transmission.
Schedule: First dose of vaccine can be administered from 5 months of age. Reconstituted 0.5ml vaccine is administered by injection into the deltoid muscle. There should be a minimum interval of four weeks between doses. The vaccine should be administered in a three-dose primary schedule, with a fourth dose provided 12–18 months after the third dose to prolong the duration of protection. Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks.
-RTS,S/AS01 can be given concomitantly with any of the following monovalent or combination vaccines: diphtheria, tetanus, whole cell pertussis, acellular pertussis, hepatitis B, *Haemophilus influenzae* type b, oral poliovirus, measles, rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines.
Shelf life: 03 years.
Vaccine safety: The RTS,S/AS01 vaccine is safe and well tolerated. The only contraindication to use of RTS,S/AS01 vaccine is severe hypersensitivity to any of the vaccine components. There is a small risk of febrile seizures within seven days (mainly within 2—3 days) of vaccination.

Newer vaccines in pipeline

- New technologies, such as DNA- and mRNA-based vaccines, the ongoing development of adjuvants, and delivery platforms such as virus-like particles (VLPs; the delivery platform used for RTS,S/AS01) and vesicle-based technologies are being explored for use in malaria vaccines. Two vaccine candidates are approaching late-stage clinical evaluation: the R21/MatrixM vaccine candidate targeting PfCSP protein and the attenuated whole sporozoite vaccine PfSPZ.
- Additional candidates targeting other malaria life-cycle stages include the Rh5 blood-stage vaccine candidate and Pfs25 and Pfs230 vaccine candidates targeting sexual-stage antigens to prevent human-to-mosquito transmission.

WHO Guidelines for malaria - 14 March 2023 - World Health Organization (WHO)

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Anti-malarial drugs: Future prospects

Antimalarial drug development follows several approaches. One way is to search for new drug(s) which inhibit parasite growth and cure malaria, and other is to find ways to reverse drug resistance mechanism. Research over the years have identified a number of potential drug targets mainly proteins in the parasite that can be utilized as drug targets.

Company	Drug Name	Remarks	Clinical Phase
AbbVie	DSM265, MMV390048, DSM421	PK studies, formulation evaluation, PD and metabolite sample analysis, pathology peer review, technical consulting	I, II, preclinical
Eisai	E6446	TLR9 antagonist for cerebral Malaria	Preclinical
	SJ733	Inhibitor of Plasmodium ATP4	Phase I
GlaxoSmithKline	Tafenoquine	Radical cure of *P. vivax*	Approved
Novartis	Coartem 80/480	Developing a new formulation with75% reduced pill burden for patients with body	Phase IV
	Imidazolopiperazines (KAF156)	Developing an NCE for patients with artemisinin-resistant strains of malaria	Phase II
	Spiroindolone (KAE609)	Developing an NCE for patients with artemisinin-resistant strains of malaria	Phase II
	Coartem	Dispersible: developing a new formulation for younger children	Phase IV
Sanofi	Oz 439/Ferroquine		Phase IIb
	Ferroquine (SSR97193)		Phase II
	MMV533		Phase-I
Takeda	DSM265		Phase II
Zydus Cadila (AstraZeneca)	MMV253		Phase-I
CDRI	CDRI97/78		Phase-II

Imatinib Augments Standard Malaria Combination Therapy Without Added Toxicity

Imatinib was originally produced by Novartis for the treatment of chronic myelogenous leukemia and other cancers. To egress from its erythrocyte host, the malaria parasite, Plasmodium falciparum, must destabilize the erythrocyte membrane by activating an erythrocyte tyrosine kinase. Imatinib acts by inhibits erythrocyte tyrosine kinases and nearly 100% effective in treating the disease in just 3 days in a Phase 2 clinical trial. The trial of Imatinib (400mg/day) with the standard treatment (40mg dihydroartemisinin+320mg piperaquine/day) shows that addition of the drug Imatinib to the customary malaria therapy enables clearance of all malaria parasites from 90% of patients within 48 hours and from 100% of patients within three days. The patients receiving Imatinib were also relieved of their fevers in less than half of the time experienced by similar patients treated with the standard therapy. There was no increase in number or severity of adverse events. (*DOI: 10.1084/jem.20210724*)

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8 May 2023: World Thalassemia Day

New Treatment Options Are on the Horizon for β-Thalassemia

- ß-thalassemia is a genetic disorder causing reduced production of hemoglobin, resulting in anemia.
- β-thalassemia is caused by mutations that affect the production of the β-globin chains.
- More than 350 causative mutations have been described up to date.
- According to the residual β-globin chains production, mutations are classified as β+ when they cause a partial reduction in β-globin chain synthesis, or β0 when they lead to its complete inactivation.
- In erythroid cells, the deficient production of β-globin chains leads to an imbalance between α-globin and β-globin chains.
- Unpaired α-globin chains accumulate and form unstable tetramers that precipitate and generate cytotoxic reactive oxidant species (ROS).
- These events hamper red-cell precursors' maturation and viability, causing ineffective erythropoiesis, premature hemolysis of circulating red cells and compensatory hematopoietic expansion.
- β-Thalassemia has limited treatment options, with the disease mainly managed with red blood cell transfusions at regular intervals, generally every 2 to 4 weeks, and chelation therapy with a product such as deferoxamine or deferasirox to remove excess iron from the bloodstream.
- The only curative treatment for β-thalassemia major is a stem cell transplant.
- The novel therapies can be classified into 3 major categories based on their efforts to address the underlying pathophysiology of β-thalassaemia; (i) addressing ineffective erythropoiesis (IE) (ii) improving iron overload; and (iii) correction of the globin chain imbalance.

Newer Drugs in pipeline for Thalassemia

Drug	Target	Route of administration	Results	Adverse reactions
Ruxolitinib	Ineffective erythropoiesis—JAK2 inhibition	Oral	• An increase in hepcidin levels	• majority grade 1 and grade
			• No significant changes in serum iron or ferritin levels	• 16.4% grade 3 or 4 anaemia
			• No clinically significant improvements in pre-transfusion Hb	• Drug induced hepatitis
				• Drug induced pneumonia
				• Pyrexia
Sotatercept (ACE-011)	Ineffective erythropoiesis	Subcutaneous injection	• Most NTDT patients sustained increase in Hb levels	• Headache
			• Most TDT achieved reduction in transfusions	• Bone pain
				• Arthralgia
				• Cough
				• Fatigue
Luspatercept (ACE-536)	Ineffective erythropoiesis	Subcutaneous injection	• 58% of NTDT achieved a mean Hb increase	• Bone pain headache
			• 81% of TDT achieved a transfusion burden reduction of ≥20%	• Myalgia
				• Arthralgia
				• Musculoskeletal pain
				• Back pain
				• Injection site pain

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Improving iron overload in β-thalassaemia

- Hepcidin is synthesized in the liver and secreted in the bloodstream.
- Once in circulation, hepcidin binds to ferroportin (iron exporter) causing the hepcidin–ferroportin to be degraded by lysosomes. This process is regulated by iron demand, iron stores, erythropoiesis, hypoxia and inflammation. In β-thalassaemia; anaemia, tissue hypoxia and increased erythropoietin production promotes the suppression of hepcidin. In doing so, iron absorption is increased, therefore the use of drugs/agents to stimulate hepcidin expression and activity in these patients would be beneficial.

* **Minihepcidins:** It restricts iron absorption. In young $Hbb^{th3/+}$ mice it was shown that minihepcidins were able to ameliorate ineffective erythropoiesis (IE), anaemia, splenomegaly and iron overload. In older $Hbb^{th3/+}$ mice, in combination with the iron chelator deferiprone, minihepcidins also improved IE, anaemia and reverse splenomegaly.
* **TMPRSS6**: Another approach to improve iron overload is to increase hepatic synthesis of hepcidin by supressing the TMPRSS6 gene. This gene regulates hepcidin production by cleaving haemojuvelin, an important modulator of hepcidin expression. A number of studies in mice with β-thalassaemia phenotype showed that deletion or downregulation of the TMPRSS6 gene improved anaemia, IE and splenomegaly, decreasing tissue iron and serum iron levels.
* **Ferroportin**: IE can also be targeted by inhibiting ferroportin. In theory, decreasing levels of ferroportin will result in an increase of cytoplasmic iron, which will trigger a negative feedback loop suppressing the absorption of iron by the macrophages, hepatocytes and enterocytes.
* **VIT-2763**: Ferroportin inhibition, can be mediated either by direct inhibition of ferroportin receptors or else by ligand-inducted internalization and degradation. After screening a library of small molecular compounds for ferroportin modulators, it was found that VIT-2763 can act as a ferroportin modulator. In $Hbb^{th3/+}$ mice, VIT-2763, triggered ferroportin internalization and ubiquitination by blocking iron efflux while competing with hepcidin for ferroportin binding. This resulted in improved anaemia and ameliorated IE.

Gene therapy

* **Betibeglogene autotemcel** is a 1-time ex vivo gene therapy for adults, adolescents, and pediatric patients with all genotypes (β 0 β0 and non-β0/β0) of transfusion-dependent β-thalassemia.
- Treatment with betibeglogene autotemcel involves extraction of the patient's stem cells, introduction of functional copies of a modified form of the β-globin gene (βA[T87Q]-globin gene) into the stem cells via a BB305 lentiviral vector, and infusion of the modified cells into the patient.
- With a functioning β A(T87Q) globin gene, the patient should then be able to produce their own functional gene therapy–derived adult hemoglobin and no longer need red blood cell transfusions.
- Currently, betibeglogene autotemcel is approved in the European Union, United Kingdom, Iceland, Liechtenstein, and Norway for patients 12 years and older with transfusion-dependent β-thalassemia who are eligible for stem cell transplant but do not have an available donor. A biologics license application (BLA) to the FDA has also been submitted.
- In the phase 3 NorthStar-2 trial (NCT02906202) investigating betibeglogene autotemcel, 23 adult and pediatric patients with non-β 0/β0 genotypes were treated with betibeglogene autotemcel. In total, there were 22 patients who were eligible for evaluation, and 20 of them achieved transfusion independence, including 6 of 7 patients under age 12 years.

* **CTX001** is a gene therapy in phase 3 clinical trials.
- Like betibeglogene autotemcel, it is a 1-time ex vivo treatment but targets an increase in production of fetal hemoglobin via CRISPR/Cas9 editing of the BCL11A gene in the patient's cells.
- Interim data from 10 adult and pediatric patients with varying genotypes enrolled in the VX21-CTX001-141 trial (NCT05356195) demonstrated increased hemoglobin and fetal hemoglobin after administration of CTX001. During the trial, all 10 patients were able to stop transfusions within 2 months of treatment.
- A biologics license application (BLA) to the FDA has been submitted.

Potential Limitations of Gene Therapy for β-Thalassemia

- Gene therapy is not without risk or safety concerns.
- There have been reports of myeloid malignancies following treatment with betibeglogene autotemcel for sickle cell disease, although the gene therapy has not been directly implicated in causing the malignancies.
- Durability of effect is also an unknown.
- Cost may be a barrier to accessing gene therapy for patients with β-thalassemia. Betibeglogene autotemcel is priced at the equivalent of $1.8 million in Europe.

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Drug- Food Interactions

-The effect of drugs on population may be different than expected because of either drug-drug interaction, drug-nutrient/food interaction or drug-disease interaction.

-Food-drug interactions occur when some foods and drugs, taken simultaneously, can alter the body's ability to utilize a particular food or drug as shown in Fig-1.

-Clinically significant drug interactions may result from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties.

-The study of drug-drug, food-drug, and herb-drug interactions and of genetic factors affecting pharmacokinetics and pharmacodynamics is expected to improve drug safety and will enable individualized drug therapy.

-In contrast to the easy access to information on drug-drug interactions, the information about food-drug interaction is not always available conveniently.

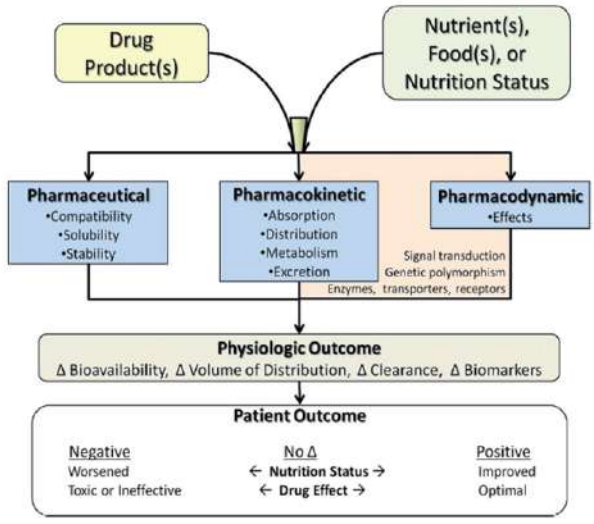

Fig. 1. Working model of drug-nutrient interactions [Boullata and Hudson 2012]

Important Drug-Food Interaction

Drugs	Food	Drug-Food Interaction
WARFARIN	High-protein diet	Raise serum albumin levels, decrease in international normalized ratio (INR)
	Vegetables containing vitamin K	Interferes with the effectiveness and safety of warfarin therapy
	Charbroiled	Decrease warfarin activity
	Cooked onions	Increase warfarin activity
	Cranberry juice	Elevated INR without bleeding in elderly patient
	Leafy green vegetables	Thromboembolic complications may develop
MONOAMNINE OXIDASES	Tyramine-containing food	Hypertensive crisis
PROPRANOLOL	Rich protein food	Serum level may be increased
CELIPROLOL	Orange juice	Intestinal absorption is inhibited
ACE INHIBITORS	Empty stomach	Absorption is increased
Ca^{2+} CHANNEL BLOCKERS	Grape fruit juice	Increases the bioavailability
ANTIBIOTICS	With milk products	Forms complex with some antibiotics and prevent their absorption (reduced bioavailability)
THEOPHYLINE	High-fat meal and grape fruit	Increase bioavailability & the risk of drug toxicity
ESOMEPRAZOLE	High-fat meal	Bioavailability was reduced
ISONIAZIDE	Medicinal herbs, oleanolic acid	Exerts synergistic effect
CYCLOSERINE	High fat meals	Decrease the serum concentration
ACARBOSE	At start of each meal	Maximum effectiveness
MERCAPTOPURINE	Cow's milk	Reduce bioavailability
TAMOXIFEN	Sesame seeds	Negatively interferes with tamoxifen in inducing regression of established mcf-7 tumor size, but beneficially interacts with tamoxifen on bone in ovariectomized athymic mice
LEVOTHYROXINE	Grapefruit juice	Delay the absorption

New Drugs Corner

(Reference: USFDA)

Tofersen

MOA: An antisense oligonucleotide
Indication: To treat amyotrophic lateral sclerosis in adults who have a superoxide dismutase 1 (SOD1) gene mutation

Pegunigalsidase alfa-iwx

MOA: Hydrolytic lysosomal neutral glycosphingolipid-specific enzyme
Indication: For the treatment of adults with confirmed Fabry disease

Fezolinetant

MOA: Neurokinin 3 (NK3) receptor antagonist
Indication: For the treatment of moderate to severe vasomotor symptoms due to menopause

Epcoritamab-bysp

MOA: Bispecific CD20-directed CD3 T-cell engager
Indication: For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

Co-package of sulbactam and durlobactam

MOA: Sulbactam, a beta-lactam antibacterial and beta lactamase inhibitor, and durlobactam, a beta lactamase inhibitor
Indication: For the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of Acinetobacter baumannii-calcoaceticus complex in patients of 18 years of age and older

Co-package of nirmatrelvir and ritonavir

MOA: Nirmatrelvir, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor
Indication: For the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death

Flotufolastat F 18

MOA: Radioactive diagnostic agent
Indication: For positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer

Sotagliflozin

MOA: Sodium-glucose cotransporter 2 (SGLT2) inhibitor
Indication: To reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit in adults with heart failure or type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

Glofitamab-gxbm

MOA: Bispecific CD20-directed CD3 T-cell engager
Indication: For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapy

Perfluorohexyloctane ophthalmic solution

MOA: Semifluorinated alkane fluid
Indication: For treatment of the signs and symptoms of dry eye disease (DED)

The Pill Box Quiz: 10

Instructions:
Scan the QR code to access the quiz.

SCAN ME