NEPALESE ARMY INSTITUTE OF HEALTH SCIENCES
September 2010

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NAIHS Drug and Therapeutics Bulletin

Published quarterly by Department of Pharmacology, College of Medicine, NAIHS

Vol 1, Issue 1, Jan-March, 2021

Editorial

The College of Medicine (CoM) of Nepalese Army Institute of Health Sciences (NAIHS) has once more provided a proof that the institution is garnering itself to become a "Centre of Excellence" in the field of medical education of the country. The NAIHS Drug & Therapeutics Bulletin "CHARAKA" has added to its honors of being one of the first in academic excellence along with its holistic and all-inclusive state of art facility in the institution. The department of pharmacology needs to be commended in starting to publish a high grade institutional bulletin that will help faculties and students alike in gaining and garnishing the modern medical knowledge by all. As per the current style the bulletin is being published as an online e-print and will be upgraded to hard copies if need be. The topics thus published in the first issue itself is a standing proof that NAIHS is going from "Strength to Strength" in advancement since the last 10 years of its establishment. With this I am sure that other departments will follow suit and come up with many more innovations to help NAIHS to reach even more academic heights in the days to come.

Thank you.

Brig. Gen. Dr. Arun Kumar Neopane
Principal, CoM (NAIHS)

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List of recently approved drugs by Food and Drug Administration (FDA)

S.N	Drug	Group/Class	Date of Approval	Indications
1	Trilaciclib (Tablets)	Cyclin-dependent kinase 4/6 (CDK4/6) inhibitor	February 12, 2021	Small Cell Lung Cancer Myelopreservation Therapy
2	Evinacumab-dgnb (Injection)	Angiopoietin-like 3 (ANGPTL3) inhibitor	February 11, 2021	Homozygous Familial Hypercholesterolemia
3	Umbralisib (Tablets)	Dual inhibitor of phosphoinositide 3 kinase (PI3K) delta and casein kinase 1 (CK1) epsilon	February 5, 2021	Marginal Zone Lymphoma; Follicular Lymphoma
4	Lisocabtagene maraleucel (Infusion)	Chimeric antigen receptor (CAR) T-cell therapy	February 5, 2021	Large B-Cell Lymphoma
5	Tepotinib (Tablets)	Oral mesenchymal-epithelial transition (MET) inhibitor	February 3, 2021	Non-Small Cell Lung Cancer
6	Voclosporin (Capsules)	Calcineurin-inhibitor, immunosuppressant	January 22, 2021	Adult patients with active lupus nephritis (LN)
7	Cabotegravir and Rilpivirine, [Extended-Release Injectable Suspension (Co-Packaged)]	Long-acting, injectable regimen of the HIV-1 integrase strand transfer inhibitor (INSTI) cabotegravir, and the HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine	January 21, 2021	Short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/ml)
8	Vericiguat (Tablets)	Soluble guanylate cyclase (sGC) stimulator	January 19, 2021	Heart Failure with Reduced Ejection Fraction (EF) less than 45%
9	Vibegron (Tablets)	Beta-3 adrenergic agonist	December 23, 2020	Overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults
10	Relugolix (Tablets)	Oral gonadotropin-releasing hormone (GnRH) receptor antagonist	December 18, 2020	Adult patients with advanced prostate cancer
11	Berotralstat (Capsules)	Plasma kallikrein inhibitor	December 3, 2020	Prophylaxis to prevent attacks of hereditary angioedema

Source: https://www.drugs.com/newdrugs.html

VOCLOSPORIN

Voclosporin, a calcineurin inhibitor, is a semisynthetic structural analogue of cyclosporine. This cyclosporine A analog was approved by the FDA on January 22, 2021 following promising results in clinical trials. It has demonstrated a more stable pharmacokinetic and pharmacodynamic relationship than cyclosporine, a higher potency than cyclosporine, and an improved metabolic profile when compared to older calcineurin inhibitors. It is being studied as a potential treatment for lupus nephritis (LN) and uveitis.

Pharmacokinetics

Absorption: When administered on an empty stomach, the median Tmax of voclosporin is 1.5 hours, but can range from 1-4 hours.

Volume of distribution: The apparent volume of distribution of voclosporin is 2,154 L. Voclosporin distributes extensively into red blood cells; distribution between whole blood and plasma is dependent on concentration and temperature. The protein binding of voclosporin is approximately 97%.

Metabolism: Voclosporin is mainly metabolized by the CYP3A4 hepatic cytochrome enzyme. Pharmacologic activity is mainly attributed to the parent molecule. A major metabolite has been detected in human whole blood, representing 16.7% of total exposure; this metabolite is about 8-fold less potent than the parent drug.

Route of elimination: It is eliminated in the urine and faeces, with about 88% detected in the feces and about 2% detected in the urine.

Half-life: The average terminal half-life of voclosporin is about 30 hours (24.9 to 36.5 hours) with peak plasma time of 1.5 hr (empty stomach). Steady-state reached at 6 days.

Clearance: The mean apparent steady-state clearance of voclosporin is 63.6 L/h. Hepatic and renal impairment significantly reduce its clearance.

Mechanism of action

It is a novel calcineurin inhibitor immuno-suppressant, with a synergistic and dual mechanism of action, blocking IL-2 expression and T-cell–mediated immune responses, as well as having a stabilizing effect on glomerular podocytes, reducing urine protein excretion. It is structurally similar to cyclosporine A (CsA) with the exception of an amino acid modification in one region. This modification changes the binding of voclosporin to calcineurin. Cyclosporine inhibitors reversibly inhibit T-lymphocytes. They also inhibit lymphokine production and release. Cyclosporine A exerts its inhibitory effects on T-lymphocytes by binding to cyclophilin. A cyclophilin-cyclosporine complex is formed, leading to the inhibition of calcium- and calmodulin-dependent serine-threonine phosphatase activity of calcineurin. Along with calcineurin inhibition, the inhibition of many transcription factors necessary for the induction of various cytokine genes such as IL-2, IFN-γ, IL-4 and GM-CSF occurs. This, in turn, reduces inflammation, treating renal glomerulonephritis associated with systemic lupus erythematosus.

Indication

Although better tolerated and safer than cyclosporine, voclosporin is inferior to cyclosporine in treating psoriasis, non-inferior to tacrolimus in organ transplantation and efficacious in treating lupus nephritis.

In combination with immunosuppressive therapy regimen for active lupus nephritis (LN). 23.7 mg PO BID initially; modify dose based on eGFR. Use in combination with mycophenolate mofetil (MMF) and corticosteroids. Consider discontinuation if no therapeutic benefit by 24 weeks.

Dosage Forms & Strengths: capsule, 7.9 mg

Before initiating therapy

- Baseline parameters: eGFR and blood pressure (BP).
  - Use not recommended in patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless benefits outweigh risks.
  - Do not initiate in if BP >165/105 mmHg or with hypertensive emergency.

During treatment

- eGFR: Every 2 weeks for first month, and every 4 weeks thereafter.
- BP: Every 2 weeks for first month, and as clinically indicated thereafter.

Adverse Effects

>10%: Glomerular filtration rate decreased (26%); Hypertension (19%); Diarrhea (19%); Headache (15%); Anemia (12%); Cough (11%),

1-10%: Urinary tract infection (10%); Upper abdominal pain (7%); Dyspepsia (6%); Alopecia (6%); Renal Impairment (6%); Abdominal pain (5%); Mouth ulceration (4%); Fatigue (4%); Tremor (3%); Acute kidney injury (3%); Decreased appetite (3%); Gingivitis (<3%); Hypertrichosis (<3%);

Frequency Not Defined: Upper respiratory tract infections (bacterial and viral); Herpes zoster; Pneumonia; Gastroenteritis; Urinary tract infections; Cytomegalovirus chorioretinitis; Cytomegalovirus infection; Herpes zoster cutaneous disseminated; Blood creatinine increased; Azotemia; Renal failure; Oliguria; Proteinuria; Hyperkalemia; QT prolongation, increased risk of developing lymphomas and other malignancies, particularly of the skin; etc.

Contraindications

- Co administration of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin)
- Serious or severe hypersensitivity reactions to voclosporin or any of its excipients

Pregnancy: Avoid use

Lactation: Breastfeeding is not recommended during treatment and for at least 7 days after last dose (~6 elimination half-lives).

Drug Interactions: The risk or severity of adverse effects can be increased when voclosporin is combined with abatacept, adalimumab, aldesleukin, alemtuzumab, anakinra, anthrax immune globulin, etc.

Food Interactions:

- Avoid grapefruit products.
- Avoid food or drink containing grapefruit when taking voclosporin, as it may decrease metabolism and increase exposure to this drug.
- Take on an empty stomach, either 1 hour before or 2 hours after a meal and as close to 12 hours between doses as possible.

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List of authorized/approved vaccines against SARS-CoV-2

S.N	Name	Vaccine Type	Primary developers	Country of Origin	Authorization/Approval
1	Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; FosunPharma	Multinational	United Kingdom, Bahrain, Canada, Mexico, US, Singapore, Costa Rica, Ecuador, Jordan, Panama, Chile, Oman, Saudi Arabia, Argentina, Switzerland, Kuwait, EU, Philippines, Pakistan, Colombia, Iraq, Israel, Qatar, Singapore, United Arab Emirates, Faroe Islands, Greenland, Iceland, Malaysia, Norway, Serbia, Hong Kong, Albania, Australia
2	Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based vaccine	Moderna, BARDA, NIAID	US	Canada, Israel, Saudi Arabia, Switzerland, United Kingdom, United States, EU, Faroe Islands, Greenland, Iceland, Norway
3	CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	China, Bolivia, Turkey, Indonesia, Brazil, Chile
4	COVID-19 Vaccine AstraZeneca (AZD1222); also known as Covishield	Adenovirus vaccine	BARDA, OWS	UK	UK, Argentina, El Salvador, Dominican Republic, India, Bangladesh, Mexico, Nepal, Pakistan, Brazil, Saudi Arabia, Iraq, Hungary, Thailand, South Africa, EU
5	Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Russia, Belarus, Argentina, Guinea (experimental use), Bolivia, Algeria, Palestine, Venezuela, Paraguay, Turkmenistan, Hungary, UAE, Serbia, Iran
6	No name announced	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China
7	BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China, Bahrain, United Arab Emirates, Egypt, Jordan, Iraq, Pakistan, Serbia, Peru
8	EpiVac Corona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	Russia
9	Covaxin	Inactivated vaccine	Bharat Biotech, ICMR	India	India
10	Convidicea (Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	China	Mexico, China (military use)

Source: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) [COVISHIELD]

Introduction

This is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.[1]

This vaccine has been given restricted use license for emergency situation (with no marketing authorization), for active immunization of individuals aged 18 years and older for the prevention of coronavirus disease 2019 (COVID-19). It has been given regulatory approval by the Medicines and Healthcare products Regulatory Agency (MHRA), UK on 31st Dec 2020, by Drug Controller General of India (DCGI) on 3rd Jan 2021 and by Department of Drug Administration (DDA), Nepal on 15th Jan 2021.[1,2]

It costs $3 to $4 per dose around the world which is cheaper in comparison to the vaccine developed by Moderna ($25 to $37) and Pfizer ($20).

Nomenclature

ChAdOx1 nCoV-19 is a chimpanzee (**Ch**) adenovirus-vectored vaccine (**Ad**), whose development was led by the University of Oxford (**Ox**). It has been shown to stimulate an immune response to nCoV-19, the novel coronavirus first identified in 2019. Another name for ChAdOx1 nCoV-19 is AZD1222, used especially in the context of the vaccine's co-development by the University of Oxford, Vaccitech, and AstraZeneca. The Oxford-AstraZeneca COVID vaccine is later called Covishield in India.[1]

Clinical efficacy

Based on an interim analysis of pooled data from four on-going randomized, blinded, controlled trials in the UK, Brazil and South Africa, the overall efficacy was 70.42% (95.84% CI).[2, 3] Final determination of COVID-19 cases was made by an adjudication committee, who also assigned disease severity according to the WHO clinical progression scale. A total of 131 participants had SARS-CoV-2 virologically confirmed (by nucleic acid amplification tests) COVID-19 occurring ≥15 days post second dose with at least one COVID-19 symptom (objective fever (defined as ≥37.8ºC), cough, shortness of breath, anosmia, or ageusia) and were without evidence of previous SARS-CoV-2 infection. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control.[3]

Immunogenicity

Following vaccination, in participants who were seronegative at baseline, seroconversion (as measured by a ≥4 fold increase from baseline in S-binding antibodies) was demonstrated in ≥98% of participants at 28 days after the first dose and >99% at 28 days after the second. Higher S-binding antibodies were observed with increasing dose interval. An immunological correlate of protection has not been established; therefore, the level of immune response that provides protection against COVID-19 is unknown.[3, 4]

Safety

The safety data published so far is from over 20,000 participants enrolled across four clinical trials in the UK, Brazil and South Africa.[2] Most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%).The majority of adverse reactions was mild to moderate in severity and usually resolved within a few days of vaccination. [3,4]

By day 7 the incidence of subjects with at least one local or systemic reaction was 4% and 13%, respectively. When compared with the first dose, adverse reactions reported after the second doses were milder and reported less frequently. Adverse reactions were generally milder and reported less frequently in older adults (≥65 years old) (Table 2).

Special populations

- Elderly population: Efficacy and safety data are currently limited in individual ≥ 65 years of age. No dosage adjustment is required in elderly individual ≥ 65 years of age.
- Paediatric population: The safety and efficacy of COVISHIELD™ in children and adolescents (aged <18 years old) have not yet been established. No data are available.[1]

Pregnancy: There is a limited experience with the use of COVID-19 Vaccine AstraZeneca in pregnant women. The full relevance of animal studies to human risk with vaccines for COVID-19 remains to be established. Administration of COVID-19 Vaccine AstraZeneca in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.[1, 3]

Breastfeeding: It is unknown whether COVID-19 Vaccine AstraZeneca is excreted in human milk.[2]

Table: Common adverse effects of Covishield [2, 3]

System	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy [a]
Metabolism and nutrition disorders	Uncommon	Decreased appetite [a]
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness [a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting
	Uncommon	Abdominal pain [a]
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis [a], pruritus [a], rash [a]
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Injection site tenderness, injection site pain, injection site warmth, injection site erythema, injection site pruritus, injection site swelling, injection site bruising [b], fatigue, malaise, pyrexia [c], chill
	Common	Injection site induration, influenza like illness [a]

[a] Unsolicited adverse reaction

[b] Injection site bruising includes injection site haematoma (uncommon, unsolicited adverse reaction)

[c] Pyrexia includes feverishness (very common) and fever ≥38°C (common)

Fertility: Preliminary animal studies do not indicate direct or indirect harmful effects with respect to fertility.[2]

Hypersensitivity: As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.[1]

Concurrent illness: As with other vaccines, administration of COVISHIELD™ should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.[1]

Thrombocytopenia and coagulation disorders: As with other intramuscular injections, COVISHIELD™ should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals[2]

Immunocompromised individuals: It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen.[1]

Interaction with other medicinal products and other forms of interaction: No interaction studies have been performed. Concomitant administration of COVISHIELD with other vaccines has not been studied.[1]

Duration and level of protection: The duration of protection has not yet been established. As with any vaccine, vaccination with COVID-19 Vaccine AstraZeneca may not protect all vaccine recipients.

List of excipients: L-Histidine, L-Histidine hydrochloride monohydrate, Magnesium chloride hexahydrate, Polysorbate 80, Ethanol, Sucrose, Sodium Chloride, Disodium edetate dihydrate (EDTA), Water for injection

Incompatibilities: In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

Shelf life of unopened multidose vial: 6 months

Special precautions for storage: Unopened multidose vial: Store in a refrigerator (2 to 8°C). Do not freeze.

Multidose vial: 5 ml of solution in a 10-dose vial (clear type I glass) with a halo butyl rubber stopper and an aluminum overseal with a plastic flip-off cap.

Administration: It is a colourless to slightly brown, clear to slightly opaque solution and particle free with a pH of 6.6. The vaccine should be inspected visually prior to administration and discarded if particulate matter or differences in the described appearance are observed. Do not shake the vial. Care should be taken to ensure a full 0.5 ml dose is administered. The vaccine does not contain any preservative. Intramuscular (IM) injection only, preferably in the deltoid muscle, two separate doses of 0.5 ml each at interval of 4-6 weeks. One dose (0.5 ml) contains 5 x 10^{10} viral particles. Use as soon as practically possible and within 6 hours. The vaccine may be stored between 2°C and 25°C during the in-use period. To facilitate the traceability of the vaccine, the name and the batch number of the administered product should be clearly recorded for each recipient. Discard any unused vaccine. Spills should be disinfected with an appropriate antiviral disinfectant (e.g. Hydrogen peroxide based disinfectants).[1]

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Article summary: Safety and efficacy of ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomized controlled trials in Brazil, South Africa and the UK. Lancet 2021; 397: 99-111 [Accessed on 15th Jan 2021]

Rapid global efforts to develop and test vaccines against SARS-CoV-2 have led to an unprecedented number of candidate vaccines starting clinical trials during 2020. Currently, 48 vaccines are under clinical evaluation of which 11 are currently being evaluated in phase III clinical trials.

ChAdOx1 nCoV-19 vaccine (AZD1222) was developed at Oxford University and consists of replication-deficient chimpanzee adenoviral vector ChAdOx1 containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene. There were four studies done across UK (2 studies), Brazil and South Africa. They were COV001 (phase ½; UK), COV002 (phase 2/3; UK), COV003 (phase III; Brazil) and COV005 (phase ½; South Africa). Three studies (COV001, COV002, and COV003) were randomized single-blind phase trial and COV005 was double-blind phase trial.

COV001 had 1077 healthy participants who received ChAdOx1 nCoV-19 dose of 5 X 10^{10} viral particles as standard dose and Meningococcal ACWY conjugate (Men ACWY) as control group. 86.7% of the participants comprised of age 18-55 years and 12.2% participants were >56years of age.

COV002 had 10673 had participants (participants with high exposure to SARS-CoV-2 such as health care and social care settings) who were divided into two dosage groups – LD/SD { Low dose (2.2 X 10^{10} viral particles) / Standard dose (5 X 10^{10} viral particles) } and SD/SD group. 53.2% in the LD/SD group received a second dose at least 12 weeks apart and 0.8% received second dose within 8 weeks of the first.

COV003 had 10002 participants (participants with high exposure to SARS-CoV-2 such as health care and social care settings). Patients with pre-existing health conditions were also included. Participants were given two doses of (3.5-6.5 X 10^{10} viral particles) 12 weeks apart.

COV005 had 2096 healthy participants aged between 18-65 years who were given two doses of ChAdOx1 nCoV-19 dose of 3.5-6.5 X 10^{10} viral particles four weeks apart.

Table 1: Comparisons of efficacy more than 14 days after a second dose

Groups	Vaccine Efficacy
COV 002	LD/SD – 90.0% ; SD/SD – 59.3%
COV 002 (>8 weeks interval)	LD/SD – 90.0% ; SD/SD – 65.6%
COV 001, COV 003, COV 005 (< 6 weeks interval)	SD/SD – 53.4%
COV 001, COV 003, COV 005 (≥ 6 weeks interval)	SD/SD – 65.4%

Table 2: Efficacy against SARS-CoV-2 more than 21 days after the first standard dose in seronegative participants who received only standard doses.

Group	Vaccine efficacy
COV 002 (UK)	55.0%
COV 003 (Brazil)	71.2%
Primary Symptomatic COVID-19	64.1%
Other non-primary symptomatic COVID-19	-32.8%
Any symptomatic COVID-19	58
Symptomatic or symptoms unknown	7.8%
Any NAAT (nucleic acid amplification test)	46.3%

Table 3: Hospitalization for COVID-19 in the safety population.

		ChAdOx1 nCoV-19 (n=12021)	MenACWY or saline control
Hospitalization (WHO clinical progression score ≥4)	≤21 days after the first dose	2	6
	> 21 days after the first dose and ≤ 14 days after the second dose	0	5
	>14 days after the second dose	0	5
	>14 days after the second dose	0	0
Severe COVID-19 (WHO clinical progression score ≥ 6	≤21 days after the first dose	0	1
	> 21 days after the first dose and ≤ 14 days after the second dose	0	1

There were 125 adverse events in 168 participants, 84 in the ChAdOx1 nCoV-19 group and 91 in control group. There was 1 case of transverse myelitis and 1 case of hemolytic anemia. Participants who received two standard doses, vaccine efficacy was 62.1% and participants who received low dose followed by dose, vaccine efficacy was 90.0%. Overall vaccine efficacy was 70.4%.

ChAdOx1 nCoV-19 has an acceptable safety profile and has been found to be efficacious against symptomatic COVID-19.

Reference

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Long Term Adverse Effects of Proton Pump Inhibitors

Proton pump inhibitors (PPI) are medicines that reduce gastric acid secretion. They have greatly improved how a number of gastrointestinal conditions are managed. These include conditions like gastroesophageal reflux disease (GERD), peptic ulcer disease and functional dyspepsia. Apart from these, PPIs are also used in short term to eradicate *Helicobacter pylori*, and to counter the side effects of non-steroidal anti-inflammatory drugs (NSAIDs) on gastrointestinal tract in some people.[1]

Common side effects of PPIs include abdominal pain, diarrhea, vomiting, flatulence, headache, constipation and nausea[2]. Though generally safe, some studies have linked the long term use of PPIs to a small increase in the risk of adverse outcomes, such as osteoporosis linked fractures, pulmonary and enteric infections, dementia and acute interstitial nephritis[3].

Kidney: Acute interstitial nephritis

Proposed mechanism for acute and chronic disease involves a rare but probably an idiosyncratic reaction of PPIs on the kidneys leading to acute interstitial nephritis; a hypersensitivity reaction leading to inflammation of the renal interstitium and the tubules.

Brain: Dementia

Long term use of PPIs induced hypochlorhydria leads to impaired release of dietary protein bound vitamin B12 which is absorbed from terminal ileum. This can potentially lead to vitamin B12 deficiency and cognitive decline. Other rationale proposed for PPIs induced dementia is enhanced brain beta-amyloid levels which is due to decreased degradation by lysosomes in microglia secondary to inhibition of vacuolar type H^+ATPase leading to increased pH and reduced clearance of beta amyloid peptides.

Bone: Fracture and osteoporosis

Mechanism for bone loss with subsequent fracture risk involves reduction of gastric acidity with subsequent hypergastrinemia. Reduction of gastric acidity leads to malabsorption of calcium and vitamin B12 and the latter leads to secondary hyperparathyroidism. Vitamin B12 deficiency in addition may lead to homocysteinemia linked to reduced bone strength.

Heart: Myocardial infarction

PPIs may compete with hepatic cytochrome p450 isoenzyme CYP2C19 and impair with clopidogrel activation in patients with acute coronary syndrome. This would increase the likelihood of clot formation and subsequent myocardial infarction. Other proposed mechanism is reduction of endothelial nitric oxide through PPI inhibition of dimethyl-arginine-dimethyl-aminohydrolase enzymatic activity thereby leading to decreased clearance of asymmetric dimethyl-arginine and subsequently to reduced synthesis of endothelial nitric oxide synthase (eNOS).

Colon: *Clostridium difficile* infection and microscopic colitis

Reduced gastric acidity may create a favorable environment for the survival of vegetative spores of *C. difficile* and hence predispose to infection. The underlying pathophysiology behind PPI induced microscopic colitis may be related to PPIs induced changes in intercellular tight junctions or alterations in the colonic microbiome.

Lungs: Pneumonia

Growth of aerobic bacteria in the stomach secondary to reduced gastric acid secretion by PPIs may subsequently lead to micro-aspiration and lung colonization with the potential of causing pneumonia.

Muscle: Myopathy

Co-administration of a PPI with an NSAID or statin may increase the risk of rhabdomyolysis due to PPI induced inhibition of statin metabolism and lead to dose related adverse effects including myopathy.

Blood: Anemia

Mechanism is reduced gastric acidity leading to decreased iron and vitamin B12 absorption.

Stomach: Fundic gland polyps

Acid suppression is theorized to produce parietal cell hyperplasia leading to histologic changes and polyposis.

Table 1: Proposed mechanisms of chronic complications of PPI Therapy

Kidney	Recurrent AIN
Brain	a) Decreased gastric acidity leading to vitamin B12 deficiency
	b) Beta-amyloid deposition
Bone	a) Decreased gastric acidity leading to reduced calcium and vitamin B12 absorption
	b) Hypergastrinemia leading to hyperparathyroidism
Heart	a) Inhibiting clopidogrel activation (Cytochrome P2C19)
	b) Increased asymmetric dimethylarginine leading to reduced endothelial nitrous oxide resulting in thrombosis
Colon	a) Decreased gastric acidity altering intestinal normal flora
	b) Trophic effect of hypergastrinemia on colonocytes
Lungs	a) Decreased gastric acidity and overgrowth of gastric bacteria
	b) Antineutrophilic effect of PPIs
Muscle	CYP3A4 enzyme inhibition
Blood	Decreased gastric acidity leading to iron and vitamin B12 deficiencies
Liver	a) Altered gut microbiota due to gastric acid suppression
	b) Vitamin B12 deficiency due to reduced gastric acid
Stomach	Acid suppression induced parietal cell hyperplasia

Conclusion

In wake of these long terms adverse effects of PPIs, their uncritical uses in symptoms unrelated to underlying acid peptic disorders is unwarranted.

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FAVIPIRAVIR

Favipiravir is an antiviral drug, initially marketed as an anti-influenza agent in Japan where it was approved in 2014. With the advent of the COVID-19 pandemic, the quest for an effective treatment is frantic. Discovery of a new and specific antiviral agent against the SARS-CoV-2 would involve a long and arduous timeline. Hence, by default, repurposed drugs, already in use against other viral infections, have been pressed into quick service. One such drug is favipiravir.[1]

Favipiravir was first used against SARS-CoV-2 in Wuhan at the very epicenter of the pandemic. Then, as the pandemic spread to Europe, this drug received approval for emergency use in Italy, and currently has been in use in many countries like Japan, Russia, Turkey, Bangladesh, India etc. As of clinicaltrials.gov, one ongoing study in Nepal has also been registered to assess the utility of this drug in the management of COVID-19.[2]

Pharmacology

Favipiravir (T-705) is a synthetic prodrug, It has an excellent bioavailability (~94%), 54% protein binding, and a low volume of distribution (10 - 20 L). It reaches Cmax within 2 h after a single dose. Both Tmax and half-life increase after multiple doses. Favipiravir has a short half-life (2.5-5 h) leading to rapid renal elimination in the hydroxylated form.[3] Elimination is mediated by aldehyde oxidase and marginally by xanthine oxidase. Favipiravir exhibits both, dose-dependent and time dependent pharmacokinetics. It is not metabolized by the cytochrome P450 system, but inhibits one of its components (CYP2C8). Thus, it needs to be used with caution when co-administered with drugs metabolized by the CYP2C8 system.[1]

Mechanism of action

Within the tissue, the molecule undergoes phosphoribosylation to favipiravir-RTP, which is the active form of this drug. It exerts its antiviral effect through the following mechanisms:

a. This molecule acts as a substrate for the RNA-dependent RNA-polymerase (RdRp) enzyme, which is mistaken by the enzyme as a purine nucleotide, thus inhibiting its activity leading to termination of viral protein synthesis.

b. It gets incorporated in the viral RNA strand, preventing further extension. This mechanism of action, along with preservation of the catalytic domain of the RdRp enzyme across various RNA viruses, explains the broad spectrum of activity of this drug.

c. It has recently been shown that favipiravir induces lethal mutagenesis in vitro during influenza virus infection, making it a virucidal drug. Whether a similar activity is demonstrated against SARS-CoV-2 or not is uncertain.[1]

Role in SARS-CoV-2

The SARS-CoV-2eRDRp complex is at least 10-fold more active than any other viral RdRp known. Favipiravir acts by inhibiting this viral RdRp enzyme, allowing facile insertion of favipiravir into viral RNA while sparing human DNA. Thus nucleoside analogs (such as favipiravir) are promising candidates for the treatment of COVID-19.[1, 3]

Side effects/adverse effects

The adverse effects are relatively minor and include hyperuricemia, diarrhea, reduced neutrophil count and transaminitis. One study showed occurrence of psychiatric symptoms in association with favipiravir. Effect of favipiravir in QTc prolongation is still uncertain. Overall, favipiravir has a good safety profile.[1]

Drug interactions

Pyrazinamide: Concomitant use of pyrazinamide with favipiravir increases the levels of uric acid. Regular uric acid level monitoring is mandatory when these drugs are used together.

Repaglinide: Favipiravir inhibits the metabolism of repaglinide through the CYP2C8 pathway, thus increasing its potential to cause toxicity (hypoglycemia, headache, increase incidence of upper respiratory tract infections, etc). Cautious concomitant use is recommended.

Theophylline: Theophylline increases the blood levels of favipiravir and adverse reactions to favipiravir may occur.

Famciclovir, sulindac: Efficacy of these drugs may be reduced when co-administered with favipiravir.

Acyclovir: Acyclovir may delay the conversion of favipiravir into the active moiety, thus reducing its antiviral efficacy.[1]

Conclusion

The main advantages of favipiravir are that it is administered orally and that it can be given in patients who are symptomatic but not ill enough to be hospitalized. As most COVID-19 patients (85%) have mild to moderate disease and can be treated at home, this drug could potentially be used in large numbers of patients. As with any antiviral, it should be stressed that favipiravir should be administered early after the onset of symptoms for it to be effective in reducing viremia. Its role in potentially shortening the duration of viral shedding could also have an epidemiological impact as it could reduce viral transmission at home and in the community.[1] It is however teratogenic and must never be used in pregnant women. The main disadvantage is a high pill burden which works out to a loading dose of 18 tablets on the first day and then 8 tablets a day for the rest of the course. The recommended duration of treatment, extending to 2 weeks may also be a disadvantage. Here again, the manufacturers specify that the drug can be stopped in a week if the patient has made a complete recovery by then. Thus, in conclusion, favipiravir may emerge as a valuable drug in the treatment of mild to moderate symptomatic SARS CoV- 2 infected cases.[1]

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REMDESIVIR- Current status in therapy against COVID-19

Introduction

Broad-spectrum antiviral agent remdesivir is an intravenous nucleotide prodrug of adenosine analog. It was initially developed during the 2013 Ebola epidemic but showed limited benefit. FDA approved an Emergency Use Authorization for remdesivir in adults and children hospitalized with severe COVID-19 on May 1, 2020.[1-4]

Mechanism of action

Remdesivir is a prodrug which upon diffusing into the cell gets metabolized to its active form and binds to viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription.

Indication

Remdesivir is approved by FDA for the treatment of coronavirus disease 2019(COVID-19) requiring hospitalization in adult and pediatric patients (12 years and older and who weigh at least 40kg). There are different dosing regimens for remdesivir according to age, body weight and severity of patients as depicted in table1.

Table 1: FDA suggested dosing pattern of remdesivir in COVID-19 in different categories of patients[3]

Category of patient	Body weight	Loading dose	Maintenance dose
Adult or pediatric patients requiring invasive mechanical ventilation and/or ECMO	≥40kg	200mg IV infusion over20-120minutes on day 1	100mg infused IV over30-120minutes for 9days (day2 through 10)
Adult or pediatric patients not requiring invasive mechanical ventilation and/or ECMO	≥40kg	200mg IV infusion over20-120minutes on day 1	100mg infused over 30-120minutes for 4 days (2 through 5) If no improvement, may be extended upto10days
Pediatric patients requiring invasive mechanical ventilation and/or ECMO	3.5-40kg	5mg/kg infused over 30-120 minutes on day 1	2.5mg/kg IV (infused over 30-120 minutes)once daily for 9 days(day2 through10)
Pediatric patients not requiring invasive mechanical ventilation and/or ECMO	3.5-40kg	5mg/kg infused over 30-120 minutes on day 1	2.5mg/kg (infused over30-120minutes) once daily for 4days (day 2 through 5). If no improvement, may be extended up to 10days

- Creatinine clearance and liver enzymes are obtained for all the patients before initiating the therapy. It should not be initiated in patient with ALT>/= 5 times the upper limit of normal at baseline
- Daily LFTs monitoring has to be done

Current status

At present, remdesivir remains an investigational drug for the treatment of COVID-19. There is lack of consensus among society and organizational guidelines on whether remdesivir should be used in management of COVID-19, given the varying results shown in existing clinical trial data.[1, 2]

Infectious Disease Society of America (IDSA) guidelines recommend use of remdesivir among hospitalized patients with severe COVID-19 (patient with SpO2</= 94% on room air or ECMO).[3] National Institute of Health (NIH) guidelines recommend use of remdesivir in hospitalized COVID-19 patients requiring supplemental oxygen through nasal cannula.[3] More recently, WHO Solidarity Trial Consortium released their report where in remdesivir along with other four available treatment option (lopinavir/ritonavir, hydroxyquinine and interferon beta-1a) failed to show benefit in mortality, initiation of ventilation or hospitalization duration. Based on this Solidarity Trial, WHO guidelines recommend against remdesivir to treat hospitalized COVID-19 patients, as there is currently no evidence that it improves survival or the need for ventilation.[4, 6, 7] However, one limitation of this study is the lack of data on the duration of symptoms prior to initiation of remdesivir.

Government of Nepal has given the permission to use remdesivir in COVID-19 patients of Nepal only as study drug on Aug 9th, 2020 and its use has been monitored by Nepal health Research Council (NHRC) to evaluate the outcome of remdesivir use in patient with COVID-19.[5]

Summary

Remdesivir does not provide an overall mortality benefit to the general group of patient hospitalized with COVID-19. However, it reduces time to clinical improvement when given in early active viral replication phase rather than in inflammatory phase (characterized by dysregulated host immune response. If patient progresses from the viral replication phase to inflammatory phase of infection, such patients with ARDS requiring mechanical ventilation, remdesivir is not effective and anti-inflammatory drugs may be beneficial. Choice of therapeutics, therefore, depends on disease phase but there is lack of data regarding the initiation of the remdesivir early in active viral replication phase.

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Antiviral activity of Glycyrrhizin against coronaviruses

Licorice *(Glycyrrhiza glabra,* Jethimadhu in Nepali) root has been traditionally used alone and as one of the components of polyherbal preparations for upper and lower respiratory infections in Ayurvedic system of medicine. Glycyrrhizin is one of the main bioactive component found in licorice root.[1] Glycyrrhizin has been used in past for peptic ulcer healing properties but with advent of effective anti-secretory agents it has been abandoned. In vitro activity of this compound against coronavirus causing severe acute respiratory syndrome (SARS-1) was experimentally shown in 2003.[2]

Mechanism of action

Glycyrrhizin might possess therapeutic benefits for COVID-19 with multisite mechanisms, including:

a) Binding ACE2 to prevent SARS-CoV-2 infection.

b) Downregulating pro-inflammatory cytokines.

c) Inhibiting the accumulation of intracellular reactive oxygen species (ROS).

d) Inhibiting thrombin.

e) Inhibiting the hyper production of airway exudates.

f) Inducing endogenous interferon to combat the SARS-CoV-2.[3]

Randomized controlled trial (RCT) done in healthy volunteers giving tea fortified with 5 herbs viz. *Withania somnifera, Glycyrrhzia glabra, Zingiber officinale, Ocimum sanctum* and *Elettaria cardamomum* on innate immunity investigated the effects on natural killer (NK) cell activity. Consumption of fortified tea significantly improved the NK cell activity of the volunteers in comparison with a population consuming regular tea.[4] NK cells are well known in defense against viruses and in SARS- CoV-2 infection it is probably very important.[5] Neutralization of SARS- CoV-2 in vitro by inhibition of viral main protease is recently reported.[4] These evidences show that glycyrrhizin has potential drug against respiratory viruses including SARS- CoV-2. Immunomodulatory and anti-inflammatory effects of glycerrhizic acid have also been explored showing multiple mechanisms involved.[3] This could be useful in preventing hyper immune response e.g. cytokine storm seen in SARS- CoV-2 infection.

Adverse effects

Adverse effects are generally seen with sustained overuse of licorice root which are mainly the effects of inhibition of the enzyme 11-ß-hydroxysteroid dehydrogenase enzyme type 2 with a resultant cortisol-induced mineralocorticoid effect and the tendency towards the elevation of sodium and reduction of potassium levels. Patients with postural hypotension caused by diabetic autonomic neuropathy may benefit with licorice ingestion while those with hypertension and hyperaldosteronism need more cautious and limited use.[4, 5]

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Patient related services provided by Department of Pharmacology, College of Medicine, NAIHS

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2. **Drug information services at College of Medicine**
   Drug and therapeutics related questions are answered from the department.
   E-mail: pharmacology@naihs.edu.np
   Phone: 01-4881259 Ext 129/168

KEY MESSAGES OF THE ISSUE

1. In last three months (Dec 20-Feb 21), six new drugs have been approved by FDA. They are voclosporin (calcineurin inhibitor, indication-lupus nephritis), cabotegravir and rilpivirine co packaged (INSTI and NNRTI, indication-virologically suppressed HIV-1), vericiguat (soluble GC stimulator, indication- heart failure with reduced ejection fraction), vibegron (beta 3 agonist, indication-overactive bladder), relugolix (GnRH receptor antagonist, indication- advanced prostate cancer) and berotralstat (plasma kallikrein inhibitor, indication- prophylaxis of hereditary angioedema).
2. There are ten vaccines approved/authorized against COVID-19 till end of Jan 2021. Out of ten vaccines, Comimaty (multinational) and Moderna (US) are mRNA based vaccine; CoronaVac, BBIBp-CorV (China), unnamed vaccine (China) and Covaxin (India) are inactivated vaccine; ChAdOX 1 (UK) and Convidicea (China) are adenovirus vector vaccine; EpiVacCorona (Russia) is peptide vaccine; and Sputnik V (Russia) is non-replicating viral vector vaccine.
3. ChAdOx1 nCoV-19 is a chimpanzee (Ch) adenovirus-vectored vaccine (Ad), whose development was led by the University of Oxford (Ox). The Oxford-AstraZeneca COVID vaccine is later called Covishield in India. Vaccine efficacy ranges from 62.10 to 70.42%. The duration of protection has not yet been established. Intramuscular (IM) injection only, preferably in the deltoid muscle, two separate doses of 0.5 ml each at interval of 4-6 weeks. One dose (0.5 ml) contains 5 x 1010 viral particles.
4. The long term use of PPIs includes osteoporosis linked fractures, pulmonary and enteric infections, fundic gland polyps, dementia, acute interstitial nephritis, etc.
5. Favipiravir is an antiviral drug, initially marketed as an anti-influenza agent in Japan and was first used against SARS-CoV-2 in Wuhan. The main advantages of favipiravir are that it is administered orally and that it can be given in patients who are symptomatic but not ill enough to be hospitalized. As of clinicaltrials.gov, one ongoing study in Nepal has also been registered to assess the utility of this drug in the management of COVID-19.
6. Remdesivir does not reduce overall mortality in COVID-19. It reduces time to clinical improvement when given in early active viral replication phase rather than in inflammatory phase. Choice of therapeutics, therefore, depends on disease phase but there is lack of data regarding the initiation of the remdesivir early replication phase.
7. Glycyrrhizin is one of the main bioactive components found in licorice root. Glycyrrhizin might possess therapeutic benefits for COVID-19 with multisite mechanisms. Patients with postural hypotension caused by diabetic autonomic neuropathy may benefit with licorice ingestion while those with hypertension and hyperaldosteronism need more cautious and limited use.

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