TENTH ISSUE
Apr - Jun
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PHARMACOALERT

NEWSLETTER

Drug Safety Alert, New Drug Marketed, Drug Interactions And Banned Drugs

Contents

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Picture Courtesy : Dr. Anupam Das

From The Desk of Editorial Team

The department of Pharmacology, Dr. RMLIMS, Lucknow, is pleased to present the TENTH issue of our newsletter. In the past years COVID 19 has created a global health crisis that had a deep impact on the way we perceive our world and our everyday lives. As a part of medical fraternity we have been at the forefront designated as COVID Warriors in battling this epidemic even when the rate of contagion and patterns of transmission threatened our sense of agency, also the safety measures to contain the spread of the virus also required social and physical distancing, preventing us from finding solace in the company of others.

As the saying says "the show must go on" we were there with all our big and small efforts and currently with the vaccination drive covering maximum population in our Country and fatality rate going down we expect the epidemic to wane out soon hoping to allow us to resume our lives as normal as in pre COVID era. Therefore our first article in this issue still focuses on COVID -19. Since the main focus is on Vaccination now, the article is a summary on all the available options for Vaccination in India.

We have also incorporated information related to Materiovigilance Program of India, a counterpart of Pharmacovigilance Programme of India, by MoHFW, Govt. of India, Important Drug Safety Alerts and New Drug Approvals during this period. As a new global emergency has arise with increasing cases of Monkey Pox. So, we have included an article highlighting the available treatment options for Monkey Pox.

The editorial committee would like to thanks all contributors and we are hopeful that this newsletter will be informative and enlightening for all its readers.

COVID - 19 Vaccines in INDIA

Approved for Manufacture, Sale and Distribution in the country

Name of the Vaccine (Company/Applicant)	Date of Approval	Type of Vaccine /Vaccine Platform	Age Group	Dosing Schedule & Route	Storage & Shelf life as on 15/06/2022
COVISHIELD (Serum Institute of India)	27.01.2022	Recombinant ChAdOx1 nCoV -19 Corona Virus vaccine	≥ 15 years	Two doses, 4 to 6 weeks apart (Overseas Data available for 12weeks) Intramuscular	2-8°C 9 months
COVAXIN (Bharat Biotech)	27.01.2022	Whole-Virion Inactivated SARS - CoV -2 Vaccine	≥ 15 years	Two doses, Day 0 & 28 Intramuscular	2-8°C 12 months

Both COVISHIELD & COVAXIN vaccines were initially approved for Restricted Use in Emergency Situation in the country on 03.01.2021

COVID - 19 vaccines approved for Restricted Use in Emergency Situation in the country

SPUTNIK -V (Dr. Reddy's Lab. Ltd. -Importer)	12.04.2021	Gam COVID Vac (component I & II)	≥ 18 years	Two doses, Day 0 (comp I) & Day 21 (comp II), Intramuscular	-18°C 12 months
SPUTNIK -V (Panacea Biotec Ltd)	02.07.2021				
SPUTNIK -V (Hetero Biopharma Ltd)	07.10.2021				-18°C 6 months
MODERNA VACCINE (Cipla Ltd. - Importer)	29.06.2021	mRNA - 1273COVID - 19 vaccine	≥ 18 years	Two doses, Day 0 & 28, Intramuscular	-25ºC to - 15ºC 7 months
JANSSEN VACCINE (Johnson & Johnson Pvt. Ltd. -Importer)	07.08.2021	COVID -19 vaccine (Ad26.COV2 -S) [recombinant]	≥ 18 years	Single dose, Intramuscular	-25ºC to - 15ºC & 2 - 8°C 6 months
JANSSEN VACCINE (Biological E Limited)	18.08.2021				
ZyCoV -D (Cadila Healthcare Limited)	20.08.2021	Novel Corona Virus - 2019-nCov vaccine (rDNA)	≥ 12 years	Three doses Day 0, 28 & 56, Intradermal	2-8°C 9 months

Materiovigilance Programme of India

Materiovigilance Programme of India (MvPI) was launched on 6th July, 2015 at the Indian Pharmacopoeia Commission (IPC), Ghaziabad by the Drugs Controller General of India (DCGI) to improve patient safety and welfare of Indian population by monitoring adverse events related to medical devices and thereby reducing the risk associated with use of medical devices.

IPC functions as the National Coordination Centre for MvPI. SreeChitraTirunal Institute of Medical Sciences & Technology (SCTIMST), Thiruvananthapuram functions as the National Collaborating Centre for MvPI. NCC-MvPI, IPC collects, collates and analyse adverse events associated with medical devices including Personal Protective Equipments (PPEs) exclusively in Indian population. To collect the safety information related to medical devices, Medical Device Adverse Events (MDAE), Field Safety Corrective Action (FSCA) and Personal Protective Equipments (PPEs) reporting forms **have been** designed by NCC-MvPI. The reports are analysed based on benefit-risk ratio, and evidence based information are generated on medical device safety, which support regulatory bodies in decision making process on medical device & communicate the safety signal on use of medical devices to various stakeholders.

Scope and Objectives

- To create a nation-wide system for vigilance on medical device related adverse event. Active system provide forum for encouraging adverse event reporting, proactive investigation, collecting risk-based information from global regulators and conducting reactive investigation. The database would enable data analysis in multiple ways
- To capture and record suspected medical device adverse events like death or serious deterioration in state of health, serious injuries and disability
- To identify and analyze new signal from the reported cases both via active as well as passive surveillance
- To analyze the benefit-risk ratio/risk analysis/causality assessment of medical devices
- To generate evidence-based information on safety of medical devices and medical generate device alert to regulator/healthcare professional
- To support regulatory agencies in the decision-making process on use of medical devices
- To communicate the safety information **on** use of medical devices to various stakeholders with an aim to minimize the risk

Functions

- To create a nation - wide system for patient safety **monitoring.**
- To analyse the benefit-risk ratio of medical devices.
- To generate evidence based information on safety of medical devices.
- To support CDSCO in the decision-making process on use of medical devices.
- To communicate the safety information on use of medical devices to various stakeholders to minimise the risk.
- To emerge as a national centre of excellence for Materiovigilance activities.
- To collaborate with other healthcare organisations for the exchange of information and data management

Who Can Report?

What to Report?

- serious or non-serious
- known or unknown
- frequent or rare

and all types of suspected adverse events associated with medical device disregarding of an established causal relationship between event and medical device

How and Whom to Report?

- The 'Medical Device Adverse Event (MDAE) reporting form' is available at www.ipc.gov.in and may be used to report any adverse event due to the use of medical devices.
- A reporter can send filled MDAE reporting form directly to NCC-MvPI via e-mail ipclab@vsnl.net/ mvpi.ipcindia@gmail.com or their nearest Medical Device Adverse Event Monitoring Centre (MDMC)/ Adverse Drug Reaction Monitoring Centre (AMC). The list of MDMCs/AMCs is available on **IPC.GOV.IN**
- A toll free **(1800 180 3024)** number is also available to report adverse event associated with use of medical devices to NCC-MvPI (on weekdays from **9:00 am - 5:30 pm**).

Courtsey: MvPI Handbook, IPC

Drug Safety Alerts

Sl No.	Suspected Drug	Indications	Adverse Drug Reactions
1	IBUPROFEN	For the treatment of chronic arthritic disorders and painful musculoskeletal conditions	Fixed Drug Eruptions
2	LOSARTAN	For treatment of Hypertension	Muscle spasm
3	CEPHALOSPORIN CLASS	For managing a wide range of gram positive and gram negative infections	Fixed Drug Eruptions

PvPI Newsletter, Jan-Mar, 2022

NOVEL DRUG DOSTARLIMAB

Recently, a name that featured **prominently in the news** is **DOSTARLIMAB. This drug from** British company, GlaxoSmithKline vanished away rectal cancer **miraculously in every patient of clinical trial and was considered nothing** less than a miracle. The finding of this study was published in **one of the most reputed journal, The New England Journal of Medicine.**

CLINICAL TRIAL

A prospective phase 2 study in which patients were **given Dostarlimab, an anti–PD-1** monoclonal antibody. It was administered every 3 weeks for 6 months in patients with mismatch **repair–deficient stage II or III** rectal adenocarcinoma(5 to 10 per cent of colorectal cancers) followed by standard chemo-radiotherapy **and surgery. Total of 12 patients** completed treatment and unvent at least 6 months of follow-up. All 12 patients had a **complete clinical response, with no evidence of** tumor on magnetic resonance imaging, 18F-fluorodeoxyglucose–positron-emission **tomography, endoscopic evaluation,** digital rectal examination, or biopsy. Adverse events of grade 3 or higher were also not reported. It was **concluded that mismatch** repair–deficient, locally advanced rectal cancer was highly sensitive to single-agent PD-1 blockade.

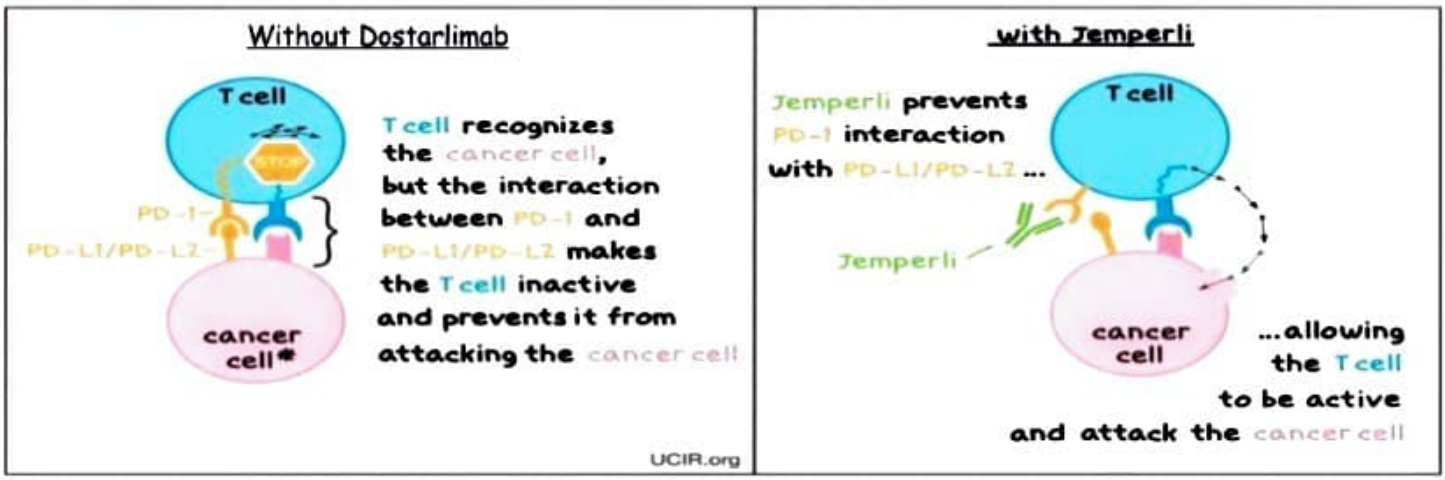
It has been approved earlier in 2021 under accelerated approval based on tumour response rate and durability of response for treatment of adult patients with mismatch repair deficient recurrent or advanced:

- Endometrial Cancer, that has progressed on or following prior treatment with a platinum-containing regimen
- Solid tumors, that have progressed on or following prior treatment and which have no satisfactory alternative treatment options

Mechanism of Action:

- Dostarlimab is a programmed death receptor-1 (PD-1)–blocking IgG4 humanized monoclonal antibody
- PD-1 ligands, PD-L1 and PD-L2 binds to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. In some tumours, there is up-regulation of PD-1 ligands and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

- Dostarlimab binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, which including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.



Pharmacokinetic: Its volume of distribution is 5.3 litre. The elimination half-life is 23.5 days. It is metabolized into small peptides and amino acids by catabolic pathways.

Dosage forms and strengths: It is approved under brand name JEMPERLI (DOSTARLIMAB-gxly) injection, for intravenous use. It is available as injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial.

Recommended Dosage:

- Dose 1 through Dose 4: 500 mg every 3 weeks
- Subsequent dosing beginning 3 weeks after Dose 4 (Dose **5 onwards): 1,000 mg every 6 weeks**
- It is given as intravenous infusion over 30 minutes.

Dosage Modifications for Adverse Reactions:

- Severe immune-mediated adverse reactions (Grade 3): **Withhold the drug**
- Recurrent Severe immune-mediated adverse reactions (Grade **3)** that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less **of prednisone** equivalent per day within 12 weeks of initiating steroids: Permanently discontinue the drug
- Life-threatening immune-mediated adverse reactions (Grade 4): Permanently discontinue the drug

Adverse effect:

- Most common adverse reactions in dMMR solid tumours patients are fatigue/asthenia, anaemia, diarrhoea, and nausea (in =20% patients).
- Most common Grade 3 or 4 laboratory abnormalities are lymphocytopenia,hyponatremia, increased alkaline phosphatase, hypoalbuminemia (in =2% patients).
- It can harm the foetus so; in female of reproductive age group it is advice to use effective contraception.

Warning and Precautions:

Immune-mediated adverse reactions can be severe or fatal in intensity, and can involve any organ or tissue, which include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection. So, we need to monitor for signs and symptoms of immune-mediated adverse reactions and evaluate clinical chemistries, including liver enzymes, creatinine, and thyroid function, at baseline and periodically during treatment.

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PDL1–blocking antibody.

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2. FDA grants accelerated approval to dostarlimab-gxly for dMMR advanced solid tumors | FDA [Internet]. [cited 2022 Jun 28]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors
3. HIGHLIGHTS OF PRESCRIBING INFORMATION. [cited 2022 Jun 28]; Available from: https://www.fda.gov/companiondiagnostics.

BARICITINIB : The First Systemic Treatment for Alopecia Areata

The U.S. Food and Drug Administration on 13th June 2022 granted approval to Lilly and Incyte's Olumiant (BARICITINIB) oral tablets to treat adult patients with severe alopecia areata. It is available as 4-mg, 2-mg and 1-mg tablets to be administered as once-daily tablet.

Mechanism of Action: It is the first FDA approval of a systemic treatment for alopecia areata. It is a Janus kinase (JAK) inhibitor which blocks the activity of one or more of a specific family of enzymes, interfering with the pathway that leads to inflammation.

Dose: The recommended dose of BARICITINIB is 2-mg/day, can be increase to 4-mg/day if treatment response is inadequate. For patients with nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss, treatment is started with 4-mg/day and decreased to 2-mg/day.

Adverse Drug Reactions: The most common side effects associated with BARICITINIB include: respiratory tract infections, headache, acne, folliculitis, urinary tract infection, genital Candidiasis, herpes zoster, anemia, neutropenia, abdominal pain, peptic ulcer, liver enzyme elevations, hyperlipidemia, increase creatinine phosphokinase, weight gain, fatigue, nausea, hypersensitivity.

Contraindications: Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants.

Warnings and precautions:

- Close monitoring for the development of signs and symptoms of infection during and after treatment.
- Evaluating patients for active/latent tuberculosis infection prior to treatment.
- **Boxed warning** for serious infections, mortality, malignancy, major adverse cardiovascular events and thrombosis.

Other Indications: BARICITINIB was originally approved in 2018 for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) blockers. It also gained approval for the treatment of COVID-19 in certain hospitalized adults.

https://www.fda.gov/news-events/press-announcements/fda-approves-first-systemic-treatment-alopecia-areata

US-FDA APPROVED NEW DRUGS (Apr-Jun 2022)

S.No	Drug	Mechanism of Action	Indication	Date of Approval
1	VUTRISIRAN	It is a double-stranded siRNA - GalNAc conjugate that causes degradation of mutant and wildtype TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues	To treat polyneuropathy of hereditary transthyretin-mediated amyloidosis	13-06-2022
2	TAPINAROF	It is an aryl hydrocarbon receptor (AhR) agonist. The specific mechanisms by which it exerts its therapeutic action in psoriasis patients is unknown	To treat plaque psoriasis	23-05-2022
3	TIRZEPATIDE	It is a GIP receptor and GLP -1 receptor agonist. It enhances first and second-phase insulin secretion, and reduces glucagon levels, both in a glucose dependent manner	To improve blood sugar control in diabetes, in addition to diet and exercise	13-05-2022
4	MAVACAMTEN	It is an allosteric and reversible inhibitor selective for cardiac myosin. It modulates the number of myosin heads that can enter "on actin" (power-generating) states, thus reducing the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation	To treat certain classes (NYHA Class II & III) of obstructive hypertrophic cardiomyo-pathy	28-04-2022
5	OTESECONAZOLE	It is an azole metalloenzyme inhibitor targeting the fungal sterol, 14a demethylase (CYP51), an enzyme that catalyzes an early step in the biosynthetic pathway of ergosterol	To reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are not of reproductive potential	26-04-2022

Monkeypox virus- The Available Treatment Options

Introduction

The monkeypox virus belongs to the Orthopoxvirus genus, which also includes camelpox, cowpox, vaccinia, and variola viruses. The virus was first identified in monkeys in a Danish laboratory in 1958, when it was given the name "monkeypox."The first case in humans was discovered in 1970 in a 9-month-old infant boy in Zaire (now the Democratic Republic of the Congo, DRC) Monkeypox(MPX) has since grown endemic in the DRC and has spread to other African nations, primarily in Central and West Africa. Monkeypox has a case fatality rate of 10%, which is in between variola major's case fatality rate of 30% and variola minor's case fatality rate of 1%. In 2003, there were the first instances of monkeypox outside of Africa.The likelihood of animal-to-human transmission is growing as a result of environmental conditions increasing the frequency of contact with potential hosts. As a result of globalization, armed conflict, and environmental factors, MPX poses a greater threat to previously unaffected nations. It is becoming more and more important to teach health professionals and to advance the availability of appropriate diagnostic procedures, immunizations, and antiviral therapies.

Symptoms and Diagnosis

A substantial percentage of exposed individuals develop clinical illness. Many people infected with monkeypox virus have a mild, self-limiting disease course in the absence of specific therapy. However, the prognosis for monkeypox depends on multiple factors, such as previous vaccination status, initial health status, concurrent illnesses, and comorbidities among others. Primary symptoms of the illness: two days before the appearance of the rash, the majority of patients present with the typical prodromal sickness, which includes fever, malaise, and lymphadenopathy. The main characteristic separating human monkeypox from smallpox is lymphadenopathy, which manifests in nearly 90% of people who contract monkeypox. In most cases, the typical monkeypox rash spreads centrifugally and starts as maculopapular lesions of 2–5 mm in diameter. Over the course of 14–21 days, the skin lesions advance from papules to vesicles to pustules, followed by umbilication, scabbing, and desquamation. Extracutaneous symptoms, such as secondary skin and/or soft-tissue infection (19% of cases), pneumonitis (12% of cases), ocular problems (4%–5%), and encephalitis are also possible.

Treatment and Immunization

Currently there is no treatment approved specifically for monkeypox virus infections. However, monkeypox and smallpox viruses are genetically similar, which means that antiviral drugs and vaccines developed to protect against smallpox may be used to prevent and treat monkeypox virus infections. CIDOFOVIR is an antiviral medication that is approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with Acquired Immunodeficiency Syndrome (AIDS). Although it has shown to be effective against orthopoxviruses in in vitro and animal studies but data is not available on the effectiveness of CIDOFOVIR in treating human cases of monkeypox. CDC holds an expanded access protocol that allows for the use of stockpiled CIDOFOVIR for the treatment of orthopoxviruses (including monkeypox) in an outbreak.

Two oral medications, BRINCIDOFOVIR and TECOVIRIMAT, have received approval for the treatment of smallpox and have shown effectiveness in animal tests against monkeypox. TECOVIRIMAT is authorised in Europe to treat monkeypox and smallpoxand US Food and Drug Administration has approved it for smallpox. Centre for Disease Control and Prevention (CDC) holds an expanded access protocol (compassionate use) that allows for the use of stockpiled TECOVIRIMAT to treat monkeypox during an outbreak. It prevents the poxvirus from spreading outside of an infected cell by blocking an envelope protein. BRINCIDOFOVIR may have an improved safety profile over CIDOFOVIR. Serious renal toxicity or other adverse events have not been observed during treatment of cytomegalovirus infections with BRINCIDOFOVIR as compared to treatment using CIDOFOVIR.

Vaccinia Immune Globulin Intravenous (VIGIV)

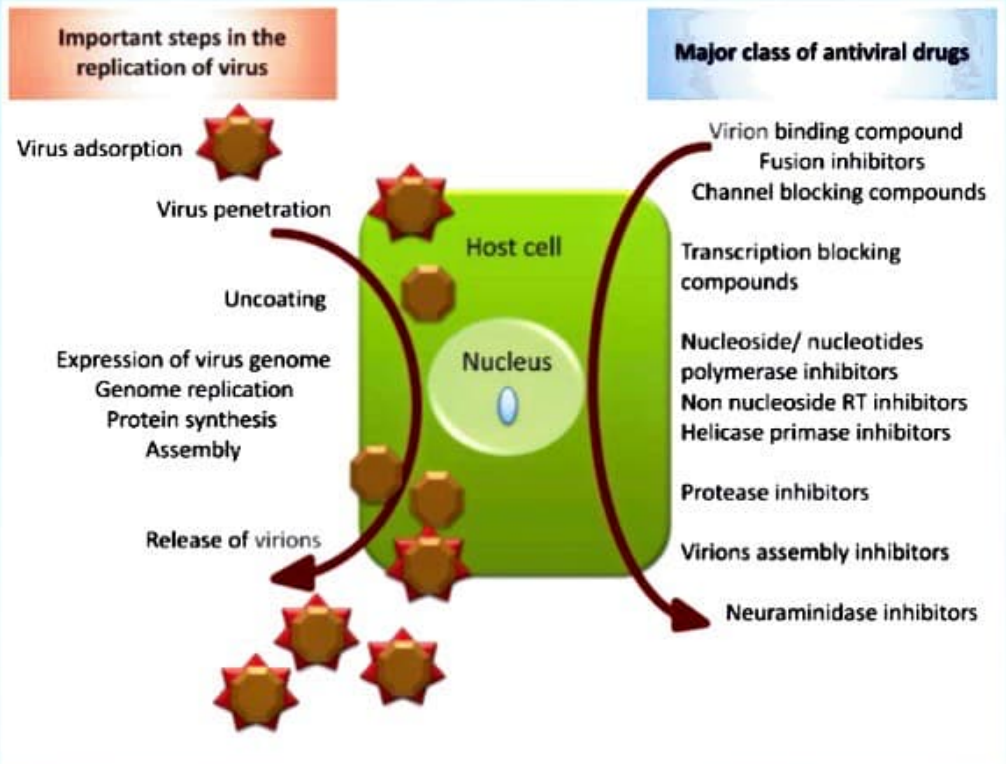
VIGIV is licensed by FDA for the treatment of complications due to vaccinia vaccination including eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, vaccinia infections in individuals who have skin conditions, and aberrant infections induced by vaccinia virus. CDC holds an expanded access protocol that allows the use of VIGIV for the treatment of orthopoxviruses (including monkeypox) in an outbreak but data are not available on the effectiveness of VIG in treatment of monkeypox virus infection. VIG can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox vaccination following exposure to monkeypox virus is contraindicated.

Reports suggest that humans are protected from both smallpox and monkeypox by the smallpox vaccine Dryvax. However, a variety of negative effects, including as contact vaccinia, can have an impact on both the vaccinated individual and those who come into touch with them. In fact, Dryvax vaccinations provide monkeypox protection for macaques. According to recent research, Abs is the primary mechanism via which the current nonattenuated smallpox vaccination protects against monkeypox. While B cell suppression before and after immunization eliminates vaccine-induced immunity, either CD4+ T cell or CD8+ T cell depletion in vaccinated animal does not influence survival before monkeypox virus challenge. As a result, passive vaccination with the vaccinia virus (VACV) 3 Abs offers protection from the deadly monkeypox.

Nanotechnology- a promising hope

Research on the interaction of nanoparticles with microorganisms has involved testing the antibacterial effectiveness of specific silver-containing nanoparticles against vegetative bacteria and the human immunodeficiency virus (HIV)-1. Previous studies on the relationship between nanoparticles and HIV-1 showed that silver-containing nanoparticles reduced HIV-1 infectivity in culture by attaching to the CD4 binding domain's disulfide bond regions. Since particles larger than 10 nm were not seen linked to the viral envelope, it appears that size affects how these nanoparticles bind to the gp120 component.

The monkey pox virus can enter a host cell via endocytosis or direct fusion with the plasma membrane. This is followed by a controlled series of actions that result in viral replication. The precise proteins or cellular receptors involved in the fusion of the poxvirus with the plasma membrane and subsequent cellular entrance are not yet understood. According to prior research on HIV-1, nanoparticles may have physically prevented the virus from attaching to the host cell in this investigation, which would explain why MPV plaque development was inhibited. The ingestion of metal-based nanoparticles by cultivated cells and the ensuing modifications in cellular biochemistry indicate there is also a chance for disruption of intracellular pathways, which might ultimately lower virus multiplication. For the purpose of creating more potent nanoscale-based anti-viral therapeutics, it would be beneficial to develop new nanoparticle technologies or modify existing ones by understanding the mechanism(s) by which silver-containing nanoparticles exhibit anti-viral properties with respect to nanoparticle size, concentration, and cellular interaction (figure 1).



Concluding remarks

Despite the fact that the smallpox vaccine protects against MPXV, the incidence is rising due to new non-immune generations. In the resource-limited endemic regions where monkeypox is found, clinical detection, diagnosis, and prevention still pose difficulties. Studies carried out before the conclusion of smallpox eradication provide information on monkeypox epidemiology, but additional evaluations are required now that routine smallpox vaccination has terminated and there is associated declining herd immunity. These crucial problems will require additional study, particularly to develop nanomaterials with a high level of biocompatibility and little host cell toxicity.

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8. *Subunit Recombinant Vaccine Protects against Monkeypox. Heraud, Jean-Michel; et.al. 4, 2006, Journal of Immunology, Vol. 177, pp. 2552-2564.*
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