An Overview of the Alternate Pathway of Approval of Tecovirimat and Its Pharmacological Aspects in the Management of Monkeypox

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Abstract

Monkeypox is a zoonotic disease caused by orthopoxvirus with akin clinical presentation like smallpox. Humans contract monkeypox when they come into contact with infected animals. There are other commonly reported methods of transmission like close contact with infected patient (sexual or skin-to-skin), airborne droplets, and fomites such as towels and bedding. , Multiple medical countermeasures are housed for the management of monkeypox. Currently available vaccines against orthopox viruses like monkeyox include JYNNEOSTM (live, replication-deficient, attenuated vaccinia virus) for the prevention of the disease and ACAM2000® (live, replication competent vaccinia virus) for active immunization for patients at high risk of infection. Antivirals like tecovirimat, brincidofovir, cidofovir and vaccinia immune globulin intravenous (VIGIV) are available for the treatment of monkeypox, despite the fact that supportive care is typically sufficient. But in cases of critical disease in paediatric patients, pregnant and lactating women, patients who are immunocompromised or those with intricate lesions, and lesions proximal to the mouth, eyes or genitalia, antivirals may be considered. This descriptive analysis aims to consolidate all the scientific information in literature related to the pharmacology of antiviral tecovirimat and with special emphasis on its interesting alternate pathway of its regulatory approval.

Keywords: Monkeypox, Tecovirimat, Antiviral

1. Introduction

Monkeypox- the Current Bioconcern

Monkeypox is a zoonotic disease caused by monkeypox virus (MPXV), an orthopoxvirus which is a close relative of variola virus, the causative agent of smallpox. MPXV was identified by Magnus et al in 1959, following an outbreak of a smallpox like disease in cynomolgus monkeys (1). The first ever diagnosed case of monkeypox in humans was observed in the Basankusu Territory of the Democratic Republic of Congo in the year 1970, in a 9 month old paediatric patient, who got successfully recovered from the illness in nearly two months after infection , but later died due to complications of measles (1)(2). Inhabitants of densely forested areas and rural places of central and western Africa, handling and cooking bushmeat, providing care to patients infected with MPXV, and not being immunised with smallpox vaccination are proven risk factors for MPXV infection. Infection risk has also been associated with male gender in the African region. But this could be due to the societal practice that men often go for hunt and come in contact with wild animals. The routes of disease transmission from human to humans are direct or indirect contact with infected patient's' bodily fluids, skin lesions, or respiratory droplets, as well as through contaminated fomites. There was limited human-to-human transmission in the past, however, mathematical modelling has demonstrated an emerging risk of disease transmission to human beings as the herd immunity to orthopoxviruses is getting diminished.

Recently, on July 23, 2022, monkeypox was declared as a Public Health Emergency of International Concern (PHEIC) by the World Health Organisation (WHO), which is considered as the agencies highest alarm. As of July 30, 2022, more than 16,500 people have been found to have confirmed infected in nearly 80 countries which usually don't report cases. It has been found that the as the virus has already entrenched in an animal reservoir in certain parts of Africa, its eradication would be hard. Adding to this concern, the virus might also spread from human to animals, which in turn can create novel reservoirs from where humans could be infected frequently.

The Centres for Disease Control and Prevention (CDC) suggests isolation in a negative-pressure room, in addition to standard contact precautions, and if possible, airborne droplet precautions in patient care. There is reportedly no clinically proven treatment available for MPXV infection. The primary treatment strategy is management of symptoms as in

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other viral illnesses. Simultaneously preventative measures that aid in preventing an outbreak like isolation of the infected person, appropriate usage of masks, and covering the lesions till all crusts have fallen off naturally and a new layer of skin has been formed. For critical disease, molecules with proven efficacy against orthopox viruses in animal studies may be regarded for investigational usage (3). The effectiveness of the oral DNA polymerase inhibitor brincidofovir, the oral intracellular viral release inhibitor tecovirimat, and the intravenous vaccinia immune globulin against the monkeypox virus is still undetermined. In this review we, have tried to organise the history of development and approval of tecovirimat, its pharmacological aspects and the evidence from a case study of MPXV infection where tecovirimat was used in the treatment.

Tecovirimat- The Drug for An Eradicated Disease

Tecovirimat, is an antiviral drug administered per oral, and developed by SIGA Technologies (Corvallis, OR, USA). The development and eventual authorization of tecovirimat as an antiviral for the management for smallpox, an epidemic that has been eradicated from the planet for nearly four decades, required a novel unique regulatory strategy based on the Animal Rule of the United States Food and Drug Administration (USFDA). This was a major landmark in biosecurity preparedness. Eventually, tecovirimat was considered for CDC response plan for smallpox and formulations for paediatric use, intravenous route as well as post exposure prophylaxis was approved (4).

Preclinical studies of tecovirimat demonstrated efficacy against invitro as well as in-vivo orthopox virus infection. It was proposed to use tecovirimat for monkeypox, vaccination associated adverse events as well as to counter the adverse effects of vaccinia oncolytic virus therapy.

The History of Alternative Pathway of Development and Approval of Tecovirimat

The biggest challenge in the development of tecovirimat which was primarily targeted for treatment of smallpox was the recapitulation of a suitable animal model of a disease which was eradicated 40 years back, even before complete understanding of the disease pathogenesis, even though the clinical features were well established. Equally challenging was the Animal Rule of FDA which is concerned with diseases which are rare or non-existent and the restriction of VARV (Variola Virus) research to only two containment labs in the world, in USA and Russia. The VARV Non-Human Primate (NHP) models available at that time were found unsuited for use in preclinical studies due to its scientific and practical limitations. The FDA in 2011 recommended adoption of an alternative development pathway, as it was unethical to conduct conventional clinical trials for demonstrating efficacy. It was recommended to use combined evidence from non variola lethal animal models of monkeypox and rabbit pox viruses in place of preclinical studies of VARV. This was later scientifically justified as the viral protein F13 through which tecovirimat acts is conserved among all the members of the orthopox virus genus (5). Even though these animal models could not mimic all aspects of human smallpox, they developed certain characteristic disease signs like fever and skin lesions and these were considered more predictable for generating data regarding efficacy and pharmacokinetics in infected animals(1) (6).

Results of Key Clinical Trials of Tecovirimat

In a phase 1 study, 30 volunteers were enrolled in a randomised double-blind placebo-controlled trial with multiple escalating (250 mg, 400 mg, 800 mg or placebo) doses in non-fasting stage to assess safety, tolerability and pharmacokinetics with once daily oral dose for 21 days. The drug was found to have good tolerability at all the doses and there were no deaths or serious adverse events (7). In a phase 2 study, 400 mg and 600 mg of tecovirimat were administered to 107 volunteers in fed state once daily for 14 days (8).. In the phase 3 pivotal safety trial of tecovirimat, 359 patients received tecovirimat at a doe of 600 mg twice daily with favourable PK parameters. Tecovirimat also exhibited favourable PK parameters in hepatic and renal impairment and additionally other studies that are part of normal drug development process like drug drug interaction and other studies were also performed

Final Approval of Tecovirimat

The FDA,on July 13 2018 approved tecovirimat for the treatment of smallpox based on the available evidence and risk-benefit profile (9). It was suggested to use tecovirimat in post exposure prophylaxis of smallpox along with vaccination. The special approval was based on the provisions of 21CFR314 Subpart I, for those diseases when human efficacy studies are not ethical or feasible (10). The approval of tecovirimat was considered to be an important milestone to tackle the re-emergence of smallpox following any threat of bioterrorism.

Mechanism of Action of Tecovirimat

The antiviral action of tecovirimat is exerted through the inhibition of a major envelope protein involved in the production of new extracellular viruses. By stopping the virus from exiting an infected cell, it also reduces the likelihood of a virus spreading within the body (11). In vitro studies demonstrated that tecovirimat inhibited plaque formation and cytopathic effects induced by the virus.

The drug specifically binds to the orthopoxvirus protein F13 (also known asVP37 and p37), which is responsible for production of new enveloped virions. The viral F13 target is highly conserved in all the members of the orthopox virus genus, hence it can be used in a wide spectrum of orthpox infections (12).

The antiviral spectrum of activity include a broad spectrum of orthopox viruses including vaccinia

virus, VARV, Cowpox virus, Ectromelia virus, MPXV, Camelpox virus, Herpes simplex virus type 1, Cytomegalovirus, respiratory syncytial virus, rota virus and some strains of arenaviridae (11)(13).

Pharmacokinetics of Tecovirimat (14)(15)(16)

Absorption, Distribution, Metabolism and Excretion

Tecovirimat appeared to be readily absorbed on oral administration in both humans and animals. Absorption is enhanced by the presence of food in the stomach. Preclinical studies demonstrated the absolute bioavailability as 45 % in mice and 50 % in monkeys. During clinical trials, tecovirimat was found to achieve Cmax in 4-6 hours after per oral administration. The curve exhibited biphasic profile and the elimination half-life was found to be 19-24 hours.

The pattern of drug distribution using radioactive labelling in mice revealed systemic distribution and within 168 hours, radioactivity was cleared from most of the tissues, with trace amounts in bone marrow and liver.

Invitro metabolic stability studies has proven that tecovirimat is not a substrate of Cytochrome P (CYP) enzymes. Similarly, human studies also demonstrated that the drug is metabolised by amide hydrolysis to form intermediary metabolites, which undergo glucuronide conjugation with uridine diphosphate glucoronosyl transferases and is excreted by kidneys. In vitro studies of these metabolites demonstrated that they do not have pharmacological activity (activity against orthopox virus).

Analysis of excretion data using radioactive material from clinical studies revealed that 73% of tecovirimat is excreted via urine and 23 % via faeces. Trace amounts of tecovirimat in unchanged form and an intermediary metabolite were detected in urine.

Plasma Protein Binding Characteristics

It is known that the free drug or unbound fraction is only pharmacologically active. Preclinical studies revealed that plasma protein binding of tecovirimat ranged from 87- 96 % and in clinical trials it ranged from 77-82%. Hence from the above data, it is evident that more unbound fraction is available in humans for pharmacological activity.

Drug Interactions

Drug-drug interaction (DDI) potential assays conducted in vitro revealed that tecovirimat does not show inhibition potentials towards major CYP enzymes and other transporters except Breast Cancer Resistance Protein (BCRP). But it may induce some CYP enzymes like CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19. In the clinical study to estimate DDI, it was found that tecovirimat did not have any effect on CYP2B6 and CYP2C9, But it was found to exert a weak inducing effect on CYP 3A4 and a weak inhibiting effect on CYP2C8 and CYP2C19.

2. Adverse Effects

Nervous system disorders, headache, dizziness, gastrointestinal disorders, nausea, diarrhoea, vomiting, upper abdominal pain, constipation, dry mouth, dyspepsia, infections and infestations, nasopharyngitis, general disorders and administration site conditions, fatigue, pyrexia, pain, chills, skin and subcutaneous tissue disorders, rash, pruritus, musculoskeletal and connective tissue disorders, injury, poisoning and procedural complications, muscle strain, psychiatric disorders, respiratory, thoracic and mediastinal disorders were reported as treatment emergent adverse effects following administration of first dose of tecovirimat in a Phase 3 clinical trial among 359 healthy adult subjects. However, the major treatment related adverse events in expanded safety trial were headache, nausea, diarrhoea, vomiting, fatigue and dizziness. Few participants reported of higher-grade headache and osteoarthritis and there was a case of pulmonary embolism as well in the ecovirimat group. However, the two major adverse effects that led to discontinuation of the drug during the trial were abnormal EEG (grade 3) and palpable purpura.

Case Study of Tecovirimat for the Management of Monkeypox

Several preclinical studies have demonstrated the efficacy of tecovirimat against monkeypox infection alone or in combination with vaccines (17)(5)(18). However evidence from clinical studies are limited with tecovirimat. Alder et al has described a series of monkeypox cases and their management from 2018 to 2021, in which one of the PCR positive (for MPXV DNA) patient was given tecovirimat.600 mg twice daily orally for two weeks. Tecovirimat was found prevent the progression to severe disease, shorten the period of illness and reduce the days of hospitalisation. It was also found to clear viral shedding from blood, upper respiratory tract and urine compared to brincidofovir. Tecovirimat also prevented formation of new lesions in this patient after 24 hours of initiation of therapy. There was no derangement of the patients haematological, renal or hepatic function tests and there was no any report of adverse effects. Alder et al has suggested the use of tecovirimat for 5 days duration to elicit a clinical response, whereas a two weeks course is essential for the development of humoral immunity and virus clearance (19)(20). Even though the above findings are reported from a single case study, together with evidences from preclinical studies, the utility of tecovirimat for the treatment of monkeypox is undebatable.

3. Conclusion

Tecovirimat is a drug with proven efficacy in post exposure prophylaxis of monkeypox. The development and approval of this drug for monkeypox through alternate pathway have paved the way for its applicability in a wide spectrum of

orthopox virus infections that might become a threat to humanity in the future.

Study Highlights

1. Monkeypox virus outbreak in 2022 has been declared as public health emergency of international concern
2. Monkeypox infection is mostly self-limiting except in paediatric, pregnant and lactating women and those with other comorbidities
3. There is no specific treatment for monkeypox, the drugs approved for smallpox has been approved by European regulators for use in critical illness
4. Tecovirimat is an antiviral drug which has been found efficacious in human monkeypox infection

4. Author Contributions

Dr Jerin James: Conceptualization, Methodology,
Dr Jamuna Rani.: Data curation and literature search
Dr Porkodi : Manuscript preparation
Dr Kala: Supervision
Dr Sathyanarayanan : Writing- Reviewing and Editing
Dr Parvathy PR: Software

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