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Correspondence

Clinical management, antiviral drugs and immunotherapeutics for treating monkeypox. An update on current knowledge and futuristic prospects

Dear Editor,

The recent appearance of monkeypox (MPX) outbreaks in multiple non-endemic countries beyond Africa has now posed a public health emergency of international concern amid its rising cases. Being a neglected/rare disease, much attention has not been paid on its management and treatment aspects. The present article provides updated information on clinical management, antiviral drugs, immunotherapeutics and prospective aspects for treating monkeypox.

Supportive care which are essential and valuable treatment options for MPX cases include rehydration (either orally or intravenously) to minimize fluid loss, hemodynamic balance, supplemental oxygen, symptomatic treatment and managing bacterial superinfections of skin lesions, and eye infections/complications with application of lubricants, topical antibiotics, and possibly topical antivirals (trifluridine) [1,2]. Monkeypox virus (MPXV) infection in humans causes a mild to moderate disease with a self-limiting course. Antivirals such as tecovirimat, brincidofovir, and cidofovir, and vaccinia immune globulin intravenous (VIGIV) can be used to treat more serious cases of MPX illness requiring hospitalization, lesions having complications, and when lesions formed near genitals, eyes and mouth are troublesome, and patients are immunocompromised, pediatrics, children under age of 8 years, pregnant or breastfeeding women [2–4].

The Food and Drug Administration (FDA) has given approval to tecovirimat (TPOXX/ST-246), a 4-trifluoromethylphenol derivative against orthopoxviruses, which has been found to show wide efficacy both *in vivo* and *in vitro*, and can be used to counter emerging MPX cases [2,5]. Tecovirimat blocks the virus' envelope protein VP37, restricts virus from being released from infected cells, thus prevents spread of viral infection within an infected host and its further transmission [4]. Clinical trials conducted on humans have proven tolerance and safety of tecovirimat. The inhibitory effect of ST-246 on the growth features of seven strains of MPXV has been demonstrated. The 50% effective concentration of the drug has been found to be < 0.04 μM [6]. There was improvement in the survival rate when initiation of tecovirimat therapy up to 8 days after a lethal MPXV challenge. The drug was shown to help in protecting from clinical disease when administered before 5 days following virus challenge. Concomitant administration of the live attenuated vaccine ACAM2000™ and TPOXX (tecovirimat) was found to be very helpful in post-exposure prophylaxis and therapy for severe MPX cases [7,8]. In *vitro* studies on animals with the use of cidofovir (a nucleoside phosphate which is acyclic in nature) and brincidofovir, an inhibiting DNA polymerase of the virus, have been found to be efficacious against monkeypox [2–4]. The effects of administration of antiviral drugs viz., cidofovir/Vistide and a nucleoside (acyclic) phosphonate analogue (related to cidofovir) and immunization (post--exposure) with smallpox vaccine, were evaluated following a deadly MPXV challenge in cynomegalus monkeys (*Macaca fascicularis*). The study revealed that antiviral treatment was significantly more effective 24 hours post lethal MPXV challenge in reduction of mortality than immunization with the smallpox vaccine (Elstree-RIVM) [9]. The drug brincidofovir has been shown to enhance cellular uptake, was converted to an active form in a better way by intracellular enzymes resulting in its anti-MPXV efficacy being better than that of cidofovir, with a higher selective index of at least 25-fold, and with better safety profile and with comparatively less toxicity [2,4,10]. Patients should receive intravenous normal saline and probenicid along with cidofovir therapy.

A tricyclodicarboxylic acid derivative named NIOCH-14, a tecovirimat precursor, has also been found potentially valuable against poxviruses, including MPXV. Because of its ease in production when compared to tecovirimat, it is now considered as a prospective future antiviral candidate [10]. Interestingly, MPXV replication has also been found to be inhibited by two inosine monophosphate (IMP) dehydrogenase inhibitors viz., ribavirin and tiazofurin, which have higher sensitivities against MPXV in comparison to other Orthopoxviruses. The activity of adenosine N1-oxide (ANO) has been found to be quite significant against Orthopoxviruses. As this drug blocks viral mRNA translation, it causes inhibition of virus replication, and thus can also be considered as a targeted therapy against MPXV [11].

The therapeutic value of the RNA interference (RNAi) pathway has been investigated for MPXV infection with the development of four dozen siRNA constructs. Replication of the virus was observed to be inhibited *in vitro* in cell culture by seven siRNA constructs by around 65–95%, without any apparent cytotoxic effect. The targets for these siRNA constructs are either the A6R gene which is essential for replication of the virus, or the E8L gene which is crucial for virus entry. Further analysis on the wild type and recombinant MPXV demonstrated that the most powerful construct to inhibit virus replication was siA6-a. These results demonstrated ultimately the potential utility of the RNAi therapeutic approach in developing anti-MPXV drug therapy [12]. Cytokine therapy has also been shown to hold promise against MPXV infection. The significance of IFN-γ in providing protection has been demonstrated in the inbred mouse strains like BALB/c, C57BL/6 and CAST/EiJ. Induction of IFN-γ and CCL5 in lungs of the mouse strain BALB/c with replication of the virus was observed, but not in the CAST/EiJ mouse strain. Administration of IFN-γ intranasally in CAST/EiJ mice with resultant protection has demonstrated the significance of IFN-γ in rendering protecting against MPX. Furthermore, the gene coding for IFN- γ or IFN- γ receptor in C57BL/6 mice on inactivation resulted in increased sensitivity to MPXV [13].

A hyperimmune globulin, the vaccinia immune globulin (VIG), has been approved by the FDA for treating vaccinia vaccination-related side effects such as eczema vaccinatum, progressive vaccinia, severe

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generalized vaccinia, and vaccinia infections in people with skin disorders, and aberrant infections caused by the vaccinia virus (except in cases of isolated keratitis, e.g., ocular infections). However, the effectiveness of VIG against MPX and smallpox is still mainly unknown, as the data in humans is lacking. Since vaccinia virus vaccine is contraindicated in individuals with severe immunodeficiency in T-cell function, patients with such a history may instead be administered VIG, which has been shown to be safe [2,4]. In case of patients having complications of smallpox immunization, tecovirimat has been used in combination with VIG [2]. The *in vitro* and *in vivo* prophylactic and therapeutic effectiveness of recombinant VIG (rVIG) against various Orthopoxviruses have been reported. In mice which have been treated with rVIG, a significant reduction in the level of viral DNA in the blood circulation was observed, and adverse reactions were not apparently evident. The level of the infectious virus in the hepatic system and markers of hepatic damage, like alanine transaminase (ALT), were also reduced. The rVIG can be a potential therapeutic candidate but it needs further research and license granting for future use of this agent under the FDA Animal Rule [14].

A healthy diet comprising of balanced food, vitamins, minerals, nutraceuticals, and probiotics should be provided along with supplementation of multinutrients to boost immunity and fight against any viral infections, including MPXV. Historically in the 1800s, the native Americans used to treat smallpox with a pitcher plant (*Sarracenia purpurea*) which was found to be beneficial against other poxviruses. Thus, this plant should be explored against MPX too (https://www.chemistryworld.com/news/rediscovered-native-american-remedy-kills-poxvirus/3003420.article). Further explorative studies are also needed on other potent herbs, plant extracts and ethnobotanicals to identify their roles in treating MPX.

Smallpox vaccination has been discontinued since the past many years. As a consequence most of the population has less or no protection against MPX. Explorative research studies, deeper disease investigations and more global efforts are required to find out better treatment and management alternatives for this viral infection. The Centers for Disease Control and Prevention (CDC) is working on producing interim treatment recommendations for monkeypox. Treatment for MPXV infection should be evidence-based to guide future treatment options. The presently available antiviral drugs, immunotherapeutics and vaccines for MPX have limited accessibility. Efforts are needed to make these accessible at a global level, especially to all countries which have reported on outbreaks. The prognosis for MPX is dependent on several factors, including past vaccination status, health status at beginning of disease and concurrent illnesses or comorbidities. Thus, tailoring treatment to each patient's unique risk of developing a life-threatening illness is the most logical course of action to be taken. Further in-depth research to find effective antiviral drugs, immunotherapeutics, alternatives, adjunctive and supportive therapies, and researching advanced fields of immunology, biotechnology, nanotechnology, CRISPR based drugs/medicines and delivery modules are all required to be given due priority for treating this disease more effectively.

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