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Review

Pharmaceutical Treatment of Monkeypox Virus: A Narrative Review and Bibliometric Analysis

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Abstract: Monkeypox virus infection is a recognized public health emergency. Little research has been done on treatment options for this disease. Until recently, there was not a single published work describing the usage of specific drugs in human patients with monkeypox virus infection. This paper gives the first bibliometric analysis of monkeypox treatment options based on data available on PubMed and Scopus. It also reviews the specific drugs used in the treatment of monkeypox. That includes data on Tecovirimat, Cidofovir, Brincidofovir, and Vaccinia Immune Globulin. Tecovirimat is a promising option in progressive disease in terms of efficacy and safety. However, Brincidofovir has been associated with discontinuation of treatment. Cidofovir is also not the preferred drug among physicians. Currently, Tecovirimat can be further used for the management of aggravating cases. More studies should be conducted on Tecovirimat to treat this condition, mainly through controlled trials.

Keywords: monkeypox virus; infection; treatment; antiviral; drug; management; public health emergency; tecovirimat; cidofovir; bibliometric analysis

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1. Introduction

While the world is finding ways to deal with SARS-CoV-2 and COVID-19, a novel threat of monkeypox has emerged in the human population. The World Health Organization (WHO) has declared this a health emergency, and the cases have risen to 74,785 and 32 deaths as of October 19, 2022 (1). Monkeypox virus (MPXV) is a member of the orthopoxvirus family. It generally invades rodents and animals but has now escaped into the human population. There are two distinct genetic clades of MPXV: African clad (Congo basin) and West Africa clade, although recently, a third apparently emerged and is responsible for the current 2022 cases (2). According to reports by the WHO, new topics have been identified from various regions of the world, irrespective of their historical distribution (3). However, the symptoms are less severe than in smallpox (4).

Monkeypox treatment is a new challenge for the healthcare system (5). There are very few studies on it, and there is an urgent need to address it. This paper briefly analyses past literature on the pharmaceutical treatment of the disease and the drugs administered. This review provides detailed information on the clinical orientation of the antivirals administered: tecovirimat (TPOXX), cidofovir, brincidofovir, and Vaccinia Immune Globulin which would be essential to improve the treatment protocol and increase the treatment efficacy of the disease treatment (6).

2. Bibliometric Analysis

The bibliometric analysis involves using mathematical methods to study books and communication media (7). It is very helpful in assessing the trend of research on a specific topic. For example, we searched using the keywords 'monkeypox' in combination with 'treatment' / 'management' / 'drug' in the title, abstract, and keywords in Scopus, PubMed, and Web of Science, yielding 568, 250, and 4 results, respectively. The distribution of studies depending on the year of publication and the type of study is shown in Table 1. A significantly increased number of studies can be observed in 2022 due to the public health emergency. This pattern highlights the relevance of research in this significantly underexplored area of public health concern.

Table 1. Results of the bibliometric analysis of the search for 'Monkeypox' in title, abstract, and keywords in Scopus and PubMed (October 18 2022)

Type (Scopus)	Frequency	Year	Scopus	PubMed	Web of Science
Article	305	2022	171	130	2
Review	163	2021	19	5	1
Note	29	2020	19	9	0
Editorial	24	2019	15	5	0
Miscellaneous	47	2018	12	3	0

Using the search mentioned above strategy results, we designed a bibliometric map of the relevant keywords using VOSviewer. Then, we performed a cooccurrence analysis of keywords across several databases using the whole counting. That helped us visualise the critical areas discussed in the scarcely available literature on the treatment of monkeypox. Fig. 1 illustrates this.

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We can observe a strong cooccurrence of the 'humans' and 'animals' keywords. Many studies on the pharmaceutical management of monkeypox virus infection have been based on animal models, and human studies have only recently begun to appear. Cidofovir is mentioned a lot. It is used in many other conditions besides monkeypox virus infection, more than any other antiviral discussed here.

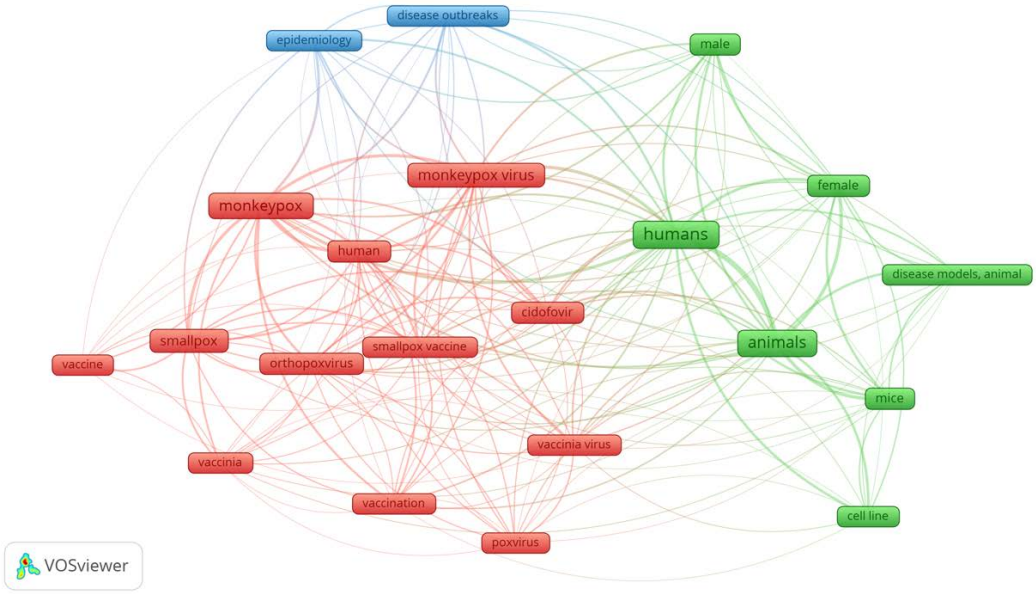

Figure 1: Visual network of keywords in the published literature related to the treatment of monkeypox infection

3. Tecovirimat

Tecovirimat is the most widely used antiviral in patients with monkeypox infection. The US FDA granted it approval in 2018, and it is indicated in smallpox disease. The regulatory process has been summarised in Figure 2 (8,9). Tecovirimat inhibits the membrane protein VP37 in the monkeypox virus, thus inhibiting the downstream actions of this protein. That interferes with the formation of enveloped virions needed for extracellular dissemination of the virus to different cells of the body, either directly to adjacent cells or through blood vessels to distant cells (6,10). Therefore, css-resistance to cidofovir or brincidofovir is not expected (11).

It is generally administered in capsules, but for those weighing less than 13 kg, the intravenous formulation is administered as a slow infusion. An essential difference between the two dosage forms is that only the latter is contraindicated in patients with renal disease (creatinine clearance of 30 ml/min or less). Even in cases with mild to moderate renal impairment (creatinine clearance ranging from 30 to 89 ml/min) or in the paediatric population younger than two years, caution is required. Therefore, clinicians should routinely test this in all patients before starting Tecovirimat infusion. The reason behind this selective toxicity is the presence of an excipient hydroxypropyl-β-cyclodextrin in parenteral preparation. This excipient is added because of the poor water solubility of Tecovirimat. When coadministered with Repaglinide or Midazolam, monitoring of hypoglycaemia or Midazolam effectiveness is recommended. Some of the common associated adverse events are headaches, gastrointestinal disturbances, and injection site complaints such as pain, swelling, erythema, and extravasation. (6,10)

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There are some case reports and case studies on the use of Tecovirimat in monkeypox disease in humans. It has been effective in arresting the aggravation of the condition. That has been seen in patients with worsening facial lesions (12), severe proctitis with opioid-requiring rectal pain(13), tongue lesions (14), and Herpes Simplex Virus 1 - Monkeypox virus coinfection (15). It has not been associated with severe adverse events. However, one patient reported loose stool after every dose. Another developed derangement of a hepatic enzyme resolved independently without discontinuing the drug (16). In summary, Tecovirimat is a promising option for both efficacy and safety in the worsening monkeypox disease.

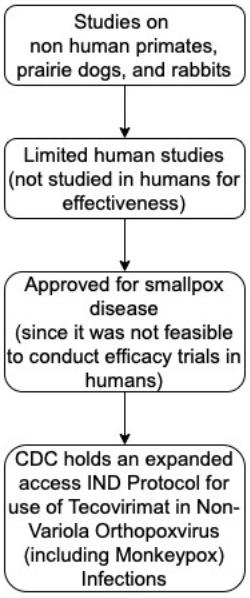

Figure 2. A flowchart showing how Tecovirimat has evolved for the treatment of monkeypox virus infection

4. Cidofovir

Cidofovir is used in diseases due to cytomegalovirus (CMV), herpesviruses, and several DNA viruses. It is indicated in certain CMV diseases in immunosuppressed people (17,18) and has been used off-label in several conditions caused by DNA viruses (19).

Cidofovir is activated intracellularly in cidofovir-diphosphate, which competitively inhibits viral DNA polymerase, thus interfering with viral DNA synthesis (20). Pharmacologically, it is an example of a hit-and-run drug. When administered intravenously, the serum concentration of the drug decreases rapidly after infusion, and it has a short plasma half-life of 2 hours. However, the intracellular half-life of the active form is as high as 65 hours. Cidofovir undergoes renal elimination, and this involves an essential drug-drug interaction. Probenecid blocks the tubular secretion of this drug, thus reducing its excretion and increasing its serum level (21,22). Nephrotoxicity is a common clinical concern with this drug, and hydration and probenecid are recommended to reduce its incidence (20,23). In addition, relevant monitoring is recommended during therapy due to the risk of ocular complications (such as hypotony, uveitis, and iritis) and myelosuppression (24,25).

In treating monkeypox, cidofovir has been used clinically in two reports. In both cases, it was only due to the inaccessibility of tecovirimat. One of the patients recovered, while the other study reported that the patient had severe ocular involvement. After two

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doses of cidofovir were administered, the lesions evolved from the last follow-up. The two studies on cidofovir did not report any adverse events (26,27).

5. Brincidofovir

Brincidofovir (BCV) is a nucleotide analogue of DNA polymerase inhibitors. It is a pro-drug composed of cidofovir conjugated to a lipid molecule. The lipid component resembles an endogenous lipid called lysophosphatidylcholine, which allows the molecule to enter the infected cells by taking on the natural lipid absorption mechanisms. Following absorption, the lipid molecule is broken down, releasing cidofovir for additional intracellular kinase phosphorylation to form cidofovir diphosphate, the active form of the drug. In contrast to cidofovir, brincidofovir does not act as a substrate for Organic Anion Transporter 1, which makes BCV less harmful to the kidneys. Therefore, brincidofovir has a higher safety profile for nephrotoxicity compared to cidofovir. When it comes to preventive measures and adverse reactions of Brincidofovir, its administration requires continuous monitoring of liver function tests as it increases the serum levels of transaminase & bilirubin levels. Other adverse effects are gastrointestinal side effects such as diarrhoea and vomiting. Pregnancy is ruled out before administering this drug, as it is teratogenic in animal studies. Contraception is advised throughout treatment and for four months afterwards. Brincidofovir is also known to have carcinogenic potential, so safety with handling is necessary. Brincidofovir is taken on an empty stomach or with a low-fat meal to increase the bioavailability of the drug. Drug-drug interactions are observed when used concomitantly with inhibitors of OATP1B1 and 1B3 (Organic Anions Transporting Polypeptide) such as rifampin, erythromycin, and protease inhibitors such as ritonavir as they increase its peak serum concentration, increasing adverse events due to Brincidofovir (28,29).

The results with Brincidofovir have not been promising. All three patients had to discontinue treatment in the solitary study of human patients because hepatic impairment led to prolonged hospitalisation(30). They were hospitalised for 26-35 days. Thus, safety remains a key concern with this drug.

6. Immune Globulin

Many medical countermeasures are kept on hand in the case of orthopoxviruses as monkeypox emerges. Although most monkeypox is minor and self-limited, supportive treatment is often enough to treat them. Most patients have moderate sickness and recover without medical help, but in very unwell or immunosuppressed people, antivirals or vaccinia immune globulin (VIG) may be used. According to the Centers for Disease Control and Prevention (CDC), supportive care is often sufficient for people with a monkeypox virus infection because no particular medications are available. Therefore, monkeypox can be prevented and treated similarly to other orthopoxvirus infections, and unless proven differently, all confirmed orthopoxvirus cases should be treated as though they are monkeypox (4,31,32).

In immunosuppressed patients exposed to monkeypox for whom vaccination with ACAM2000 is contraindicated, VIG, an injectable preparation of hyperimmune globulin made from the pooled blood of smallpox vaccine recipients, can be considered. The antibodies acquired from these people against the smallpox vaccine are removed and purified. Furthermore, VIG can treat vaccinia virus-related aberrant infections related to the vaccinia virus caused by autoinoculation, eczema vaccinatum, or severe generalised or progressive vaccinia (33,34). VIG is used to treat some vaccine-related side effects, such as infections from the vaccinia virus in people with preexisting skin disease and aberrant infections caused by the vaccinia virus. VIG is not recommended to treat postvaccine encephalitis or encephalomyelitis, myopericarditis after smallpox vaccination, moderate

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cases of widespread vaccinia, erythema multiforme, or isolated vaccinia keratitis. Its use has not been evaluated in people with monkeypox or smallpox, even though it is a potential treatment. Data on its efficiency against these conditions are primarily sparse. Clinicians should use an Investigational New Drug (IND) application to administer VIG treatments. If tecovirimat is not available, current Australian recommendations reserve VIG as a backup treatment for monkeypox infection (35).

7. Conclusions

This review elaborates on the different pharmaceutical treatment options for monkeypox infection. A bibliometric analysis was also performed in PubMed and Scopus. We observed that four drugs are used mainly for specific management of monkeypox disease in humans: Tecovirimat, Cidofovir, Brincidofovir, and Vaccinia Immune Globulin. Tecovirimat has emerged as an exciting option with efficacy in progressive disease. Also, no signals for safety concerns have been detected. All other options are used infrequently. Cidofovir and its related compound Brincidofovir are also used. Unfortunately, the latter is associated with liver impairment, and treatment had to be discontinued in all three cases in a study. Vaccinia immune globulin has not been used much and is mainly preferred for other indications, such as post-vaccination complications.

These drugs have not yet been adequately tested in well-designed studies in patients with monkeypox infection. The main reason behind the lack of such studies might be feasibility issues. More studies, including randomised controlled trials, must confirm and optimise the dosage range.

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Supplementary Table 1. The adjusted search terms as per searched electronic databases

Database	No	Search Query	Results
PubMed			
	#1	"monkeypox"[Title/Abstract]	1740
	#2	"treatment"[Title/Abstract] OR "management"[Title/Abstract] OR "drug"[Title/Abstract]	6,756,803
	#3	#1 AND #2	250
Scopus			
	#1	TITLE-ABS-KEY (monkeypox)	1,311
	#2	((TITLE-ABS-KEY (treatment) OR TITLE-ABS-KEY (management) OR TITLE-ABS-KEY (drug)))	19,325,834
	#3	#1 AND #2	568
Web of Science			
	#1	ALL=(Monkeypox virus (All Fields) or MPXV (All Fields) or monkey pox (All Fields) or Monkeypox (All Fields) or MPXV (All Fields))	8
	#2	((ALL=(treatment)) OR ALL=(management)) OR ALL=(drug)	9,097,319
	#3	#1 AND #2	4