Treatment of severe human mpox virus infection with tecovirimat: A case series

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Abstract

Background: Tecovirimat (TCV, TPOXX®) is an orthopox-specific antiviral drug indicated for the treatment of smallpox. There is also a mechanistic basis for its use in mpox infection. However, its approval was based on animal studies, and its efficacy and side-effect profile in human patients with disease is unknown.

Methods: During the 2022 international mpox epidemic, clinicians in Canada were permitted by Health Canada to access TCV for severe cases of mpox disease. We describe the use of TCV in nine adults with severe mpox virus infection in Montréal, Canada.

Results: Five patients were treated for severe and potentially life-threatening head and neck symptoms, while four were treated for genitourinary or anorectal disease. Two-thirds of patients were also treated for suspected bacterial superinfection. All patients recovered (median time to resolution of severe symptoms: nine days) without relapse or hospital readmission. No patients reported adverse events attributable to TCV and no patients stopped their treatment early.

Conclusion: Our experience suggests that TCV is well tolerated and may accelerate recovery in severe cases. These preliminary, observational data may also be explained by concomitant treatment for superinfection and are limited by the absence of a control group. Controlled, clinical trials should be conducted to clarify the attributable benefit of TCV in severe mpox infection.

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Introduction

The mpox virus is an orthopoxvirus that causes human mpox infection, a disease classically characterized by systemic symptoms associated with a disseminated vesiculo-pustular rash. Though most cases are self-limited, severe illness and death can occur in a subset of the population, depending on the viral clade and patient-specific risk factors (1). Fortunately, the case fatality rate in the ongoing 2022 international outbreak has been below 1%, though severe symptoms requiring emergency consultation and hospitalization have been frequently reported (2). Patients do not typically receive specific antiviral therapy, as effective treatments for mpox have not generally been widely available.

Tecovirimat (TCV, TPOXX®, formerly ST-246) is a first in class antiviral drug that was designed for the treatment of variola virus, which causes smallpox in humans. Its molecular target, the p37 protein, is a highly conserved molecule among orthopoxviruses which is responsible for transit of virions outside the cell and is indispensable for virulence (3). Because variola virus is no longer in circulation, clinical efficacy was extrapolated from animal studies in which subjects were inoculated with other orthopoxviruses, including lethal doses of mpox in non-human primates. In these experiments, survival was 95% among non-human primates infected with mpox that received TCV, as compared to 5% in non-human primates that received

placebo, with benefits also seen in number of lesions and viral load (4). A subsequent clinical trial in healthy human volunteers confirmed that a treatment course of 14 days was generally well tolerated, with only 1% of patients discontinuing treatment due to adverse events associated with TCV (4). Based on these data, the United States Food and Drug Administration approved TCV under its Animal Rule in 2018 (5).

To our knowledge, TCV had only been used in disparate, exceptional circumstances for the off-label treatment and prophylaxis of different orthopoxviruses (6–10). Its use in multiple patients with severe manifestations of disease has not been reported. We describe the outcomes of nine patients with severe mpox infection who received TCV as part of their treatment.

Methods

In May 2022, multiple outbreaks of mpox virus infection were reported among gay and bisexual men in Europe and North America. Since then, over 60,000 cases have been declared in 104 countries (11). In Canada, Montréal was quickly recognized as the national epicentre of the 2022 mpox epidemic, with nearly all Canadian cases being concentrated in the city's downtown area.

In response to the growing number of cases in Montréal, a multifaceted public health campaign was launched, including variola immunization for people at high risk of infection and community awareness efforts in 2SLGBTQI+ venues. In addition, the federal government authorized the use of TCV for certain cases under a special access program, requiring centralized approval from a coordinating infectious diseases physician and pharmacist. Since mpox is a generally self-limited illness, TCV was restricted to patients who were deemed to have severe symptoms, or in other exceptional circumstances, at the judgment of the treating infectious diseases specialist.

To be eligible to receive TCV, patients were first required to have polymerase chain reaction-confirmed orthopoxvirus infection in at least one clinical specimen. Testing was performed at the provincial public health laboratory (*Laboratoire de santé publique du Québec*, Montréal, Québec) using primers and probes specific for human orthopoxviruses, which in the current epidemiologic setting were considered diagnostic of mpox infection. Confirmatory testing with an mpox-specific polymerase chain reaction assay was performed subsequently at the National Microbiology Laboratory, in Winnipeg, Manitoba.

Two Letters of Authorization were issued by Health Canada pursuant to C.08.010 of the Food and Drug Regulations Special Access Programme, authorizing the use of TCV for emergency treatment of patients. Informed consent was obtained from eligible individuals to ensure they were well informed of the possible risks and benefits of the drug and its development status and that a report on the outcome and results would be provided to Health Canada. The Council for International Organizations of Medical Sciences form was used to report any serious and/or unexpected adverse drug reactions.

Eligible and consenting patients received TCV free of charge at a dose of 600 mg by mouth, twice daily for 14 days as part of their clinical care. All patients were followed until the end of therapy to determine their clinical evolution.

Results

Between May 12 and June 14, 2022, mpox infection was confirmed in 135 individuals in the Province of Québec, Canada. Nine patients (7%) presented with severe symptoms of mpox infection and received TCV. All patients were adult men (mean age: 40 years) who acquired their infection after sexual contact with other men. Five patients (55%) were people living with human immunodeficiency virus (HIV) and on antiretroviral therapy at the time of infection, with undetectable HIV viral loads and a median CD4 cell count of 513 cells/uL. One patient had a CD4 cell count of 100 cells/uL. No patient had received smallpox immunization prior to their infection, though one patient had received the non-replicating, third generation smallpox vaccine (Imvanune®) the day he presented to care with active lesions.

Patients received TCV a median of nine days after onset of symptoms. Five patients were considered to have severe head and neck symptoms (including dysphagia and dysphonia) including one patient who presented with trismus and one with a peritonsillar abscess. Four patients were treated for highly symptomatic genital and/or anorectal lesions. Six patients were concomitantly treated for bacterial superinfection, of whom two had positive throat cultures for *Streptococcus pyogenes*. Three patients were hospitalized during their care. None required admission to the intensive care unit or surgical intervention during their stay. The full characteristics of patients are shown below in **Table 1**.

At the time of writing, all patients experienced resolution of the symptoms that justified TCV use (median length of use prior to recovery: nine days). No patients were re-hospitalized for clinical deterioration and no patients died. No patients described adverse drug reactions attributable to TCV and no patients stopped the medication early.

Table 1: Clinical characteristics of the patients at baseline

Characteristic	Patients (n=9)	%
Mean age, years (range)	40	29–63
Sex (n, %)		
Male	9	100%
Female	0	0%
Epidemiological risk factors and comorbidities (n, %)		
Male sexual partners	9	100%
Prior smallpox immunization	0	0%
Median duration of symptoms before treatment, days (range)	9	5–22
Hospitalized	3	33%
Suspected or proven bacterial superinfection[a]	6	66%
Human immunodeficiency virus	5	55%
Median CD4 count of patients living with human immunodeficiency virus (cells/uL)	513	N/A
Median viral load	Undetectable	Undetectable
Symptoms (n, %)		
Head and neck	5	55%
Neurological	2	22%
Genitourinary and anorectal	5	55%
Fever	5	55%
Lymphadenopathy	9	100%
Myalgias	3	33%

Abbreviation: N/A, not applicable
[a] Culture proven *Streptococcus pyogenes* infection, including one peritonsillar abscess

Discussion

This is the first Canadian case series of TCV use during a mpox outbreak for severely symptomatic cases. All patients experienced rapid clinical improvement. The medication was well tolerated, without any patient-reported adverse events. These findings are globally consistent with trial data that show improved clinical outcomes in non-human primates and a favourable adverse event profile. Our data also align with a large American case series of patients who received TCV and were at risk of severe disease (12). In the American experience, only a small proportion of patients reported minor adverse events and 90% of patients were cured at the time of the post-treatment follow-up.

A unique feature of our study is that all patients in our cohort presented with severe manifestations of disease, including concern of possible impending respiratory compromise. This is a historically rare manifestation of mpox infection, which was not reported among adults in a previous North American outbreak caused by contact with prairie dogs (13). It is possibly more common in this current outbreak as a function of direct viral inoculation in oropharyngeal mucosa during suspected person-to-person sexual transmission and severe manifestations have more recently been described (2). While previous uses of TCV did not specifically address this patient population, we were reassured to note that all patients progressed favourably despite their initial severe manifestations.

In addition, over half of patients in our cohort had suspected or culture-proven bacterial superinfection of their viral lesions. Though superinfection has been reported in previous mpox outbreaks, it is not common (1). However, because of some patients abnormally severe presentations and clinical concern for possible bacterial infection, several in our cohort were also treated with antibiotics. This is similar to another cohort in the United Kingdom (14) and could have contributed to the globally favourable outcomes seen in our group. In both cases of culture-positive bacterial infection, *Streptococcus pyogenes* was isolated in throat cultures; therefore, one could surmise that oropharyngeal mpox lesions might have served as a portal of entry.

None of the patients in this study had been vaccinated for smallpox prior to the onset of their symptoms—either in the setting of the current outbreak or in their youth. Data from cohorts in historically endemic countries suggests that patients with prior variola virus immunization have less severe disease (15). The impact of antivirals in these cases has not yet been studied and thus remains uncertain.

Limitations

The limitations of this study include its observational nature, the small number of cases and our inability to follow their evolution with a prospective assessment of blood, urine and upper respiratory tract viral loads. We are unable to draw firm conclusions from this cohort in the absence of a control group, and our results are primarily hypothesis-generating.

Conclusion

Overall, our experience suggests that TCV appears to be a safe adjunct to supportive care in the treatment of mpox infection and may accelerate recovery in severe cases. Because mpox is generally a self-limited condition and because of the presence of other variables, such as treated bacterial superinfection, the magnitude of TCV's clinical impact in this setting remains uncertain. Controlled, clinical trials should be conducted to clarify the attributable benefit of tecovirimat in severe mpox infection.

Authors' statement

KKD — Original draft, collection of data, review draft manuscript
MD — Conceptualization, methodology, supervision of the project, collection of data, review draft manuscript
JL — Conceptualization, methodology, supervision of the project, collection of data, review draft manuscript

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The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

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