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Clinical experience with use of oral Tecovirimat or Intravenous Cidofovir for the treatment of Monkeypox in an Italian reference hospital

Dear Editor,

We read with interest the manuscript by Li D. and colleagues, recently published in this Journal, in which the authors revealed the potential binding mode for tecovirimat with a poxvirus phospholipase from monkeypox (MPX) virus [1].

Tecovirimat and cidofovir are potential options for severe cases of MPX, but limited data on their efficacy and safety are available [2–6].

Here we retrospectively describe clinical presentation, evolution, management and viral kinetics of the first 19 MPX cases treated with antivirals at the INMI Lazzaro Spallanzani IRCCS in Rome, Italy. The decision regarding treatments was based on international medical consensus and availability of drugs.

Viral DNA was extracted by the automatic extractor QiAsymphony (Qiagen, Hilden, Germany), and amplified using the real-time PCR method targeting the tumor necrosis factor receptor gene, G2R. Monkeypox virus (MPXV) DNA concentration was measured using threshold cycles (Ct) values of the MPXV-specific PCR. To obtain an absolute quantification of MPXV DNA in the clinical samples, the PCR assay was adapted to run in digital droplet PCR (ddPCR). The nucleic acid extracted from each sample was loaded into specific nanoplate and distributed, amplified and read in each one of the 26,000 partitions of each well, with a detection limit of the assay of 5 copies/μL.

The study was conducted as a part of biological studies on emerging infections approved by the Ethical Committee of the Lazzaro Spallanzani Institute (approval number 14/2015 and amendments). Patients provided written informed consent.

As of September 19, 2022, 19/128 (15%) diagnosed cases of MPXV infection at INMI L. Spallanzani received antiviral treatment. All patients were males aged between 27 and 50 years, all but one patients self-identified as men who have sex with men or bisexual and seven patients (37%) were HIV-positive. Systemic symptoms were reported in all but one patient. Muco-cutaneous lesions were observed in all patients (skin lesions in 89% and mucosal lesions in 95%) and in half of them preceded systemic symptoms.

The majority (79%) of patients complained of a painful lymphadenopathy. Patients were admitted to hospital within a median of 8 days (IQR 5–10) from date of symptoms onset (OD), mainly for mucosal inflammation caused by MPXV and/or superinfection of the lesions and/or management of severe pain due to the lesions. Specifically, proctitis was diagnosed in four patients (21%) and severe pharyngo-tonsillitis in six patients (32%). One patient presented ocular localization complicated by peri-orbital edema and conjunctival hyperemia. Nine patients (47%) presented with superinfection of the soft tissues, one of which was complicated by abscess of a finger. Finally, one patient was admitted and treated for worsening of genital lesions.

Antiviral treatment was started with a median time of 11 days (IQR 8–12) from OD with oral tecovirimat in 15 (79%) patients and intravenous (IV) cidofovir in 4 (21%) patients. All patients treated with oral tecovirimat completed a 14-day course of therapy. Similarly, IV cidofovir was well tolerated. Symptoms improvement and no new lesion appearance were observed 72 hours after the start of treatment in all but one patient treated with cidofovir.

No significant alterations of blood tests were observed, apart from a transient increase of alanine aminotransferase after cidofovir. Complete recovery was observed in all patients with a median of 15 days (IQR 11–19) from treatment start. Three patients had still persistence of signs of MPX-mucosal involvement after the resolution of lesions (Table 1).

Finally, viral kinetics have been evaluated in 12 patients (Fig. 1). In all of them, MPXV-DNA was detected in at least one sample from at least one compartment. Particularly, during the follow-up, MPXV-DNA was detected by real-time PCR in: 10/12 patients on oropharyngeal swab (OPS), including 9 at the start of antiviral treatment, with a median Ct of 36 (IQR 33–41); 8/9 patients on blood samples with a median Ct of 41 (IQR 37–41); 6/6 patients on feces with a median Ct of 41 (IQR 36–41); 3/3 patients on saliva with a median Ct of 38 (IQR 32–40); 3/3 patients on seminal fluids with a median Ct of 39 (IQR 37–41). In almost all patients, a progressive decline in viral load was observed over the course of treatment. Most biological samples were negative at the last available observation. DdPCR results approximately mirrored the viral shedding expressed with real-time PCR. It is worth noting that, given the low threshold used for the ddPCR, several samples with high Ct values in real-timePCR, resulted negative in ddPCR.

Limited data on clinical effectiveness of tecovirimat are available, however, several recent reports on its use has shown good tolerability and no evolution versus severe disease in treated subjects [2–4,7]. Additionally, preliminary results from the first 549 MPX-positive patients treated with tecovirimat in United States (US), showed median time to subjective improvement of 3 days [7]. To the best of our knowledge, this is the first report of the use of antivirals for MPX with both clinical and virological results in this current outbreak. One case series of patients treated in 2018–2021 reported viral decay in one patient during tecovirimat treatment showing a shorter duration of viral shedding compared to the other patients [2]. Additionally, in a pre-print publication, outcomes, including viral kinetics, of 14 patients treated before February 2022 with tecovirimat were reported [8]. In contrast to that report, where rate of appearance of lesions decreased during treatment with a median of 5 days from treatment start [8], in our patients clinical improvement and no new lesions were reported in

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Table 1: Patients’ characteristics and clinical course.

| No. | Ethnicity | Gender | HIV status | ART regimen | CD4 count | Clinical symptoms |
|-----|-----------|--------|------------|-------------|-----------|------------------|
| P1  | Caucasian | M/35   | Pos(BIC/3TC/DTG; TDF/FTC; Raltegravir) | 253/22 cp/mL | Headache, fatigue, myalgias, diarrhea |
| P2  | Hispanic | M/27   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P3  | Caucasian | M/47   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P4  | Caucasian | M/38   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P5  | African   | M/50   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P6  | Hispanic | M/35   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P7  | Caucasian | M/27   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P8  | Caucasian | M/47   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P9  | Caucasian | M/38   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P10 | African   | M/50   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P11 | Caucasian | M/27   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P12 | Caucasian | M/47   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |
| P13 | Caucasian | M/38   | Neg/Neg    | Cobicistat/Emtricitabine/emtricitabine/tenofovir disoproxil fumarate | ND/ND | Headache, myalgias, rectal pain |

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| Number of lesions | Systemic symptoms onset after lesions | Lymphadenopathy | Localized disease | Type of treatment reason for admission | Reason for clinical presentation | Days from OD to admission/treatment | Days from treatment to recovery |
|-------------------|----------------------------------------|-----------------|-------------------|----------------------------------------|---------------------------------|-----------------------------------|-------------------------------|
| PT1               | PT2                                    | PT3             | PT4               | PT5                                    | PT6                             | PT7                               | PT8                           | PT9                           | PT10                          | PT11                          | PT12                          | PT13                          | PT14                          | PT15                          | PT16                          | PT17                          | PT18                          | PT19                          |
| Number of lesions | Systemic symptoms onset after lesions | Lymphadenopathy | Localized disease | Type of treatment reason for admission | Reason for clinical presentation | Days from OD to treatment | Days from treatment to recovery |
| 11-20             | Yes                                    | Inguinal        | No                | Cidofovir                              | Superinfection of cutaneous lesion | 5/12                              | 13                             | 10                            | 21                            | 9                             | 12                            | 11                            | 14                            | 4                             | 7                             | 18                            | 6                             | 21                            | 14                            | 20                            | 7                             | 18                            | 17                            | 27                            | 15                            |
almost all patients 72 hours after tecovirimat initiation. The longer time elapsed from symptoms onset to treatment start (21 days) compared to our study (12 days) might partially explain this different result. Of note, in our case series, 15% of MPX cases diagnosed received antiviral treatment, consistently with US data [9].

Concerning viral kinetics, it should be noted that low viral loads were observed. Additionally, some patients had all available samples negative in ddPCR since antiviral starting, in line with previous evidence showing that viral shedding occurs mainly during the first two weeks of the disease [10]. Due to the median time of 12 days from symptoms onset to starting treatment in this series, we cannot exclude a reduced impact of antiviral therapy on viral shedding or clinical resolution.

The main limitations of this study was the lack of control group, so that any conclusions on the effectiveness of antiviral therapy cannot be drawn, the small number of patients included, the heterogeneity of samples and the impossibility to collect samples for all the patients at each timepoint.

Data collected on observational studies such as this can help improve our knowledge of the use of antivirals for MPXV, waiting more robust results from the placebo-controlled randomized trial of tecovirimat for MPX.
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Conflicts of interests

The authors declare no conflict of interest for the present study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.11.001.

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