Pharmaceutical Sciences, 2021, 27(Suppl 1), S68-S77
doi:10.34172/PS.2021.38
https://ps.tbzmed.ac.ir/

Review

Acyclovir as a Potential Add-on Therapy in COVID-19 Treatment Regimens

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Article Info

Article History:
Received: 6 April 2021
Accepted: 22 June 2021
ePublished: 8 July 2021

Keywords:
-2019 nCoV Infection
-Acyclovir
-COVID-19
-Herpes Simplex Virus Infection
-Herpes Zoster
-Reverse Transcriptase PCR

Abstract

Background: There are successful reports of the concomitant management of herpes infection and coronavirus disease 2019 (COVID-19), using both acyclovir (ACV) and COVID-19 treatment regimens. Furthermore, ACV has been proposed to effectively treat COVID-19, through various mechanisms, such as inhibition of viral proteases, multiple viral gene expressions, and RNA-dependent RNA polymerase (RdRP). Therefore, this study aimed to review the reported cases of patients with concomitant herpes infection and COVID-19, receiving concurrent antiviral drugs for herpetic lesions.

Methods: A search was done to find the relevant articles, published between December 2019 and December 2020, with no language limitations, in the PubMed database, using the Medical Subject Headings (MeSH) terms related to herpes simplex virus or herpes zoster (namely, shingles) combined with COVID-19. Accordingly, the reports of the concomitant herpes infection and COVID-19, receiving concurrent antiviral drugs for herpetic lesions were included.

Results: Out of 90 articles, 11 records reporting the cases of herpes infection and concurrent laboratory-confirmed COVID-19, receiving antiherpetic therapies, were reviewed. There were 28 patients (age range of 7-82 years) with laboratory-confirmed COVID-19, concomitant with reactivation of herpes infection, receiving antiviral drugs alongside candidate COVID-19 treatment regimens, but no mortality. The mean (standard deviation [range]) age of these 28 patients during treatment was 56.4 (18.6 [7-82]) years, and the majority were male (n=18, 64.3%). A total number of 20 patients had also received ACV and eight cases had been administered with other two antiviral compounds, including seven cases with valacyclovir, and one case with famciclovir, with no mortality.

Conclusion: The potential use of ACV, as an add-on therapy, along with candidate COVID-19 treatment regimens was proposed in this study. However, further clinical trials are recommended to test this hypothetical adjuvant therapy.

Introduction

Coronavirus disease 2019 (COVID-19) has become a major health challenge worldwide.[1] From the beginning of this pandemic, innumerable treatments have also been proposed.[2,3] Remdesivir as an inhibitor of the viral RNA-dependent, RNA polymerase proposed as candidate COVID-19 treatment and the clinical trial confirmed its effect on shortening the time to recovery.[4] Hydroxychloroquine which had an inhibitory effect on the growth of COVID-19 in an in vitro study, was efficient in clearing viral nasopharyngeal carriage of COVID-19 in most patients. Despite promising drugs such as remdesivir (brand name Veklury) and hydroxychloroquine (HCQ),[4-6] limited or no comprehensive studies have so far confirmed their effectiveness; thus, the World Health Organization (WHO) has not included such medications in the list of recommended treatments.[7-10] Nevertheless, until the development of an effective COVID-19 vaccine,[11] many articles have been proposing cost-effective and safe treatment modalities to manage COVID-19.[12-17] Certainly, the safety and efficacy of these potential treatments should be verified in randomized clinical trials (RCTs). For example, in a meta-analysis,[18] the probability of reinfection or reactivation of the latent infection in patients recovered from COVID-19 had been proposed. Similar to varicella-zoster virus (VZV),[19] the inactivated COVID-19 virus can remain dormant, and recur or reactivate following

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unknown immunological mechanisms.[17,18]

The coincidence of COVID-19 with other infectious diseases, such as recurrent herpes simplex virus (HSV) and herpes zoster (namely, shingles) has been thus far reported. Laboratory-confirmed COVID-19 cases with concurrent clinical manifestations of HSV or herpes zoster have been also reported, wherein the possibility of this coincidence has been attributed to COVID-19-induced lymphopenia. Although distress associated with COVID-19 has been proposed as a persuasive reason for herpes zoster recurrence, the exact cause is yet to be known. The highlight of these reports, including the age range of children, adults, and the elderly, has been the successful treatment of patients with routine acyclovir (ACV) regimen for herpes infection, along with conventional COVID-19 treatments. Although some of these patients had been admitted to intensive care units (ICUs), they had eventually good prognoses.[20-23]

In addition to the above-mentioned successful reports of the concomitant management of herpes infection and COVID-19, other studies have suggested the effectiveness of ACV in the management of COVID-19, based on docking and molecular dynamic simulations,[24] connectivity map (CMAP) database,[25] and review of potential repurposed drugs.[2] However, the proposed mechanisms to reflect on ACV efficacy, as an acyclic guanosine analog, in these articles have been different. The range of mechanisms proposed for this hypothetical effect include inhibition of viral proteases,[24] multiple viral gene expressions,[25] and RNA-dependent RNA polymerase (RdRP). [2] Compared to native COVID-19 protease, COVID-19 protease complex with the designed derivative of acyclovir was stable with less fluctuation. With this observance authors proposed this drug as an inhibitor for COVID-19.[24] Furthermore, Cmap prediction identified acyclovir along with amantadine, acyclovir, podophyllotoxin, adiphenine, and monensin as candidate drugs to treat COVID-19.[25]

Considering that ACV could be introduced as a potential add-on therapy alongside COVID-19 treatment regimens, this review aimed to summarize the treatment outcomes and the characteristics of the patients reported with concomitant COVID-19 and herpes infection, receiving concurrent antiviral therapy for herpetic lesions to support the given hypothesis.

Methods

A search was done to identify the relevant articles, published between December 2019 to December 2020, with no language limitations, in the PubMed database, using the following Medical Subject Headings (MeSH) terms; "Herpes Simplex Virus Infection" or Zona or Zoster or Shingles, in combination with COVID* or "COVID-19" or corona* or SARS-CoV-2* or 2019-nCoV* or "Severe Acute Respiratory Syndrome Coronavirus 2"; and 90 studies were ultimately retrieved. Two reviewers (FH and SM) also independently reviewed and selected the articles. Finally, 11 studies reporting the concurrent laboratory-confirmed COVID-19 (detected using reverse transcription-polymerase chain reaction [RT-PCR]) and herpes infection, with prescribed antiviral medications for herpetic infections, were included and analyzed. The data were extracted and stored for each patient in the Microsoft Excel 2016 software (Microsoft Corporation, Redmond, Washington, USA), including age, gender, and type of antiviral treatment. Table 1 summarizes the main characteristics of the selected articles.

Results

Out of 90 studies, 11 records met the inclusion criteria, in which 28 patients out of 32 laboratory-confirmed COVID-19, concomitant with reactivation of herpes infection, had received concurrent antiviral therapy for herpetic lesions in addition to candidate COVID-19 management based on the severity of the disease. The mean (standard deviation [range]) age of these 28 patients during treatment was 56.4 (18.6 [7-82]) years, and the majority were male (n=18, 64.3%). Accordingly, a total number of 20 patients had received ACV (administrated six days after oral famciclovir [FACV] in one case), seven patients had been administered with valacyclovir (VACV), and one case had received FACV, with no mortality. The details of the cases are highlighted in Table 1.

The above-mentioned 28 patients were as follows. The first reported case was a 49-year-old woman with concurrent COVID-19 and herpes zoster, seven days after the onset of COVID-19 symptoms. The patient had been treated with VACV 1 g three times daily.[26] The subsequent two cases with clinically diagnosed herpes zoster had been also treated with VACV or ACV and had good prognoses.[27] Four COVID-19 cases with VZV reactivation had further received the standard ACV dosage with the candidate COVID-19 treatment. All the cases had been managed without postherpetic neuritis.[20] As well, 11 out of the 15 patients with COVID-19 and concomitant reactivated HSV or herpes zoster had been treated with ACV or VACV, in addition to the candidate COVID-19 treatment.[23] Another case was a 57-year-old man who had developed cutaneous herpes zoster manifestations, five days after the symptom onset of COVID-19, and had recovered after receiving FACV 500 mg every eight hours for seven days.[28] A 58-year-old patient with COVID-19, meningitis, and cutaneous manifestations of herpes zoster, had further received FACV for six days (then intravenous [IV] ACV) in addition to meningitis treatment.[29]

Moreover, a 70-year-old woman with laboratory-confirmed COVID-19 had developed herpes zoster -induced skin lesions, and had received IV ACV 250 mg three times a day for 16 days, followed by oral ACV 400 mg, five times daily for one week.[22] Similarly, Ferreira *et al.*[30] had successfully managed a 39-year-old man with COVID-19 and cutaneous herpes zoster-related lesions with five days of IV administration of ACV 10 mg/kg.Quite interesting, a 73-year-old critically ill man with COVID-19 and concomitant VZV and HSV-1, upon treatment with an IV drip of ACV 0.5 g every eight hours, had improved

Table 1. Summary of the main characteristics of articles presenting concurrence of COVID-19 and herpes infection with acyclovir or other antiviral compounds in treatment regimens.

Article	Gender, Age (Y)	PMH	Herpes Virus species	Site of Herpetic lesions	Treatment for COVID-19	Medication for Herpes	Outcome	Remarks
Shors[26]	F, 49	None	HZ	Left upper lip and V2 dermatome	NA	Valacyclovir 1 g, 3 times daily, 7 days; analgesia	OPM	Herpetic skin lesions 7 days after COVID-19 symptoms, Allodynia, Severe neuralgia of left cheek
Elsaie *et al*.[27]	M, 68	Untreated HTN Hypercholesterolemia	HZ	Right half of right loin	NA	Valacyclovir 1g, twice daily, 7 days; acyclovir cream; paracetamol	OPM	Hemorrhagic blisters, Herpetic skin lesions 2 days before COVID-19 symptoms
	F, 60	Controlled HTN	HZ	Left side of chest, nape of the neck	NA	Acyclovir 800 mg, 5 times a day, 5 days; prednisolone 5 mg twice daily; calamy lotion	OPM	None
Tartari *et al*.[20]	F, 68	None	HZ	CN-V, 2nd branch	Hydroxychloroquine	Acyclovir 10 days, analgesic	MV-ICU	Herpetic skin lesions 6 days after hospitalization, Necrotic lesions, Leukopenia (CD3+ CD8+ lymphocyte decreased)
	F, 74	None	HZ	CN-V, second branch	Hydroxychloroquine	Acyclovir 10 days, analgesic	MV-ICU	Herpetic skin lesions 5 days after hospitalization, Necrotic lesions, Leukopenia (CD3+ CD8+ lymphocyte decreased)
	F, 71	None	HZ	CN-V, second branch	Hydroxychloroquine Tocilizumab	Acyclovir 10 days, analgesic	MV-ICU	Herpetic skin lesions 7 days after hospitalization; Necrotic lesions, Leukopenia (CD3+ CD8+ lymphocyte decreased)
	M, 70	Cardiac transplant, on immunosuppressive drugs (tacrolimus, mofetil mycophenolate, and prednisone)	HZ	Classic herpes lesions on dorsum	Hydroxychloroquine, azithromycin	Acyclovir 10 days, analgesic	OPM	Herpetic skin lesions 4 days after COVID-19, Leukopenia (CD3+ CD8+ lymphocyte decreased)
Fernandez-Nieto *et al*.[23]	M, 69	None	HSV	Orolabial	Hydroxychloroquine, azithromycin, ceftriaxone	Acyclovir	NA	Herpetic skin lesions 16 days after COVID-19 symptoms
	F, 96	HTN, chronic kidney disease, Hyperuricemia	HSV	Orolabial	Hydroxychloroquine, azithromycin, prednisone	None	NA	Herpetic skin lesions 27 days after COVID-19 symptoms
	F, 77	Primary biliary cholangitis, Alzheimer disease	HSV	Orolabial	Hydroxychloroquine, lopinavir/ritonavir, azithromycin, prednisone	None	NA	Herpetic skin lesions 14 days after COVID-19 symptoms

Table 1. Continued

Article	Gender, Age (Y)	PMH	Herpes Virus species	Site of Herpetic lesions	Treatment for COVID-19	Medication for Herpes	Outcome	Remarks
Fernandez-Nieto *et al.*[23]	M, 65	HTN, Dyslipidemia	HSV	Orolabial	Lopinavir/ritonavir, azithromycin, prednisone, tocilizumab, remdesivir	Acyclovir	NA	Herpetic skin lesions 32 days after COVID-19 symptoms
	M, 38	Colorectal cancer (on chemotherapy treatment)	HSV	Orolabial	Lopinavir/ritonavir, tocilizumab, remdesivir, prednisone	Acyclovir	NA	Herpetic skin lesions 9 days after COVID-19 symptoms
	M, 61	None	HSV	Orolabial	Hydroxychloroquine, lopinavir/ritonavir, tocilizumab, prednisone	Acyclovir	NA	Herpetic skin lesions 15 days after COVID-19 symptoms
	F, 45	None	HSV	Orolabial	Hydroxychloroquine	None	NA	Herpetic skin lesions 18 days after COVID-19 symptoms
	M, 76	HTN, Dyslipidemia	HSV	Orolabial	Hydroxychloroquine	None	NA	Herpetic skin lesions 24 days after COVID-19 symptoms
	F, 56	None	HZ	Localized Cutaneous	Hydroxychloroquine	Valacyclovir	NA	Herpetic skin lesions 22 days after COVID-19 symptoms
	M, 52	None	HZ	Localized Cutaneous	None	Valacyclovir	NA	Herpetic skin lesions 14 days after COVID-19 symptoms
	F, 63	HTN	HZ	Localized Cutaneous (Ophthalmic)	None	Valacyclovir	NA	Herpetic skin lesions 26 days after COVID-19 symptoms
	M, 56	Dyslipidemia	HZ	Localized Cutaneous (Ophthalmic)	None	Valacyclovir	NA	Herpetic skin lesions 26 days after COVID-19 symptoms
	M, 82	HTN, DM	HZ	Localized Cutaneous	Hydroxychloroquine	Acyclovir	NA	Herpetic skin lesions 7 days after COVID-19 symptoms
	F, 73	Dyslipidemia	HZ	Localized Cutaneous	Hydroxychloroquine, prednisone	Acyclovir	NA	Herpetic skin lesions 12 days after COVID-19 symptoms
	M, 78	HTN	HZ	Localized Cutaneous	Hydroxychloroquine	Acyclovir	NA	Herpetic skin lesions 6 days after COVID-19 symptoms
Saati *et al.*[28]	M, 57	HTN	HZ	Right T4 dermatome	None	Famciclovir 500mg, every 8 hours, 7 days, acetaminophen when needed, tramadol	Hospitalized	Herpetic lesions 5 days after COVID-19 symptoms

Table 1. Continued.

Article	Gender, Age (Y)	PMH	Herpes Virus species	Site of Herpetic lesions	Treatment for COVID-19	Medication for Herpes	Outcome	Remarks
Pckwood *et al*.[29]	M, 58	Hyperlipidemia	HZ	Right T9 and T10 dermatomes	Supportive and symptomatic treatment. He received various treatments including lopinavir/ritonavir, for a six-day, hydroxycholorquine and azithromycin,as well as remdesivir. His antibiotics was continued.	Famciclovir 6 days then IV Acyclovir 14 days	MV-ICU	Headache, fever, pain in neck movement, and concern for meningitis which has received in a stepwise approach IV vancomycin, IV ceftriaxone, and IV doxycycline. Herpetic skin lesions 3 days after COVID-19 symptoms
Cao *et al*.[22]	F, 70	Type 2 DM, Myasthenia gravis on acarbose, pyridostigmine, prednisone, and tacrolimus.	HZ	Right L10 to L12 dermatomes	Supportive and symptomatic treatment; Oral arbidol (0.2 g every 8 h) and moxifloxacin (0.4 g every day); and tacrolimus was withheld for 10 days	IV acyclovir 250 mg, 3 times a day, 16 days, and restarting oral prednisone 20mg once a day, infrared therapy, and pregabalin. IV acyclovir was replaced with 5 times a day oral acyclovir 400 mg for 1 week.	Hospitalized, Discharged	Herpetic skin lesions 47 days after COVID-19 symptoms, Developed postherpetic neuralgia
Ferreira *et al*.[30]	M, 39	None	HZ	Intraoral mucosal lesions, left trigeminal nerve	NA	Oral Acyclovir 2 days with pregabalin then IV Acyclovir 10 mg/Kg, three times a day for 5 days	Hospitalized	Photosensitive, but normal Fundoscopy. Left trigeminal nerve enhancement on MRI. Responded well to the treatment
Xu *et al*.[31]	M, 73	None	HZ and HCV-1	Diffuse erosions on right lateral arm, shoulder, and neck	Supportive and symptomatic treatment.	Acyclovir 0.5 g, Ivdript, every 8 hours	ICU admission, Veno-venous extracorporeal membrane oxygenation/ Discharged	Several cluster of Haemorrhagic blisters and numerous small ulcers on bronchial mucosa on fibreoptic bronchoscopy exam. Responded well to the treatment

Table 1. Continued.

Article	Gender, Age (Y)	PMH	Herpes Virus species	Site of Herpetic lesions	Treatment for COVID-19	Medication for Herpes	Outcome	Remarks
Nofal *et al.*[21]	M, 42	None	HZ	Blepharitis, conjunctivitis, mild keratitis	Supportive and symptomatic treatment.	Acyclovir 800 mg, 5 times a day for 1 week, topical acyclovir, topical prednisolone acetate 1% eye drops	OPM	Herpetic lesions 4 days after COVID-19 presentation Lymphopenia
	M, 42	None	HZ	Blepharitis, conjunctivitis, mild keratitis	Supportive and symptomatic treatment.	Acyclovir 800 mg, 5 times a day for 1 week, topical acyclovir, topical prednisolone acetate 1% eye drops	OPM	Herpetic lesions 4 days after COVID-19 presentation Lymphopenia
	F, 7	None	HZ	Blepharitis, conjunctivitis	Supportive and symptomatic treatment.	Acyclovir 20mg/Kg, 5 times for 1 week, , topical acyclovir, topical prednisolone acetate 1% eye drops	OPM	Herpetic lesions 5 days after COVID-19 presentation Lymphopenia
	M, 28	None	HZ	Blepharitis, episcleritis, conjunctivitis	Supportive and symptomatic treatment.	Acyclovir 800mg, 5 times for 1 wee, , topical acyclovir, topical prednisolone acetate 1% eye drops	OPM	Herpetic lesions 5 days after COVID-19 presentation Lymphopenia
	M, 9	None	HZ	Blepharitis, eyelid edema, conjunctivitis	Supportive and symptomatic treatment.	Acyclovir 20 mg/Kg, 5 times for 1 week, , topical acyclovir, topical prednisolone acetate 1% eye drops	OPM	Herpetic lesions 4 days after COVID-19 presentation Lymphopenia
Elsaie and Nada[32]	M, 44	None	HZ	Left upper chest and back	Oral Oseltamivir every 12-hour, azithromycin 500 mg every day, paracetamol, and Vitamin C.	Valacyclovir 1 g, every 8 hours for 1 week	OPM	Herpetic lesions 7 days after COVID-19 presentation

Articles arranged in order of publishing date on PubMed. Abbreviations: Y: years; M: male; F: female; PMH: Past Medical History; g: gram; NA: not available; g: gram; mg: milligram; CN-V: the trigeminal nerve; HZ: herpes Zoster; HSV: Herpes simplex Virus; HTN: hypertension; DM: Diabetes mellitus; MV-ICU: Intensive care unit admission and mechanical ventilation; OPM: outpatient management. Note: Necrotic herpes zoster is more common in HIV-positive patients or in those with iatrogenic immunosuppression.

gradually.[31] Finally, five patients, with COVID-19 and developing herpes zoster skin lesions, had been successfully managed with antiherpetic therapy and the candidate COVID-19 treatment regimens.[21,32]

Discussion

In this review, the treatment outcomes and the characteristics of 28 patients with concomitant COVID-19 and herpes zoster, receiving COVID-19 treatment regimens alongside antiviral medications, including ACV, VACV, or FACV, were summarized. The mean age of the patients was 56.4 years, and 64.3% (n=18) of them were male. As well, a total number of 20 patients had received ACV and eight cases had been administered with other two antiviral compounds, including seven cases with VACV, and one case with FACV, with no mortality.

Recalcati *et al.*[33] had reported skin manifestations in 18 (20.45%) patients with COVID-19, one of them having chickenpox-like vesicles. However, they had not mentioned the details

of the diagnostic work-up and the treatment outcomes.[33] Subsequently, Marzano *et al.*[34] had examined 22 patients with COVID-19 and varicella-like papulovesicular exanthem. However, no additional information had been provided on antiviral therapy to manage skin lesions neither in this article nor in their reply to the editor,[35] regarding the queries raised by Lamas-Velasco *et al.*[36] Therefore, there was no conclusion with respect to their study findings and the effect of ACV on COVID-19 outcomes.[34]

Shors[26] had also reported a 49-year-old woman with concurrent COVID-19 and herpes zoster, appeared on the seventh day since the onset of COVID-19 symptoms and diagnosed through telemedicine consultation. The diagnosis of COVID-19 had been confirmed using the RT-PCR, and the patient had been treated with VACV 1 g three times daily. As well, the skin lesions had shown a slow response to the treatment, and she had developed severe neuralgia, relatively controlled with oral gabapentin and topical lidocaine.[26] Thereafter, LIamas-Velasco *et al.*[36] had reflected on three hospitalized Spanish patients with laboratory-confirmed COVID-19, diagnosed with HSV-1, HSV-6, and Epstein-Barr virus (EBV) (59-year-old woman), HSV-1 and HSV-7 (69-year-old man), and VZV (79-year-old man), with lymphopenia, confirmed via the RT-PCR using their vesicle fluid. In the 59-year-old woman admitted to the ICU with mechanical ventilation, some lesions had been observed in the perioral region as peristomatous punched-out ones and vesicles. In the 79-year-old man with a history of Parkinson's disease and melanoma, the lesions had been spotted on the anterior and posterior trunk and upper limbs as hemorrhagic blisters. However, the outcomes and the treatment approaches for the skin vesicles with ACV or similar drugs, routinely prescribed for HSV and VZV had not been mentioned.

Besides, Elsaie *et al.*[27] had presented two cases of COVID-19 with clinically diagnosed herpes zoster. These patients had been treated with VACV or ACV and had good prognoses. Tartari *et al.*[20] had also reported four laboratory-confirmed COVID-19 cases with VZV reactivation, in which the patients had been prescribed the standard ACV dosage with the candidate COVID-19 treatments. All cases had been also managed without postherpetic neuritis. In three cases, necrotic herpes zoster-induced lesions of the second branch of the trigeminal nerve had been noted. In the fourth case, classic herpes zoster lesions had been also reported. Moreover, Fernandez-Nieto *et al.*[23] had administered ACV or VACV plus COVID-19 candidate treatments for 11 laboratory-confirmed COVID-19 cases, having HSV or herpes zoster reactivation. Accordingly, eight patients had recurrent HSV-induced orolabial lesions, and seven cases had localized herpes zoster; two of them presented with herpes zoster ophthalmicus. The latency time between the onset of COVID-19 symptoms and the herpes skin lesions was 6-32 days. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had not been detected in the vesicle fluid of three patients, undergoing RT-PCR. This article had not mentioned any cases with poor prognosis or death.[23]

Pona *et al.*[37] had comparably reported a 70-year-old African-American woman with laboratory-confirmed COVID-19 and herpes zoster. She had been successfully managed on an outpatient basis despite the comorbidities of hypertension and complicated type 2 diabetes mellitus, with no antiviral therapies. The patient had shown no lymphopenia, and the herpes related skin lesions had been observed on the left hip and the superior buttock as numerous vesicles and hemorrhagic crust. In this case, the physician had prescribed gabapentin for her pain relief, with no antiviral therapy.

Likewise, Saati *et al.*[28] had reported the successful treatment outcome of a 57-year-old man, developing cutaneous herpes zoster manifestations, five days after the symptom onset of COVID-19. The patient (with a history of hypertension) had recovered after receiving FACV 500 mg every eight hours for seven days. Packwood *et al.*[29] had also presented a 58-year-old patient with laboratory-confirmed COVID-19 with a diagnosis of meningitis and cutaneous manifestations of herpes zoster, discharged in a stable condition after one month. At the time of admission, the patient had received FACV for six days (then IV ACV) in addition to meningitis treatment. The patient had been also discharged in a stable condition after a month.

Correspondingly, Ayaz *et al.*[38] had reported a patient with laboratory-confirmed COVID-19 with disseminated herpes zoster, discharged with a good condition after successful treatment. However, the details of the treatment regimen had not been mentioned.A 70-year-old woman with laboratory-confirmed COVID-19, a history of type 2 diabetes mellitus, and myasthenia gravis, had developed skin lesions related to herpes zoster. The patient had been discharged following treatment with IV ACV 250 mg three times a day for 16 days, followed by a week of oral ACV 400 mg five times daily. However, she had developed postherpetic neuralgia and responded poorly to treatment.[22] Similarly, a 39-year-old man with laboratory-confirmed COVID-19 and no past medical history had developed cutaneous herpes zoster lesions in the left trigeminal nerve distribution and responded well to the treatment, five days after IV administration of ACV 10 mg/kg.[30] Xu *et al.*[31] had also reported a 73-year-old critically ill man, admitted to ICU owing to severe manifestations of COVID-19. On day 35 of admission, VZV and HSV-1 reactivation had been further confirmed using the next-generation sequencing test and observation of numerous bronchial-mucosal ulcers during fibreoptic bronchoscopy. Despite deteriorating conditions, upon treatment with an IV drip of ACV 0.5 g every eight hours, the patient had gradually improved.[31] Finally, five patients, aged 7-44 years, with laboratory-confirmed COVID-19 and developed herpes zoster-induced skin lesions, a few days after COVID-19 diagnosis, had been successfully managed as outpatients treated with the candidate COVID-19 treatment regimens, in addition to ACV[21] or VACV[32] administration.

Accordingly, it was proposed that ACV could be considered a potential add-on therapy in COVID-19 treatment regimens with the following supports; firstly, the outcomes of successful treatment of herpes infection and COVID-19, in few studies,[20,23,26,32] secondly, the results of studies that suggested the effectiveness of ACV in the treatment of COVID-19,[2,24,25] thirdly, the possibility of COVID-19 reactivation in successfully treated patients due to a weakened immune system or stress, similar to the causes of herpes infection recurrence,[18] and fourthly, the long history of safety of ACV in the management of viral infections, its affordability, and availability.[39-44] However, clinical trials should be performed to test the safety and efficacy of this hypothetical adjuvant therapy.

Perhaps, the global control of COVID-19 requires the provision of cost-effective and safe treatments that can be accessible to the public. Thus, providing treatment only to a specific population (such as vaccination of certain communities) can challenge the control of the disease, and may lead to the reemergence of this pandemic. Therefore, a useful, safe, cost-effective, and accessible resolution to manage this crisis is required.

This review was to support the hypothesis concerning the potential effectiveness of ACV on COVID-19. However, further systematic reviews and meta-analyses are required to shed light on this subject. Here, only a single database was searched, which limited the findings. Moreover, not all studies reporting the concurrence of COVID-19 and recurrent herpes infection had provided the details of treatments. However, this review reflected the idea of the potential effectiveness of ACV for COVID-19 concerning the favorable outcomes of patients who had both COVID-19 and herpes infection and had received ACV. Further studies are required to confirm the effectiveness of ACV use in the management of COVID-19. Moreover, as the selected studies in this review revealed promising clinical improvements, possible molecular mechanisms of ACV in SARS-CoV-2 eradication yet to be determined.

Conclusion

In this review, the possibility of ACV as an add-on therapy alongside the candidate COVID-19 treatment regimens was proposed. Subsequently, the successful treatment outcomes in patients with concomitant COVID-19 and herpes infection, receiving concurrent ACV, was proposed to support this hypothetical adjuvant therapy in the COVID-19 management. However, further trials are highly recommended, to test and prove this hypothetical treatment, optimum dosage and route of administration at different stages of COVID-19.

Acknowledgements

Authors wish to thank the International Virtual Ophthalmic Research Center (IVORC) for the continuous academic support.

Author Contributions

FH and RG: Conception or design of the work, acquisition, analysis, or interpretation of data for the work, drafting the work and Revising the work. SM and FA: Acquisition, analysis, or interpretation of data for the work and Drafting the work. The final manuscript has been read and approved by all authors.

Conflict of Interest

The authors did not have any conflict of interest.

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