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Cyclosporine Attenuates Covid-19: Ensnare or Victory

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1. Abstract

Coronavirus disease 2019 (Covid-19) is a recent worldwide pandemic caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In critical cases it causes acute lung injury (ALI) due to severe acute respiratory distress syndrome (ARDS). It has been proposed that initial immunological activation in SARS-CoV-2 infection is necessary for elimination and clearance of viral infection; however exaggerated late immune response is associated with immunological-mediated tissue injury. Thus, regulation of immune response by immunosuppressive agents may prevent exaggerated immune response-mediated development of ALI and/or ARDS. Cyclosporine A (CsA) is an immunosuppressive drug that has been suggested by different studies to be effective against Covid-19 owing to potential antiviral and anti-inflammatory properties. In this case study, we report cases of five Covid-19 patients with psoriasis, rheumatoid arthritis and ulcerative colitis on CsA therapy compared with five control Covid-19 patients not placed on CsA therapy. CsA therapy was given concurrently with the standard treatments in Covid-19 patients that received the therapy. The objective of the present study was to evaluate the outcome of including CsA therapy in management of Covid-19. The primary outcome parameters were hospital discharge time and mortality, while the secondary outcomes were clinical score severity and radiological resolution. CsA therapy in the reported cases led to significant attenuation of Covid-19 severity as revealed through good primary outcomes of short hospitalization period and no mortality compared with control Covid-19 patients. The secondary outcomes of Covid-19 patients on CsA therapy showed a significantly improved clinical signs. The biomarkers used for clinical score severity, CT scan scores, oxygen saturations, inflammation evaluation suggested better outcome compared to control Covid-19 patients. In conclusion, preexistent CsA therapy attenuates Covid-19 severity and mortality with significant reduction of inflammatory state. Therefore, CsA may reduce Covid-19 severity through anti-inflammatory and anti-SARS-CoV-2 properties/mechanisms. However, we cannot give an ultimate conclusion concerning use of CsA in managing of Covid-19.

2. Background

Coronavirus disease 2019 (Covid-19) is a recent worldwide pandemic triggered by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first recognized in Wuhan, China according to the initial epidemiological reports [1]. Covid-19 affects millions of population, and up to 15 April 2021, the number of infected peoples has been reported to be more than 135 million. However, about 80% of affected subjects were asymptomatic or had mild presentation of the infection while 15-20% of infected patients needed to be hospitalized due to development of acute lung injury (ALI) caused by acute respiratory

distress syndrome (ARDS) [2]. Critical Covid-19 patients need mechanical ventilations and intensive monitoring at intensive care units (ICU). Severe and critical Covid-19 cases were linked with hyper inflammations and hyper cytokinemia with progress of cytokine storm [3].

The underlying mechanisms of inflammatory and immunological disturbances in patients with severe Covid-19 were related to over activations of T cells and macrophages with subsequent release of huge amount of pro-inflammatory cytokines such as interleukins (ILs) and chemokines [4]. Of note, IL-6, IL1β, IL-8 and tumor necrosis factor alpha (TNF-α) during severe SARS-CoV-2 infections were linked with development of ALI/ARDS and multi-organ failure (MOF) [5]. Besides, one of most recognized entry-point of SARS-CoV-2 is angiotensin converting enzyme 2 (ACE2). The interaction between SARS-CoV-2 and ACE2 leads to significant down-regulation of this anti-inflammatory receptor. ACE2 is involved in regulation of renin-angiotensin system (RAS) through metabolism and conversion of inflammatory vasoconstrictor angiotensin II (Ang II) into vasodilator anti-inflammatory Ang 1-7 and Ang 1-9 [6]. Therefore, down-regulation of ACE2 and elevation of circulating AngII during SARS-CoV-2 infection might be the probable mechanism behind induction of inflammatory disturbances [7].

It has been proposed that initial immunological activation in SARS-CoV-2 infection is necessary for elimination and clearance of viral infection; however exaggerated late immune response is associated with immunological-mediated tissue injury [8]. Thus, regulation of immune response by immunosuppressive agents may prevent exaggerated immune response-mediated MOF and development of ALI/ARDS in severe SARS-CoV-2 infections [9].

Cyclophilins are intracellular proteins present in the prokaryotic and eukaryotic cells. They regulate synthesis, transportation and folding of proteins, which involves signal transduction and immunomodulation [10]. There are different types of cyclophilins, type A (CyPA) is the most dominant one and closely linked with various viral infections and cardio-metabolic diseases. CyPA is important and involved with replication of different viruses such as hepatitis C virus (HCV), hepatitis B virus (HBV), bovine pox virus, human immunodeficiency virus (HIV) and coronaviruses (CoVs) [11]. CyPA is highly involved in the replication of various types of CoVs including; SARS-CoV-2, SARS-CoV, MERS-CoV, hCoV-NL63 and hCoV-229E, thus CyPA is regarded as a drug target in the management of SARS-CoV-2 infections [12].

CD147 is a surface receptor molecule which interacts with CyPA and acts as entry-point for SARS-CoV-2. CyPA/ CD147 is also involved in different inflammatory diseases, therefore targeting this axis might be beneficial in different inflammatory disorders [13].

Cyclosporine A (CsA) is an immunosuppressive drug. It was first isolated from Tolypocladium inflatum fungi in 1971, and was used as an anti-inflammatory agent in 1976, which later was approved by food and drug administration (FDA) in 1983 for clinical use. CsA is indicated for autoimmune disorders, psoriasis, rheumatoid arthritis and lupus nephritis [14].

CsA is a natural cyclic peptide; consist of 11 amino acids and not synthesized by human ribosomes. CsA binds with cytosolic CyPA of T lymphocyte leading to inhibition of calcineurin, which is necessary for transcription and activation of IL-2 through activation of nuclear factor of activated T cells (NFAT) [15]. Also, CsA binds with CyPD of mitochondrial permeability transition pore (MPTP) leading to mitochondrial protection and prevents mitochondrial dysfunction-induced by hypoxia and oxidative stress [16]. It has been reported that CsA has antiviral activity against different CoVs and other enveloped RNA viruses, and recent retrospective and clinical trial studies as well as theoretical reports concerned CsA therapy in the management of Covid-19 [17].

3. Study Outlines

In this sense, we report a case sequence of five Covid-19 patients with psoriasis, rheumatoid arthritis and ulcerative colitis on CsA therapy compared with five control Covid-19 patients not on CsA therapy. CsA therapy was continued in addition to the standard treatments in selected Covid-19 patients for the case study.

Objective of the present study was to demonstrate possible favourable and valuable outcome of CsA therapy in management of Covid-19. The primary outcome parameters measured were discharge time and mortality, while the secondary outcomes were clinical score severity and radiological resolution.

This study was permitted by Scientific Ethical Committee in College of Medicine, Al-Mustansiyriah University in cooperation with Al-Shifaa Specialized Medical Center for Covid-19, Iraq, and Bagdad in March, 2021. Informed consent was obtained from all recruited Covid-19 patients for their contributions in the present study.

Standard therapy including; combination of the following, azithromycin capsule 500 mg/ day for 5 days, ivermectin tablet 16 mg/ day, famotidine tablet 40 mg/day, zinc tablet 500 mg/day, acetaminophen tablet 1500 mg/ day as an analgesic, favipiravir tablet 800 mg/day and /or remdesivir 100 mg/vial used intravenously.

Assessment of lung computed tomography (CT) scan was done according to lung involvement score (0-100), score 0 = normal lung, score 1< 5%, score 2 (5-25%), score 3(26-50%), score 4(51-75%), score 5 >75% [18]. Clinical score severity was performed according to the hospitalization and oxygen supplement, score 1= hospitalization not needed + resumed normally, score 2= hospitalization not needed + not resumed normally, score 3= need hospitalization only, score 4= need hospitalization +oxygen supplement, score 5 = need hospitalization + oxygen supplement + non-invasive ventilation, score 6= need hospitalization + oxygen supplement +mechanical ventilation [19]. Comparing of Covid-19 patients on stan-

dard therapy plus cyclosporine with Covid-19 patients on standard therapy only was done by using paired and un-paired t-test.

3.1. Case I

On 30, February 2021, a 41 years-old man, a known case of psoriasis and has been on oral therapy of 50 mg/day (cyclosporine capsule, PSORID IP, Biocon, India) of CsA for five (5) years and 6 month, presented with headache, low-grade fever, cough, anosmia and profuse sweating for about five days without response to the out-patients empirical therapy . Physical examination illustrated high body temperature 38.7oC, respiratory rate (RR) 14 time/minute , heart rate (HR) 99 beat/minute, oxygen saturation (SaO 2%) 93%, blood pressure 135/90 mmHg. Chest X-ray and computed tomography (CT) scan revealed bronchopneumonia and bilateral ground glass appearance (GGA) in the lower parts of both lungs scores 2 with 3 clinical score. A real-time polymerase-chain reaction (RT-PCR) from nasopharyngeal swab was positive. Complete blood count (CBC) showed leukocytosis, lymphopenia and high neutrophil-lymphocyte ratio (NLR). Inflammatory, tissue injury and coagulation biomarkers were increased; CRP was 12 mg/L (N.V 0.0-5 mg/L), D-dimer was 376 ng/ ng/mL (N.V <230), lactate dehydrogenase (LDH) 294U/L (N.V100-190), and serum ferritin 322 ng/mL (N.V 20-250). Other routine investigation such as fasting blood glucose (FBG), blood urea, serum creatinine and uric acid were within normal ranges. The patient was treated with standard supportive therapy and advised to continue CsA therapy. Subsequent 10-days of therapy, the patient was observed for clinical, laboratory and radiological improvement with negative RT-PCR test; he got well without any complications and was discharged and still on the same dose of CsA.

3.2. Case II

On 23, February, 2021 a 53-year old man with known case of ulcerative colitis since 11 years on CsA treatment 50 mg/day (cyclosporine capsule, PSORID IP, Biocon, India) for about 7 month duration was presented at the emergency unit with nausea, anorexia, vomiting, bloody diarrhea, sore throat, dry cough, dyspnea, headache, sweating, generalized malaise and joint pain. Physical examination showed high body temperature 38.95oC, respiratory rate (RR) 17 time/minute, heart rate (HR) 102 beat/minute, oxygen saturation (SaO2%) 92%, blood pressure 130/80 mmHg with 3 clinical score. Chest X-ray and computed tomography (CT) scan discovered bronchopneumonia and bilateral ground glass appearance (GGA) scores 3. Laboratory findings illustrated positive RT-PCR, lymphopenia, leukocytosis, high NLR, CRP 14 mg/L, D-dimer 382 ng/mL, LDH 311U/L, ferritin 362 ng/mL, general stool examination revealed pus and epithelial cells with profuse RBCs in the stool. Other investigation such as fasting blood glucose (FBG), blood urea, serum creatinine and uric acid were within normal ranges. The patient was treated by standard supportive therapy and advised to continue CsA therapy. Following two weeks of therapy, the patient illustrated remarkable clinical, laboratory and radiological improvement with negative RT-PCR test; he was discharged and still continue on previous dose of CsA.

3.3. Case III

On 13, February, 2021 a 43-year old woman, who is a teacher, a known case of rheumatoid arthritis since 3 years, who has been on CsA therapy 50 mg/day(cyclosporine capsule IP , panimun Bioral, Panacea Biotec, India) for about 3 month, was presented at the emergency unit of Al-Shiffa Medical Center with dyspnea, headache, sore throat, dry cough, fever, sweating, generalized malaise and joint pain for four days without response to an outpatient empirical treatment for flu like illness. On examination, body temperature was 38.8oC, heart rate (HR) 88 beat/minute, respiratory rate (RR) 16 time/minute, oxygen saturation (SaO2%) 91%, blood pressure 135/75 mmHg and clinical score severity was 4.

Chest X-ray and computed tomography (CT) scan discovered GGA (score 3). Laboratory findings showed positive RT-PCR, lymphopenia, leukocytosis, high NLR, CRP 22 mg/L, D-dimer 400 ng/mL, LDH 350 U/L, ferritin 390 ng/mL. Additional investigation such as blood urea, serum creatinine and uric acid were normal. However, FBG on the 9th day of hospitalization increased to 390 mg/dL and was treated with soluble insulin 10 IU tid/day, and this was normalized on the 13th day. She was managed with standard supportive therapy and instructed to continue CsA therapy. After 14 days of therapy, she demonstrated noteworthy clinical, laboratory and radiological improvements with negative RT-PCR test; she was discharged from the hospital and still continued on the same dose of CsA.

3.4. Case IV

On 4, March, 2021 a 39-year old man, a known case of rheumatoid arthritis, since two years on CsA therapy 50 mg/day (cyclosporine capsule IP, panimun Bioral, Panacea Biotec, India) for about 4 month period presented with dyspnea, headache, sore throat, dry cough, fever, sweating, generalized malaise and joint pain for one week. Clinical examination revealed, body temperature 39.2oC, heart rate (HR) 98 beat/minute, respiratory rate (RR) 18 time/minute, oxygen saturation (SaO2%) 92%, blood pressure 140/60 mmHg and clinical score severity was 4.

Chest X-ray and computed tomography (CT) scan showed GGA (score 4). Laboratory findings illustrated positive RT-PCR, lymphopenia, leukocytosis, high NLR, CRP 23 mg/L, D-dimer 422 ng/mL, LDH 359 U/L, ferritin 432 ng/mL. Other investigation such as blood urea, serum creatinine and uric acid were normal. Nevertheless, FBG on the 7th day of hospitalization increased to 220 mg/dL and was treated with soluble insulin 10 IU tid/day, and this was normalized on the 12th day. He was treated with standard supportive therapy and directed to continue CsA therapy. Following 16 days of therapy, he demonstrated notable clinical, laboratory and radiological improvements with negative RT-PCR test; he was discharged thereafter and to continue with the same dose of CsA.

3.5. Case V

On 15, March 2021, a 43 years-old man, a known case of psoriasis and hypertension for over 3 years on oral CsA therapy 50 mg/day (cyclosporine capsule, PSORID IP, Biocon, India) and amlodipine 10mg /day for about 4 month duration, presented with dry cough , sore throat , dyspnea, anosmia, headache, sweating, generalized body ache for 3 days. On examination, body temperature 38.3oC, respiratory rate (RR) 17 time/minute, oxygen saturation (SaO2%) 92%, heart rate (HR) 90 beat/minute, blood pressure 140/90mmHg with 4 clinical score. Radiological investigations through Chest X-ray and computed tomography (CT) showed bilateral GGA of lung score 4. Laboratory investigations illustrated leukocytosis, lymphopenia, high neutrophil-lymphocyte ratio (NLR), CRP was 19mg/L, serum ferritin 331 ng/mL, LDH) 291U/L and D-dimer was 390 ng/ ng/mL. He was treated by standard supportive therapy in addition to the CsA therapy. Following 18-days of therapy, he showed remarkable clinical, laboratory and radiological improvement with negative RT-PCR test; he discharged from the hospital to resume his daily activity but still placed on the same dose of CsA.

4. Clinical Summary

In the present case-series study, all cases were hospitalized with moderate-severe cases and treated with the standard therapy for Covid-19 in addition to the CsA therapy. None of the patients received dexamethasone drug, which is commonly used in the management of Covid-19. Male to female ratio was 4:1, with 2 psoriasis, 2 rheumatoid arthritis and 1 ulcerative colitis. All patients presented with typical presentation of Covid-19 pneumonia with clinical score severity range from 3-4, and CT scan score ranged from 2-4. The duration of hospitalization ranged from 10-18 days without any recorded mortality. All reported cases revealed leukocytosis, lymphopenia, high neutrophil-lymphocyte ratio (NLR) with elevation of CRP, ferritin, LDH) and D-dimer serum levels, however case 3 and case 4 developed transient hyperglycemia that was managed transiently with soluble insulin for about four days and returned to normal level at time of discharge. Only case 5 had additional comorbidity of hypertension and was on amlodipine treatment. At time of discharge, radiological score was zero, biochemical variables were near normal values, and the clinical score severity was 1. In Covid-19 cases that were not on CsA therapy, there were significant differences in their laboratory findings and other variable that were unfavourable compared with Covid-19 cases that were on CsA therapy. One case of Covid-19 cases that was not on CsA therapy died, making a mortality rate of 20% (Table 1).

Table 1: Demographic, clinical, radiological and biochemical biomarkers in Covid-19 patients on cyclosporine therapy compared with controls.

Variables	Covid-19+CsA+ST(*n*=5)		P value	Covid-19+ ST(*n*=5)		P value
	A	B		A	B	
Age (years)	43.0±5.8	43.0±5.8	1.00	44.0±4.86	44.0±4.86	1.00
M:F ratio	4:1	4:1	1.00	3:2	3:2	1.00
Clinical score (%)	3.6±0.54	1.1±0.1	0.0001	5.1±0.82	2.1±0.71*	0.0001
CT scan score (%)	3.2±0.0.83	0.3±0.01	0.0001	4.9±0.63	1.9±0.07#	0.0001
SaO2%	92.0±0.70	97.0±0.80	0.0001	89.0±0.60	94.0±0.50#	0.0001
HR (beat/min)	95.4±6.06	88.12±4.82	0.0001	97.53±7.05	86.74±4.45	0.0001
RR(time/min)	16.40±1.51	13.31±1.53	0.01	18.94±1.49	14.90±1.31	0.001
MAP (mmHg)	105.0±1.50	106.6±1.8	0.16	102.63±1.4	103.88±1.1*	0.15
CRP (mg/L)	18.0±4.84	4.0±1.02	0.0001	25.0±5.56	8.0±1.62#	0.0001
Ferritin (ng/mL)	367.40±44.99	230.31±14.01	0.0001	495.52±49.61	311.21±32.57#	0.0001
LDH (U/L)	321.0±31.67	121.4±9.78	0.0001	495.98±43.61	241.0±22.91#	0.0001
D-dimer(ng/mL)	394.0±18.5	221.63±8.74	0.0001	431.79±32.92	254.81±11.84#	0.0001
WBC(×10³/µL)	23.51±6.86	10.21±2.93	0.0001	39.74±7.63	13.62±4.79#	0.0001
Neutrophil (%)	84.31±12.95	66.96±8.19	0.001	89.93±11.57	71.48±9.31	0.001
Lymphocyte (%)	16.81±2.06	22.91±1.59	0.0008	12.05±3.85	19.69±2.41*	0.0001
NLR	5.01±1.63	2.92±1.02	0.04	7.46±2.60	3.96±1.73	0.03
Hospitalization period (days)		14.2±2.9			26.41±2.3	0.0001

Results are expressed as mean± SD, *P<0.05, #P<0.01 compared at time of discharge, A: at time of hospitalization, B: at time of discharge, M:F male female ratio, SaO2%: oxygen saturation, HR: heart rate, RR: respiratory rate, MAP: mean arterial pressure, CRP: C-reactive protein, LDH: lactate dehydrogenase, WBC: white blood cell, NLR: neutrophil lymphocyte ratio, Covid-19+CsA+ST: Covid-19 patients on standard therapy plus cyclosporine, Covid-19+ ST: Covid-19 patients on standard therapy only.

5. Discussion

In the present case-series study, we recruited five cases on CsA therapy because of different immune-inflammatory disorders which include rheumatoid arthritis, psoriasis and ulcerative colitis that developed Covid-19 pneumonia and compared their treatment outcome with five other cases of Covid-19 pneumonia without CsA therapy as controls. CsA therapy in the reported cases led to significant attenuation of Covid-19 severity as revealed through good primary outcomes of short hospitalization period and no mortality compared with control Covid-19 patients. It has been reported that short hospitalization period and low mortality are indicators of better outcomes in Covid-19 patients [20]. Regarding the secondary outcomes, in Covid-19 patients on CsA therapy, clinical score severity, CT scan scores and oxygen saturations were significantly better as compared to control Covid-19 patients. This is in an agreement with recent studies that proposed the possible value of CsA therapy in Covid-19 [21,22]. Xiao et al., [23]. Experimental study revealed that administration of CsA attenuates lipopolysaccharide-induced ALI in mice through inhibition release of pro-inflammatory cytokines and mitochondrial DNA. Besides, Cour et al., [24] suggested that CsA therapy may prevent acute respiratory failure in Covid-19 patients through prevention of SARS-CoV-2 replication, ALI and exaggerated immune-inflammatory response. These verdicts and findings may explain the lowered CT scan and clinical severity scores in Covid-19 patients on the CsA therapy. However, Covid-19 patients on the CsA showed slightly increased blood pressure compared to the control Covid-19 patients. This effect might be due to prolonged use of CsA (3-7 months) since long-term CsA therapy is linked with development of hypertension as an important adverse effect [25]. All reported cases denied history of hypertension or antihypertensive treatments except case 5 that is well-known to be hypertensive and on amlodipine treatment. Thus, hypertension in the presented cases could be adverse effect of CsA therapy; nonetheless none of other CsA-related adverse effects were reported of recruited cases. Moreover, inflammatory biomarkers (ferritin and CRP), injury biomarker (LDH), and coagulation biomarker (D-dimer) were significantly reduced in Covid-19 patients on the CsA therapy as compared with Covid-19 control patients. Joo et al., [26] disclosed that CsA has an effective anti-inflammatory effect equivalent to that of corticosteroid in experimental mice. Recently, CsA therapy reduces CRP in patients with ulcerative colitis [27]. In addition, CsA therapy being an effective anti-inflammatory treatment has been reported to have reduced inflammatory biomarkers in patients with influenza flu [28]. In the present study, CsA improved lymphocyte count but did not affect NLR in Covid-19 as compared with Covid-19 controls. Flores et al., [29] showed that low dose of CsA as used in the present study had paradoxical improvement of T lymphocyte functions.

Till now, there is no specific prospective clinical study regarding effect of CsA therapy on Covid-19 patients. However, a retrospective, longitudinal observational study was done in Madrid Spain regarding use of low dose of CsA within 72 hour of admitted patients with Covid-19 pneumonia for 7-10 days or up to 21 days in patients that did not respond to the standard therapy. This study suggested that CsA therapy reduces mortality in severely affected patients with Covid-19 pneumonia through inhibition of NF-κB signaling pathway, which is commonly activated during SARS-CoV-2 infection [30]. Likewise, CsA therapy reduced Covid-19 severity and mortality in psoriatic patients [46].

More specifically, case 3 and 4 developed hyperglycemia on 9th and 7th day respectively during SARS-CoV-2 infection; this effect might be due to induction of insulin resistance and pancreatic-β cell injury [31, 32]. However, this transient hyperglycemia was resolved upon initiation of insulin, thus this hyperglycemia might be due to SARS-CoV-2-induced oxidative stress rather than pancreatic-β cell injury, due to rapid improvement experienced by insulin therapy [33].

The present reported cases have underlying high pro-inflammatory cytokines due to associated psoriasis (cases 1, 5), rheumatoid arthritis (cases 3, 4) and ulcerative colitis (case 2). It has been reported that psoriasis is associated with high pro-inflammatory cytokines mainly TNF-α [34]. Both rheumatoid arthritis and ulcerative colitis are also linked with systemic inflammatory disorders due to exaggerated pro-inflammatory cytokine responses [35, 36]. It has been suggested that preexistent high pro-inflammatory cytokines in different metabolic diseases may increase Covid-19 severity [37]. Prolonged use of CsA in the reported cases may have mitigated high pro-inflammatory cytokines and inflammatory disorders thereby decreases inflammatory burden during SARS-CoV-2-induced hyperinflammation [38].

Indeed, despite immunosuppressive effect of CsA, none of reported cases developed secondary bacterial infections. Some previous studies reported risk of secondary bacterial infections in patients treated with CsA, however this risk is low [39]. Zegarska et al., [40] reported that high but not low dose of CsA therapy that is associated with significant immunosuppression and secondary bacterial infections. Colombo et al., [39] illustrated that patients treated with CsA for one year duration did not experience any viral infections or reactivation of preexistent infectious diseases. Therefore, CsA is regarded as safe drug in critical Covid-19 infection. The potential effects of CsA on SARS-CoV-2 infection in Covid-19 are related to various mechanisms including;

Antiviral effects: CsA has broad-spectrum antiviral effects against hepatitis C virus, hepatitis B virus, HIV virus, influenza A virus, Zika virus and Rift-Valley virus through inhibition of RNA-dependent polymerase [41]. CsA inhibits replication of different coronaviruses such as SARS-CoV, MERS-CoV, HCoV-229E , HCoV-NL63 and SARS-CoV-2 directly or through inhibition of immunophilin pathway ,which is essential for growth of coronavi-

ruses [42]. Besides, CsA blocks non-structural protein 12 (nsp 12) of SARS-CoV-2, prevents alteration of cytosolic PH and binding of SARS-CoV-2 to the ACE2. This binding is higher at low cytosolic PH [43].

Anti-inflammatory effects: CsA prevents SARS-CoV-2-induced activation of hemophagocytic lymphohistiocytosis , which is involved in the development of cytokine storm, inhibits release of IL-2 , which is responsible for proliferation and activation of T cells [44]. Moreover, CsA prevents cytosolic protein unfolding response and mitochondrial dysfunction in SARS-CoV-2 infection through anti-inflammation and blocking of mitochondrial cyclophilin D [45]. Mitochondrial dysfunction in SARS-CoV-2 activates releases of nod-like receptor pyrin 3 (NLRP3) inflammasome, which is involved in activation of NF-κB and release of pro-inflammatory cytokines [47]. Also CsA inhibits NLRP3 inflammasome [48]. Interestingly, CsA attenuates SARS-CoV-2-induced release of pro-inflammatory cytokines through inhibition of mTOR pathway [49]. The p38 mitogen activated protein kinase (MAPK) is activated during SARS-CoV-2 infection, and it is linked with development of ALI, coagulopathy, peripheral vasoconstriction and hyperinflammation [50]. Therefore, p38MAPK inhibitors might be a promising therapeutic strategy in the management of Covid-19. Previously, Matsuda et al., [51] illustrated that CsA and other calcineurin inhibitors inhibit p38MAPK pathway.

Taken together, antiviral and anti-inflammatory properties of CsA give it a merit to be a potential candidate in the management of patients with severe Covid-19.

Limitations of the present study is that pro-inflammatory cytokines mainly IL-6, IL-18 and TNF-α were not assessed in relation to CsA therapy. However, the present study has a novel worth in evaluating of CsA in management of Covid-19 pneumonia.

6. Conclusion

In the current reported case-series, preexistent CsA therapy attenuates Covid-19 severity and mortality with significant reduction of inflammatory state. Therefore, CsA may reduce Covid-19 severity through anti-inflammatory and anti-SARS-CoV-2 properties. Despite present findings, we cannot give an ultimate conclusion concerning use of CsA in managing of Covid-19. Thus, large-scale studies are warranted to confirm these finding in this regards.

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