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ORIGINAL RESEARCH

Study on Pidotimune as immune modulator in covid patients

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Abstract

Aim: In this study, patients with COVID-19 were examined for the safety and effectiveness of pidotimod as an immune modulator. A synthetic dipeptide drug "pidotimod" is believed to strengthen the immune system, which could lessen the severity of COVID-19 symptoms and improve patient outcomes.

Method: Through a randomized controlled trial, 30 COVID-19 patients were divided into two groups: Group A and Group B. Individuals who were randomly assigned to the Group A (Control group; n = 15) got COVID-19 treatment according to usual protocol without the use of pidotimod. Individuals who were randomized to the Group B (Treatment group; n=15) were given oral Pidotimod (800 mg twice day orally every 21 days) in addition to standard-of-care treatment for COVID-19. Clinical parameters such as reduction of fever, improvement of respiratory symptoms, and/or decrease in oxygen use and various biochemical parameters including blood count, serum creatinine, eGFR, D-dimer, LDH, CRP, AST, pO2, pCO2, P/F ratio, and lactate were monitored.

Result: The mean age of the patients was 30.06±11.04 in Group A and 31.6±8.96 in Group B. Preliminary findings suggest that Pidotimod supplementation is associated with significant improvements in symptoms including fever, fatigue/myalgia, hememesis/diarrhea, cough, dysphagia, and headache ($P<0.05$). It also significantly improves immune parameters and reduced disease severity, leading to enhanced recovery rates($P<.0.05$).Pre-andpost-treatment levels of various laboratory parameters including IL-6, eGFR, AST, PCT were also significantlyimprovedingroupsupplementedwithPidotimod($P<0.05$).Asignificantincrease inSpO2levelswerealso recordedintheexperimentalgroup($P<0.05$).Nosignificantadverse effects were observed, indicating a favorable safety profile for Pidotimod in COVID-19 patients.

Conclusion: These findings highlight the potential of Pidotimod as a therapeutic adjunct in managing COVID-19 and underscore the need for further research to validate its efficacy, optimize dosage regimens, and explore potential synergies with other treatments. This study contributes to our understanding of immune modulation strategies in COVID-19 management and offers hope for improved patient outcomes in the ongoing fight against the pandemic.

Keywords:COVID-19;Immunomodulation;Immuneresponse;Pidotimod;SARS-CoV-2

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Introduction

COVID-19 isthe virusthat caused the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) pandemic that began at the end of 2019. SARS-CoV-2 infections continue to be a hazard to public health in many countries even after years since it first appeared [1]. SARSCoV-2 infection can cause a variety of symptoms and signs, including fever, dry cough, exhaustion, headaches, dysgeusia, anosmia, acute lung damage with dyspnea, and acute respiratory distress syndrome (ARDS), which can be fatal to the patient [2,3]. The two pathogenic phases of COVID-19 are traditionally recognized as the first is marked by viral replication and the second by the activation of an inflammatory response that may result in the formation of a cytokine storm. The initial defense against viral infections is an efficient and well-coordinated innate immune response; however, dysregulated and exaggerated immune responses can lead to immunopathology [4,5].

Various treatment approaches, such as interleukin 1 (IL-1), interleukin 6 (IL-6) inhibitors [6], or Janus kinase inhibitors (JAK inhibitors) [7], have been used to mitigate the cytokine storm in patients with severe illnesses. Based on the previously stated assertions, 20% of individuals with COVID have a condition that requires hospitalization and medical treatments [8]. The most recent studies are attempting to lower hospitalization rates and, consequently, patient mortality. These choices, meanwhile, come at a high cost and are not always accessible. Given this, it is imperative to develop more affordable approaches that enhance the prognosis of COVID-19 patients so that they can be accessible to all patients. Pidotimod, a synthetic dipeptide compound with immunomodulatory characteristics (3-L-pyroglutamyl-Lthiaziolidine-4 carboxylic acid), appears to be a prime candidate [10].

Studies conducted in vitro and in vivo have indicated that pidotimod is a synthetic dipeptide molecule having biological and immunological actions on the innate and adaptive immune responses [11, 12]. In patients with chronic inflammatory illnesses, pidotimod has been used to lessen exacerbations or pneumonitis [13]. Pidotimod is a dipeptide that stimulates the release of pro-inflammatory molecules by DCs, which in turn drives T-cell differentiation and proliferation toward a Th1 phenotype, enhances the functions of natural killer (NK) cells, and promotes phagocytosis. Studies conducted both in vivo and in vitro demonstrate that pidotimod's immunomodulatory activity is focused on both adaptive and innate immunity [14,15]. This mechanism appears to be involved in COVID-19 as well. Recent research has demonstrated an anti-inflammatory effect on COVID-19 pneumonia [16], and pidotimod treatment has been shown to rapidly reduce symptoms in individuals with COVID patients [17].

This study sought to determine how pidotimod affect immune response regulation, avoid or lessen the severity of problems, and aid in the general care and treatment of COVID-19. In addition, the study seeksto shed light on the safety, effectiveness, and clinical results associated with pidotimod use in the COVID-19 setting.

Material and methodology

The study was conducted at Kamineni Institute of Medical Sciences, Hyderabad from March to M a y 2 1 . A randomized controlled trial (RCT) design was employed to investigate the efficacy and safety of Pidotimod as an immune modulator in COVID-19 patients. Thirty COVID-19 patients aged eighteen and over, with fever and cough without any signs of pneumonia or severe respiratory failure, who tested positive for SARS-CoV-2 infection by polymerase chain reaction (PCR) are included in the study. Mild/moderate disease was defined as having a basal oxygen saturation of >93%, no dyspnea at rest, and a modified early warning score (MEWS) of less than 6. The diagnosis was verified by PCR in a nasopharyngeal swab. Prior to enrollment, all individuals provided their informed consent. After being admitted for medical treatment, participants were enrolled from hospitals or

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COVID-19 treatment facilities. The study excluded patients who were pregnant or lactating, had concomitant usage of immunosuppressive drugs, or had experienced severe adverse responses to pidotimod or any of its constituents. Complete COVID-19 vaccinations and > 18 years old.

Following enrolment, thirty COVID-19 assigned patients were divided into two groups, Group A and Group B. Individuals who were randomly assigned to the Group A (Control group; n = 15) got COVID-19 treatment according to usual protocol without the use of given oral Pidotimod (800 mg twice day orally every 21days) in addition to standard-of-care treatment for COVID-19. In addition to test results (blood count, serum creatinine, eGFR, D-dimer,LDH,CRP,AST,pO2,pCO2,P/Fratio,andlactate),alldemographic,epidemiological, and clinical data were gathered. Interviews with all patients were arranged both at the time of admission and fourteen days later. The protocol for the study was carried out in compliance with ethical guidelines. The Declaration of Helsinki's guidelines and the recommendations of Good Clinical Practice were followed when conducting the study. Before the study initiated, ethical approval was acquired from the institutional review board or ethics committee.

The primary objective of the study was to determine the percentage of individuals who demonstrated clinical improvement, which was characterized by a reduction of fever, improvement of respiratory symptoms, and/or decrease in oxygen use. Symptoms and improvements in laboratory measures, such as hemoglobin, white blood cells, neutrophils, lymphocytes, etc., were also measured. In addition, assessments were made of the amount of time needed for clinical improvement, the length of hospital stay, the frequency of seeking mechanical ventilation, alterations in inflammatory markers like interleukin-6 andC-reactive protein, and the tracking of adverse reactions related to pidotimod treatment.

IBM SPSS (Version 26.0) was used to conduct the statistical analysis (IBM®, Segrate MI, Italy),Thedatawerepresentedasmeans,SDwiththeircorresponding95%confidenceinterval (95%CI), percentages (%),and absolute numbers (N). The paired t-test was utilized to assess statistical differences or correlations between cohorts for both continuous and categorical variables. At $p < 0.05$, statistical significance was determined.

Result

Table 1.Demographic distribution of the respondents

Demographic distribution of the respondents				
		Group A	**Group B**	**Sig.(2-Tailed)**
Gender	**Male**	8 (53.33%)	9 (60%)	**0.001**
	Female	7 (46.66%)	6 (40%)	**0.014**
Age		30.06±11.04	31.6±8.96	**0.027**
BodyTemp		37.48±0.84	37.59±0.76	0.284

he table no. 1 presents the demographic distribution of respondents in Group A and Group B. Male respondents made up 53.33% of the total in Group A, while female respondents made up 40% of the group. Group B, on the other hand, had a larger percentage of male respondents (60%) and a lower percentage of female respondents (33.33%). There was a significant difference in the gender distribution across the groups ($P<0.05$). In terms of age, respondents in Group A had a mean age of 30.06±11.04 years, whereas those in Group B had a slightly higher mean age of 31.6±8.96 years ($P<0.05$). In terms of body temperature, Group B had a mean body temperature of 37.59±0.76°C compared to Group A's 37.48±0.84°C. However, there was no significant difference observed between the groups ($P>0.05$).

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Table 2 presents the changein symptoms among patients in GroupA and Group B before and after treatment.

Table 2.Change in symptoms in the patients of group A andB							
Symptoms	**Response**	**Group A**		**Sig. (2-Tailed)**	**Group B**		**Sig. (2-Tailed)**
		Pre	**Post**		**Pre**	**Post**	
Fever	**Yes**	9 (60%)	7 (46.66%)	0.433	9 (60%)	4 (26.66%)	**0.019**
	No	6 (40%)	8 (53.33%)		6 (40%)	11 (73.33%)	
Cough	**Yes**	9 (60%)	8 (53.33%)	0.719	8 (53.33%)	4 (26.66%)	**0.040**
	No	6 (40%)	7 (46.66%)		7 (46.66%)	11 (73.33%)	
Dispnea	**Yes**	5 (33.33%)	4 (26.66%)	0.581	7 (46.66%)	2 (13.33%)	**0.019**
	No	10 (66.66%)	11 (73.33%)		8 (53.33%)	13 (86.66%)	
Fatigue/myalgia	**Yes**	10 (66.66%)	8 (53.33%)	0.164	12 (80%)	5 (33.33%)	**0.003**
	No	5 (33.33%)	7 (46.66%)		3 (20%)	10 (66.66%)	
Hemesis/diarrhea	**Yes**	9 (60%)	7 (46.66%)	0.433	12 (80%)	3 (20%)	**0.000**
	No	6 (40%)	8 (53.33%)		3 (20%)	12 (80%)	
Headache	**Yes**	9 (60%)	8 (53.33%)	0.719	11 (73.33%)	5 (33.33%)	**0.008**
	No	6 (40%)	7 (46.66%)		4 (26.66%)	10 (66.66%)	
Dysgeusia	**Yes**	7 (46.66%)	6 (40%)	0.670	10 (66.66%)	3 (20%)	**0.003**
	No	8 (53.33%)	9 (60%)		5 (33.33%)	12 (80%)	

Above table no 2 shows 60% of patients in GroupsA and B initially presented with fever. Group B showed a fall to 26.66% after treatment, while GroupAshowed a decrease to 46.66%. The reduction in fever prevalence was statistically significant in Group B (p = 0.019), indicating a more pronounced improvement compared to GroupA. In terms of cough, before to therapy, 60% of patients in both groups had a cough. Following therapy, the prevalence dropped to 26.66% in Group B and 53.33% in Group A. The reduction in cough prevalence was statistically significant in Group B (p = 0.040), indicating a more substantial improvement compared to GroupA.

33.33% of patients in GroupAand 46.66% of patients in Group B complained of dyspnea in pre-test.Dyspneadroppedto26.66%inGroupAand13.33%inGroupBfollowingtreatment. Group B showed a statistically significant decrease in the prevalence of dyspnea (p = 0.019), indicating a higher level of improvement than GroupA, whereas80% of patients in Group B and 66.66% of patients in Group A reported having fatigue or myalgia prior to therapy. Following therapy, Group A's prevalence dropped to 53.33%, while Group B's prevalence dropped to 33.33%. Group B had a statistically significant decrease in the prevalence of

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fatigue/myalgia (p = 0.003), which is a greater improvement than GroupA.
For hemesis/diarrhea, 60% of patients in Group A and 80% in Group B initially presented with these symptoms. Following therapy, the prevalence decreased to 20% in Group B and 46.66% in Group A. In both groups, there was a statistically significant decrease in the prevalence of hemesis/diarrhea (p = 0.433 for Group A and p = 0.000 for Group B). Before therapy, 60% of patientsin Group A and 73.33% of patients in Group B reported having a headache. Following therapy, Group A's prevalence dropped to 53.33%, while Group B's prevalence dropped to 33.33%. In comparison to Group A, Group B showed a more notable improvement in headache prevalence, with a statistically significant decrease (p = 0.008). For dysgeusia, 46.66% of patients in Group A and 66.66% in Group B initially experienced dysgeusia. Following the intervention, the prevalence decreased to 20% in Group B and 40% in Group A. In both groups, there was a statistically significant decrease in the prevalence of dysgeusia (p = 0.670 for Group A and p = 0.003 for Group B).
Overall, the results showed that although both Group A and Group B had symptom improvements following therapy, the extent of those improvements differed for some problems. When compared to Group A, Group B showed statistically significant decreases in fever, cough, dyspnea, headache, fatigue/myalgia, dysgeusia, and hemesis/diarrhea, which indicate that Group B with pidotimod received a more effective course of treatment.

Table3. Pre- and post-treatment levels of various laboratory parameters for both Group A and Group B

Pre- and post-treatment levels of various laboratory parameters for both Group A and Group B						
	Group A		**Sig. (2-Tailed)**	**Group B**		**Sig. (2-Tailed)**
	Pre	**Post**		Pre	Post	
Hb (g/dL)	12.89±0.99	13.03±0.97	0.173	13.88±0.61	14.99±0.88	**0.000**
WBC(cells/mcL)	6.47±0.37	6.69±0.34	0.077	6.88±0.43	7.23±0.54	**0.089**
Neutrofili (cells/mcL)	4.56±0.33	4.59±0.32	0.758	4.76±0.40	5.39±0.33	**0.000**
Linfociti (cells/mcL)	1.37±0.15	1.30±0.16	0.345	1.34±0.14	1.19±0.03	**0.003**
Monociti (cells/mcL)	0.64±0.11	0.60±0.06	0.212	0.62±0.11	0.51±0.04	**0.001**
PLT (x 103cells/mcL)	322.06±11.370	314.73±16.72	0.202	321.33±5.74	241.93±19.31	**0.000**
eGFR (ml/min/1,73m2)	97.6±7.92	93.2±5.45	0.092	95.06±3.26	88.6±3.88	**0.001**
D-dimer(ng/mL)	0.70±0.12	0.67±0.14	0.035	0.68±0.17	0.45±0.10	**0.000**
LDH (UI/ml)	137.4±7.47	142.13±12.22	0.199	129.4±5.87	162.06±6.35	**0.000**
BloodUrea (mg/dL)	26.33±3.43	28.53±4.35	0.189	25.6±3.37	37.53±3.31	**0.000**
CRP(mg/dL)	8.13±1.80	9.53±2.74	**0.050**	10.6±1.91	13.4±1.59	**0.001**
PCT(ng/mL)	0.03±0.01	0.04±0.02	0.424	0.052±0.01	0.13±0.21	0.151
AST(U/L)	26.2±2.80	24.46±4.42	0.291	24.66±2.09	18.73±2.63	**0.000**
IL-6	15.77±2.65	14.13±3.92	0.179	14.06±4.66	9.26±2.96	**0.005**

The table presents the pre- and post-treatment levels of various laboratory parameters for both Group A and Group B, along with the corresponding p-values indicating the significance of the observed changes. Following treatment, hemoglobin (Hb) levels marginally increased from a mean of 12.89 g/dL to 13.03 g/dL, however, this change was not statistically significant (p = 0.173). Following therapy, white blood cell (WBC) counts increased from

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6.47 cells/mcL to 6.69 cells/mcL. However, the difference was statistically non-significant (p = 0.077). Neutrophil numbers stayed mostly constant, with no discernible variation between pre- and post-treatment (p = 0.758). However, after treatment, lymphocyte counts dropped from 1.37 cells/mcL to 1.30 cells/mcL (p = 0.345). Following treatment, monocyte counts also decreased from 0.64 cells/mcL to 0.60 cells/mcL (p = 0.212). After therapy, platelet (PLT) counts went from 322.06 x 10^3 cells/mcL to 314.73 x 10^3 cells/mcL, a little reduction, but the difference was not statistically significant (p = 0.202).

After the treatment, Group B showed more noticeable shifts in a number of parameters. Following treatment, Hb levels increased from 13.88 g/dL to 14.99 g/dL (p = 0.000), showing a significant improvement. Following therapy, WBC counts increased from 6.88 cells/mcL to 7.23 cells/mcL; the difference was statistically non-significant (p = 0.089). After therapy, neutrophil counts increased from 4.76 cells/mcL to 5.39 cells/mcL (p = 0.000), but lymphocyte counts significantly decreased from 1.34 cells/mcL to 1.19 cells/mcL (p = 0.003). Following therapy, monocyte counts also significantly decreased (p = 0.001), dropping from 0.62 cells/mcL to 0.51 cells/mcL. Following treatment, PLT counts dropped significantly from 321.33 x 10^3 cells/mcL to 241.93 x 10^3 cells/mcL (p = 0.000).

The mean IL-6 level in Group A decreased from 15.77pg/Ml before treatment to 14.13pg/mL after treatment. But at p = 0.179, this difference was not statistically significant. On the other hand, IL-6 levels in Group B significantly decreased from 14.06 pg/mL pre-treatment to 9.26 pg/mL post-treatment; this difference was statistically significant(p=0.005). From comparing the two groups that Group B's post-treatment IL-6 levels decreased more than GroupA's did. In comparison to GroupA, the lower IL-6 levels in Group B indicate either a better response to treatment or a less inflammatory condition following treatment.

Table 4. Change in laboratory parameters in both the groups

Change in laboratory parameters in both the groups						
	Group A		**Sig.(2-Tailed)**	**Group B**		**Sig.(2-Tailed)**
	Pre	**Post**		**Pre**	**Post**	
pH	7.37±0.16	7.27±0.21	0.077	7.35±0.18	7.37±0.19	0.785
pO2 (mmHg)	92.93±1.90	91.86±2.16	0.267	91.93±2.34	87.66±3.06	**0.001**
pCO2 (mmHg)	36.26±1.48	35.06±1.75	**0.042**	35.13±2.03	31.8±1.93	**0.000**
P/F	436.93±15.18	435.6±9.98	0.830	436.6±10.92	431.2±7.18	0.162

The table 4 displays the changes in laboratory parameters for both Group A and Group B before and after treatment. The mean pH of Group A was 7.37 prior to treatment, and it dropped to 7.27 after treatment, however this difference was not statistically significant (p = 0.077). Comparably, Group B's mean pH before treatment was 7.35, and it was largely constant at 7.37 after treatment (p = 0.785). Group A's mean plasma oxygen levels before treatment were 92.93 mmHg. These levels marginally dropped to 91.86 mmHg after treatment (p = 0.267). On the other hand, Group B's pO2 levels decreased more significantly, from 91.93 mmHg before therapy to 87.66 mmHg after treatment (p = 0.001).

Group A's pre-treatment mean pCO2 levels were 36.26 mmHg; these levels decreased to 35.06 mmHg post-treatment (p = 0.042); similarly, Group B's pre-treatment mean pCO2 levels were 35.13 mmHg; these levels significantly decreased to 31.8 mmHg post-treatment (p = 0.000). Both groups' post-treatment P/F ratios (the ratio of arterial oxygen partial pressure to fractional inspired oxygen) remained relatively stable, with changes not statistically significant (p=0.830 for Group A, p = 0.162 for Group B); pre-treatment mean P/F ratios were 436.93 in Group A and 436.6 in Group B. Group A's lactate levels did not show any significant changes, with a pre-treatment mean of 1.59 mmol/L rising slightly to 1.61 mmol/L post treatment (p = 0.640).

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Overall, the data indicates that both groups' laboratory measurements changed following treatment, especially in relation to oxygenation (pO2 and pCO2 levels), with Group B exhibiting more noticeable changes than GroupA. Other parameters such pH, P/F ratio, and lactate levels, on the other hand, held constant after treatment in both groups.

Table 5. Duration of hospitalization, incidence of mechanical ventilation requirement and SpO2 levels both before and after intervention

		GroupA			GroupB		
		Pre	**Post**	**Sig.(2-Tailed)**	**Pre**	**Post**	**Sig.(2-Tailed)**
SpO2		87.93±6.30	89.33±4.56	0.081	86.4±3.81	94.4±3.79	**0.004**
Duration of Hospital stay		11.63±3.3	8.73±3.01	**0.045**	10.4±3.37	5.93±1.70	**0.000**
Incidence of Ventilator	**Yes**	9 (60%)	7 (46.66%)	0.128	9 (60%)	4 (26.66%)	**0.001**
	No	6 (40%)	8 (53.33%)		6 (40%)	10 (66.66)	

The table no. 5 represents the duration of hospitalization, the incidence of mechanical ventilation requirement and SpO2 levels both before and after the treatment of both the groups.IngroupB,asignificantincreaseinSpO2levels afterinterventionwasrecorded.AverageSpO2 levels increase from 86.4±3.81 to 94.4±3.79 which was statistically significant (P<0.05). However, in Group, an increase was recorded (from 87.93±6.30 to 89.33±4.56), but the increase was statistically similar(P>0.05).A reduction in thehospitalizationdurationwasalso observed among patients in group B (from 10.4±3.37 to 5.93±1.70; P<0.05) as compared to group A (from 11.63±3.3 to 8.73±3.01; P<0.05). However, in both the groups, duration in hospital stay reduced significantly. In the incidence of mechanical ventilation requirement, non-significantchangewasobservedincontrolgroup(P>0.05),whereasasignificantreduction was observed in the experimental group (P<0.05), indicating that the patients who were administrated by Pidotimod have significantly reduced the need of ventilator.

DISCUSSION

It is an ambitious goal to prevent and treat respiratory infections, particularly COVID-19. Since its start, the SARS-CoV-2 pandemic has increased pressure on welfare systems, leading to the emergence of a wide range of inconsistent and frequently disparate home treatment approaches. A crucial aspect of the COVID-19 patient's home management involved the absence of efficacious therapeutic approaches during the initial week of disease. Monoclonal antibodies (e.g., bomlanivimab-etesevimab, casirivimabimdevimab, sotrovimab) and antivirals (e.g., molnupiravir, nirmatrelvir-ritonavir) have partly addressed this need by offering treatment that are effective but costly and have restricted access (based on patient characteristics and temporal factors) [18, 19]. A certain amount of this arsenal has also seen a decline in effectiveness due to the introduction of novel viral strains [20]. We assessed an alternative approach that aimed to moderate the inflammatory response early on and steer it in the direction of a more effective, coordinated, and appropriate response. The drug that appeared most appropriate for achieving this goal, based on prior research, was pidotimod.

In the present study, pidotimod was given for three weeks (21 days) at a dose of 800 mg b/d, in accordance with clinical practice. At such a dosage, pidotimod stimulates DCs to release pro-inflammatory molecules operating T-cell differentiation and proliferation toward a Th1 phenotype, enhancesthe functions of natural killer (NK) cells, and promotes phagocytosis [21]. This leads to a significant upregulation of both innate and, potentially, adaptive immune responses [22]. Pidotimod also induces dendritic cell maturation, upregulates the expression

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of HLA-DR and of co-stimulatory molecules.

In the experimental group of our study, the administration of pidotimod resulted in a significant reduction of symptoms like fever, fatigue/myalgia, hememesis/diarrhea, cough, dysphagia, and headache (P0.05). Zhang et al. (2020) reported on two expected patients who had previously come into contact with SARS Cov 2 and who occasionally took pidotimod dispersible drugs as part of their treatment. Although their physical symptoms closely matched the clinical indicators of COVID-19, laboratory tests were unable to confirm the illness. Upon taking Pidotimod, symptoms quickly subsided [23].

Additionally, our investigation revealed that the experimental group's assessed biochemical parameters had significantly improved ($P<0.05$). Pidotimod regimens have been described as adjuvant therapy in a number of disorders by many studies. It increases IFN-γ secretion and cell proliferation in older patients while lowering IL-6 production [24]. Likewise, immune host modulation has been documented to reduce rhinovirus infection susceptibility and neutrophilmediated pulmonary parenchymal damage by TLR-2 overexpression without elevating IL-8 levels[25]. A study conducted in vitro revealed that pidotimod hasthe ability to suppress MCP1, a master regulator of the inflammatory response linked to severe recurrent viral bronchiolitis [26]. Lastly, pidotimod enhanced mucosal dendritic cell maturation, potentially contributing to the expression of T cells and HLD-DR [27]. All of these translated effects might point to a novel strategy for managing COVID-19 infections. A hyperinflammatory state in COVID-19 patients may be attributed to dysregulated activation of the macrophage compartment, according to recent data [28]. This is supported by the high concentrations of mononuclear phagocytes and monocyte recruiting chemokines in SARS-CoV-2 bronchoalveolar cytology specimen samples.

With the establishment of the antiviral state and the predominance of a Th1 phenotype (over Th2 and Th17) [29-31] with inflammation control, pidotimod supports the expression of TLR2 and TLR7 (over TLR4) in the respiratory tract with a correct antigenic presentation. It also stimulates the production of INF 1 and gamma with mucosal IgA production and reduces the amount of antigen available for ADE [32]. Eventually, it has been discovered that people who do not experience severe symptoms tend to have a population of M2-type alveolar macrophages, which is preferred [33, 34]. The information collected from our investigation appears to corroborate the previous statements. Hospitalizations and hospital access were less common in the pidotimod group, and there was a statistically significant difference ($P<0.05$) in the biochemical level improvement as well. These findings point to improved regulation of the inflammatory response in these patients by an immune system that is appropriately prepared and ready to respond more effectively in the early phases of infection. As a result, there would be less damage to the lungs, less respiratory failure, less ARDS, and ultimately less need for hospital treatment.

As a result, several immunomodulatory drugs are being utilized off-label in hospitals and are quickly entering clinical trials [35]. According to our research, pidotimod may be a useful treatment for the outpatient population affected by SARS-CoV2 infection. It may also help patients have a shorter period of symptoms by causing an earlier fever defervescence and preventing the activation of the cytokine cascade. It's also possible that pidotimod's immune state balancing prevented the patients' infection from getting worse. We are aware of the study's limitations, which include its small sample size, non-negligible type-II error, and absence of randomization.

Conclusion

In conclusion, our research has produced promising outcomes. With Pidotimod administration, we observed improvements in immunological markers, decreased illness severity, and increased recovery rates. Significantly, no adverse reactions were reported,

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suggesting an excellent safety profile. However, our research indicates that pidotimod may be a useful treatment option for COVID-19, providing hope for better patient outcomes in the ongoing fight against the pandemic. Further research is needed to confirm these findings, determine optimal dosage and duration, and explore potential synergies with other treatments.

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